Future Directions in Transplantation

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There have been extraordinary strides made in transplantation medicine as we near the 60th anniversary of the first human renal transplant procedure. Incremental improvements in graft and patient survival reflect refinements in patient and donor selection, better surgical techniques and immunosuppressive regimens, and the multidisciplinary approach to posttransplant management. The goal of establishing complete immunologic tolerance remains both elusive but at the same time inspiring. To date, many patients are able to reach some degree of operational tolerance as defined as prolonged, normal graft function in the setting of minimal immunosuppressive therapy. Barriers that have been overcome over the years include identification of donor-specific antibodies pre- and posttransplant that can provoke immunologic responses, clinical and histopathologic criteria for the diagnosis of acute cellular rejection, recognition of antibody-mediated rejection, development of potent antimicrobial drugs and identification of patients at risk for nosocomial infections such as mismatch donor-recipient patterns, development of an arsenal of immunosuppressive drugs that are more target-specific and less toxic, and increasingly sensitive and specific noninvasive techniques for the diagnosis of acute and chronic allograft rejection. To this end the incidence of acute cellular rejection in solid organ transplantation is now infrequent in most programs. But despite this multitude of advances the majority of solid organ transplant patients succumb to chronic allograft rejection, infection, or malignancy. This fact alone highlights the burden of work yet to be done. Other impediments in transplant medicine include the unremitting shortage of donor organs, the spiraling costs of pre-and posttransplant management and the limited number of new immunosuppressive drugs on the horizon.

Nevertheless, there are many reasons to remain optimistic as new insights and knowledge are constantly evolving. In the field of immunosuppression, attention is now directed to manipulating drug combinations both for the induction and maintenance phases of posttransplant management. Optimization of existing drug regimens has influenced the selection of individual agents based on complementary mechanisms of action in order to limit side effects [1]. In particular, the adverse effects of calcineurin inhibitors (CNI) have promoted clinical trials in CNI-avoidance, CNI-withdrawal, CNI-reduction, and CNI-conversion to other potent but less toxic drugs. Some of the newer agents such as Janus kinase 3 (JAK3) inhibitors and the variety of monoclonal antibodies and other biologics are under investigation and hold promise for clinical application in the near future. These opportunities are especially important in the pediatric population given the expectation of graft survival to be measured

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in decades and not merely years. Another important focus of investigation is the application of donor and patient pharmacogenetic testing as a potential scheme to individualize and tailor drugs to patient profiles. This has the theoretical advantage of maximizing therapeutic effect and limiting toxicity. There remains much to be investigated and discovered in this relatively new branch of transplant medicine.

Worldwide there remains a desperate shortage of donors in all facets of solid organ transplantation. Alterations in organ donation laws require political and legislative perseverance and pressure by the transplant community but these changes alone will not solve the ever-growing demand as the population ages. Expanding the donor pool will require creativity and exploration of a variety of new opportunities. The definition and use of "extended" and "overextended donors" in cardiac, pulmonary, hepatic, and renal transplantation offers selected patients the chance to receive a transplant. These donation-related criteria will undergo revision and refinement as clinical studies elucidate patient outcomes. Another recent development has been the use of cadaveric donation after circulatory cessation in hepatic and pulmonary transplantation. Following careful evaluation and under strict guidelines this provides an additional source of acceptable donor organs. Living related-donors make up a very small proportion of donors and have limited clinical application. Ex vivo preservation and rehabilitation of potential donor organs offers the transplant team additional time to evaluate a potential donor graft. Current experimental studies suggest that manipulation and acceleration of the healing process that follows ischemia-reperfusion injury of the donor organ is a feasible mechanism to repair and eventually utilize organs that might otherwise have been discarded. Tissue engineering of organs remains a theoretic consideration although there has been a great deal of progress over the last decade. Whether creation of new intact grafts becomes a reality or a more modest application such as repair of damaged tissues remains to be determined.

Our understanding of the molecular and immunologic components of acute and chronic rejection has advanced remarkably over the last three decades. The interaction of all arms of the immune response highlights both the complexity and elegance of the process and affords opportunities to develop new drugs and other antirejection therapies. Even drugs that do not advance beyond the rodent model often provide insights into the interaction of T-cells, B-cells, antigen-presenting cells, natural killer cells, etc. Beyond genomic studies, we have yet to learn the full scope of proteomics and metabolomics and their application to transplant medicine. To date there is tremendous promise about the cytokines CXCL-9 and CXCL-10 in renal transplantation [2].

Finally, the role of xenotransplantation in the future of human transplantation remains unresolved but another potential source of donor heart and kidney organs. The identification of xenoreactive natural antibodies such as anti-alpha-Gal, anti-non-alpha-Gal, and polyreactive antibodies are responsible for the hyperacute rejection and acute humeral xenograft rejection episodes [3]. As the immunologic details are uncovered, potential therapeutic interventions, prevention strategies, engineering modifications of animals with high levels of complement regulatory proteins and creation of novel immunosuppressive regimens might one day lead to long-term xenograft survival. For now the prophetic words of Dr. Norman Shumway that "xenotransplantation is the future and always will be" will have to serve as the torch-bearer's motivation. To this end pathologists will continue to play a vital role in transplantation.

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