Progress in Transplantation: Will It Be Achieved in Big Steps or by Marginal Gains?

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A wish for progress in transplantation assumes that there are needs not met by the currently available therapy and that the barriers to resolving the problems can be surmounted. There are 5 major unmet needs: the potential to avoid transplantation either by prevention of disease or provision of an alternative to natural biological organ replacement; geographic heterogeneity of access to, and quality of, transplantation; availability of transplantation to those in need of it; survival of the patient and the transplant; and the avoidance of adverse effects of immunosuppression. During the past 50 years, there have been advances on at least 4 of these 5 fronts that illustrate the interplay of “big steps” and “marginal gains” in the following areas: surgical technique, testing the immunologic barriers, introduction of chemical and biological immunosuppression, and prophylaxis for microbial infections. The potential for further improvement comes in 5 major areas: blood biomarkers for monitoring of rejection, drug-free transplantation through the development of stable tolerance, eliminating the impact of ischemia-reperfusion injury, xenotransplantation of porcine kidneys, and finally, the possibility of autologous regeneration of functioning kidney tissue to treat advanced kidney disease.

INDEX WORDS: Kidney transplantation; renal transplant; end-stage kidney disease; immunosuppression; viral prophylaxis; graft survival; biomarkers; rejection; ischemia-reperfusion injury; xenotransplantation; health disparities; review.

UNMET NEEDS IN CLINICAL TRANSPLANTATION OF THE KIDNEY

You’ve got to be very careful if you don’t know where you are going, because you might not get there.

Yogi Berra

In news media in almost every country, there is an assumption that there is a greater need for transplantation than is being met by the prevailing rate of organ donation. The aligned need is to improve patient and transplant survival and minimize the adverse events attributed to the immunosuppressive drugs that tarnish the shining success of transplantation. Are these claims true? Do they constitute the “burning platform” needed to drive universal improvements? There is considerable variability between countries and it may be that a critical need in one environment is not present in another. Before accepting them as the critical goals for progress in transplantation, these claims must be critically examined.

Prevention of the Need for Kidney Transplantation

The most effective therapy for chronic kidney disease (CKD) stage 5 is the preservation of glomerular filtration rate at earlier stages of CKD. The failure of modern society to improve nutrition and encourage physical activity leads to obesity, diabetes, and
hypertension, which initiate and advance CKD. Alarming ly, the increasing incidence of diabetes has yet to feed fully into the incidence of end-stage kidney failure in both developed Western societies and emerging economies. Secondary prevention measures, implemented through primary care settings, can screen for disease and implement measures known to retard the progression of kidney disease, in particular blood pressure control, use of angiotensin blockade, and improving glycemic control. Effective preventive measures for other causes of CKD stage 5, such as the glomerulonephritides and inherited disorders such as polycystic kidney disease, are clearly important, but treatment options remain limited. The incidence of CKD stage 5 has recently stabilized in Australia, which provides some comfort that prevention strategies may deliver part of the solution.

Global Availability of Transplantation

The World Health Organization publishes national statistics for transplantation annually as part of the Global Observatory on Donation and Transplantation. Kidney transplantation rates vary substantially by country, based on wealth and stage of development reflected by the Human Development Index (Fig 1).

It is one of medicine’s greatest tragedies that human organ trafficking has been generated by the great disparities in access to transplantation and the ability of the rich to prey upon the poor and vulnerable. The health ministries of the world have responded to this problem through an agreement at the World Health Assembly in 1991, which was reaffirmed in 2010. The Declaration of Istanbul of 2008 enunciates the principles of ethical health policy and clinical practice. These 2 documents should be regarded as equally significant as the original Harvard ad hoc committee’s report on brain death. They were undoubtedly big steps, but implementation has required a journey of a thousand small steps.

Number of Transplants in Relation to Patients Using Renal Replacement Therapy

The number of patients developing end-stage kidney failure globally is unknowable, but reliable estimates are available with advanced public health data. In developing economies, the incidence of end-stage kidney failure is hidden by undiagnosed disease, but it is possible to measure the incidence of dialysis treatment. This approach demonstrates the disparities in treatment rates, which clearly show the relationship between national wealth and renal replacement therapy. The relationship between the proportion of patients treated by transplantation compared to dialysis is also closely related to national wealth (Fig 2), but there are other factors that influence this ratio. Norway, Costa Rica, and Namibia all treat >70% of their patients by transplantation, whereas Japan, Singapore, and Tunisia treat only 5% by transplantation. Even within the United States, it has been shown that the rates of transplantation vary greatly. For example, an analysis has shown that patients treated in dialysis units run by large for-profit chains have a lower likelihood of being placed on the deceased donor waiting list than those in small unaligned programs. Moreover, access to transplantation also varies considerably across the 58 donor service areas, with median waiting times ranging from 0.61 to 4.57 years.

In some countries (eg, Pakistan), transplantation is exclusively from living donors. The number of living donors might theoretically be sufficient to meet the needs of the community because of large family size; however, the impact of donation in such countries without

Figure 1. Kidney transplants per million population by Human Development Index, 2013. Reproduced from the Global Observatory on Organ Donation and Transplantation, a collaboration of the World Health Organization and the Organización Nacional de Trasplantes, with permission of the World Health Organization. Abbreviations: AFR, African; AMR, Americas; EMR, Eastern Mediterranean; EUR, European; HDI, Human Development Index; SEAR, South East Asian; WPR, Western Pacific.
long-term medical care for the donors has until recently been unknown. In developed countries, the tendency for donation to be from willing young and healthy individuals to minimize surgical risks has recently been questioned because of the lifetime risk for reduced kidney function.\textsuperscript{13,14}

**Patient and Transplant Survival**

Although short-term patient and transplant survival rates are considered acceptable, there is clearly a disparity between what the individual patient may find acceptable and what can be achieved in the longer term. Figure 3 demonstrates overall deceased donor transplant survival in Australia over the long term and shows steady improvement over 4 decades, with a substantial step change at the time of the widespread introduction of cyclosporine in 1983.\textsuperscript{15} Comparison of the age-specific mortality of dialysis and transplant populations with the apparently healthy population in Australia provides the clarity needed to understand the unmet clinical need. There is an approximately 10-fold difference in survival still to be overcome if we are to return transplant recipients to normal life expectancy (Fig 4).\textsuperscript{16} There remain significant differences between health care environments that may be related to underlying biological differences, such as race, or to mechanisms of health care delivery, such as withdrawal of medication funding 3 years after transplantation.\textsuperscript{17}

**Adverse Impacts of Immunosuppression**

That immunosuppression is associated with adverse events is unarguable. However, there is a real concern that the field is now frozen in time from a pharmacologic perspective because of 2 commercial realities. The first is that some drugs initially trialed for transplantation have been dropped from transplant-related clinical research in favor of their use in autoimmune disease treatment at low doses that are associated with favorable adverse-event profiles. The argument for using a drug in millions of people with rheumatoid arthritis or multiple sclerosis rather than in thousands of transplant recipients has proved hard to refute. An example is the use of JAK3 kinase inhibitors.\textsuperscript{18} The second commercial reality is the advent of generic pricing structures for standard therapy that has dropped the competing

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**Figure 2.** Proportion of kidney replacement therapy made up by kidney transplantation, by gross domestic product (GDP) per capita using international dollars. Copyright World Health Organization; reproduced with permission.

**Figure 3.** Primary graft survival of deceased donors by year of transplant through December 2007 Australia and New Zealand. Copyright ANZDATA Registry; reproduced with permission.
market price for innovators. Thus, it has been a struggle for an excellent drug like belatacept to be established to the level that the underlying characteristics of the drug would support. Reducing adverse-event profiles of immunosuppressive drugs is thus a major challenge in the current market-driven environment.

ADVANCES IN TRANSPLANTATION DURING THE PAST 50 YEARS

Those who cannot remember the past are condemned to repeat it.

George Santayana, The Life of Reason

Kidney transplantation has one of the best records of change in clinical outcomes in human disease. We can see how this was achieved using the “retroscope” to examine the interplay between seminal advances and small incremental gains. Are we waiting for the next big advance? Is it already here but failing to be implemented? Or do we need to take multiple small steps to achieve progress?

Surgical Technique

Alexis Carrell defined the surgical technique required to replace the magnesium tubes that had been used by Unger in experiments in which he connected the kidneys and blood vessels of dogs to the animals’ necks. The Carrell patch technique was transformative and was the critical surgical advance that facilitated transplantation surgery, though perhaps not as spectacularly as the media of the day suggested in celebration of Carrell’s Nobel Prize. This press coverage recalled the apocryphal feat of Saints Damian and Cosmas, who were said to have performed the miracle of transplanting a leg. However, it was 50 years between the description of Carrell’s technique and the report of the first technically successful clinical transplantation, demonstrating that there may be considerable delay between a seminal discovery or innovation and the impact of that invention. In contrast, it has been interesting to see the rapid switch from open to laparoscopic kidney donation surgery, which in just a few short years has advanced rapidly from the initial surgical descriptions to the standard of care.

Chemical Immunosuppression and Cyclosporine

David Hume performed the first series of allogeneic kidney transplantations in the early 1950s after many years of animal-based research and concluded that transplantation could be successful in the absence of an immune reaction between donor and recipient. The first transplantation to test that hypothesis properly was performed in Boston between identical twins in 1954 and was both a technical and clinical success. Despite the historic significance with which we have imbued the event, it was not really the big step in kidney transplantation. The surgical technique had been developed by Carrell and then refined by Hume. The unremarkable lack of immunologic loss was in its turn fully predicted by animal experiments. The real advance required to make transplantation widely available was to provide immune suppression without lethal adverse events. Immunosuppression was the big step, in particular 6-mercaptopurine and then azathioprine, which in the 1960s were shown to be effective in canine models of transplantation. They were soon applied to clinical transplantation with success and reported about 10 years after Hume’s series.

The magnitude of the effect of these advances is shown in Fig 3, which illustrates the long-term kidney survival of patients undergoing transplantation in Australia.
from the mid-1960s to the present. The dramatic improvement in results seen in the early 1980s is attributed—on the evidence of randomized controlled clinical trials—to the immediate and general use of cyclosporine throughout all clinical programs after 1983. This major advance originated in the laboratories of a then small Swiss company exploring the products of fungi from diverse environments, including Norway. The resulting drug was shown to be immunosuppressive in small animal models and then was tested in a pig model of cardiac transplantation in Cambridge, when it was found to extend survival from 6 days in control animals to more than 68 days. It is remarkable that a drug first shown to be effective in a large-animal model in 1978 should be translated into a significant change in national organ transplant survival rates within only 5 years. This truly was a big step. Marginal gains continued, as also demonstrated by Fig 3. It took another 10 years to learn how best to use the drug. Marginal gains have thus continued with the better understanding of chronic nephrotoxicity and how to avoid it.

Testing the Immunologic Barrier

Paul Terasaki developed the lymphocytotoxicity crossmatch test, which was widely applied to clinical transplantation following his seminal paper in 1969. This test was a major advance. It was developed over a period of several years in the early 1960s and then required a collaborative project to accumulate the samples and clinical data for 225 patients. In this study, transplants failed to function immediately in 24 of 30 with a positive crossmatch test result, but only 8 of 195 with a negative crossmatch result. The clear effect of that single study convinced all clinical programs that a negative crossmatch test result was required as protection against hyperacute rejection, but the many research endeavors over the intervening years have yielded the marginal but steady gains that have progressively improved our understanding of antibody-mediated rejection. Therefore, again there is evidence of a big step being followed by marginal gains.

However, the lymphocytotoxicity crossmatch test proved to be an imprecise tool because it was shown to both miss important immune reactivity and yield false-positive results, especially in the presence of autoantibodies. The theme of dissecting the immune barrier to transplantation developed further with the technical advance of a solid-phase assay for antibodies to HLA antigens using an enzyme-linked immunosorbent assay and then flow bead technology and was critical to the next stage of understanding antibody-mediated rejection. Changing the test system from imprecise complement-mediated cytotoxicity to measuring antibody binding to a specific molecule on the surface of a latex bead was undoubtedly a big step. Application of the new test system occurred progressively over the next 5 years and delivered advances in predicting outcomes and avoiding transplant loss. The small and incremental gains of this technologic innovation have continued because it has proved possible to change the way positive alloreactivity is predicted: from a physical crossmatch test to a virtual crossmatch. The change in outcomes may be due in part to reduced ischemia times and lower delayed transplant function rates, as well as less frequent rejection. There are further gains to be realized through better understanding of the precise biology of antibody reactivity, such as the complement-binding ability of antibodies, to avoid rejection and modify therapy.

The development of the technology has also allowed for both desensitization strategies relying on antibody removal and practical national programs for paired kidney exchange.

Viral Prophylaxis

Cytomegalovirus was one of the most feared infectious complications specific to the transplant recipient in the 1970s and early 1980s. Many patients who underwent successful transplantation with good kidney function died between 6 and 10 weeks after the procedure due to primary cytomegalovirus infection contracted from the donor, thus limiting overall success rates and restricting the urge to increase the “strength” of immunosuppressive protocols. The late 1980s saw the introduction of drugs (acyclovir and then ganciclovir) that changed the prospects for such patients and altered the outcomes of viral infections in immunosuppressed patients. Moving these nucleoside analogue drugs from treatment to prophylaxis and increasing their absorption with the introduction of the valine ester valacyclovir, together with use of polymerase chain reaction for diagnosis and monitoring of cytomegalovirus infection, transformed the field more than most have been prepared to admit, but the accumulated evidence of clinical trials is incontrovertible. On this occasion, the timeline from the big step, in the form of the discovery of the drug and widespread acceptance, to the immediate and general use of cyclosporine throughout all clinical programs after 1983 was perhaps slow enough to be classified as a progressive gain.

The force of these examples is to emphasize that a single seminal discovery, innovation, or technical advance is required to make a substantial impact on so-called hard outcomes. However, implementation of that discovery can be as short as a year or 2, as in the case of the crossmatch test, many years in the case of viral prophylaxis, and as long as 50 years for...
the initial surgical techniques. However, our ability to translate and implement discovery into general clinical practice quickly seems to be slipping because “risk” dominates the thinking of our regulatory and commercial institutions. Financial imperatives all too often trump human need.

**AREAS OF POTENTIAL PROGRESS IN CLINICAL TRANSPLANTATION**

Will the next big step in transplantation occur by speeding implementation of a discovery, as discussed in the previous section, or perhaps through a more dramatic advance? Despite the warning “prediction is dangerous, especially about the future”—attributed to many, including Niels Bohr and Samuel Goldwyn, Nostradamus, and K.K. Steincke, and perhaps believed by none—it is tempting to speculate about possible seminal discoveries to come.

**Genetic Biomarkers of Rejection**

Acute transplant rejection remains the critical event for which a simple noninvasive test would be transformative. The present gold-standard test, the kidney biopsy, is insufficient because it is based on the light microscopy technology of the 19th century and sampling is invasive. Improvements in the use of the biopsy include routine staining of the endothelium for the presence of the complement molecule C4d. There have been 3 new strategies: understanding the biological events of rejection at a genetic level, examining urine as a noninvasive source of cells and molecules from the transplanted kidney, and looking in the blood for reliable signals of intrarenal immune responses.

The biology of rejection, infection, and acute kidney injury are much better understood, but there is a gap between our understanding of biology and the commercialization of biomarker tests that can be broadly implemented in clinical practice. The current processes of bringing a health care test to market will ensure that a large investment of time and money is required in clinical trials and marketing. Does the US or European market have the appetite for this investment, or will it first happen in Asia under simpler regulatory processes? Are there enough transplantations performed globally to justify the investment? The answers to these questions will dictate the future utility of research into diagnosing the transplant immune responses.

**Transplant Tolerance**

There is a small number (perhaps no more than 20) of kidney transplant recipients who have long-term functioning transplants despite cessation of all immunosuppression. The data from these patients have directed attention to differences in the B-cell compartment, but the weakness in this research is that the control groups are all on immunosuppressive drugs. This, and not the tolerant state, may account for the observed differences.

Very early experiments pointed to the potential for using stem cell transplants to create allogeneic chimerism, in which the patient has both self and nonself immune systems. This has been achieved by clinical programs in Palo Alto, Boston, and Chicago/Louisville. Each of these programs has delivered a number of tolerant patients through design, but 3 issues remain: the requirement for some form of conditioning radiotherapy and chemotherapy, the demonstrated failure to prevent antibody-mediated rejection and transplant loss, and concerns over the long-term stability of the transplant tolerance in the face of immune-stimulatory events such as viral infection.

Understanding of the normal regulation of T-cell immunity has suggested new strategies to create a tolerant state in a kidney transplant. The clinical question being asked is whether infusion of naive or antigen-specific regulatory T cells (Tregs) can lead to tolerance of the transplant.

**Ischemia-Reperfusion Injury**

Another possibility for changing the field of transplantation entirely will be in prevention of injury from ischemia and reperfusion. The resultant fibrosis may be preventable or even reversible. Research into perfusion techniques and molecular targets for intervention has been identified, such as perfusion of donor organs with small interfering RNA cocktails or approaches to epithelial cell repair and regeneration. Few therapeutic approaches have been tested in clinical trials beyond simple perfusion solutions and optimized donor management. The prospect for such trials has increased recently with the market potential of both warm and cold organ perfusion devices. There will need to be a big step, which I predict will have to be in understanding the underlying biology, before clinicians will be able to increase the number of kidneys available for transplantation by transforming the numbers of organs that can be successfully recovered and transplanted.

**Xenotransplantation**

Many transplantation enthusiasts still believe that “xenotransplantation is the future of transplantation, and always will be.” This rather cynical statement is hard to counter because the barriers to xenotransplantation have resembled the opening of a series of Russian dolls: as soon as one problem has been resolved, it reveals the next one. The most promising candidate in xenotransplantation is islet transplantation from a genetically modified pig. The reasons for renewed optimism include...
successful use of genetic modification techniques for multiple gene deletions and additions in pig-to-baboon preclinical models; the technology of gene editing, which will allow rapid selection and modification of genes; and the effectiveness of porcine insulin in humans. The costs of development remain formidable because of the need for sterile production facilities and specific gene editing and deletion of porcine zoonoses, such as the porcine endogenous retroviruses.

The need for a better long-term therapy for type 1 diabetes mellitus remains a powerful justification for investment, which is probably sufficient to sustain this effort.

Regenerated Kidneys

Will it be possible to grow a replacement kidney when an individual’s native kidneys fail? The problem is that nephron development is completed before the fetus leaves the womb, and there is no stem cell lineage analogous to hematopoietic stem cells that can be used to recreate the kidney structure. The demonstration that human embryonic stem cells can be guided chemically to create both ureteric buds and metanephric mesenchyme, from which self-forming nephrons grow in vitro, is very exciting. To be able to drive differentiation from human embryonic stem cells sufficiently to create glomeruli is clearly a major advance in the right direction.

CONCLUSION

The reasonable man adapts himself to the world: the unreasonable one persists in trying to adapt the world to himself. Therefore all progress depends on the unreasonable man.

George Bernard Shaw, “Man and Superman”

What then of the question framing this Forum: will progress in transplantation be achieved in big steps or by marginal gains? The reader will likely have arrived at the same answer as the author. For those who have skipped ahead to read the conclusion, I give an answer akin to the one provided in Douglas Adams' The Hitchhiker’s Guide to the Galaxy. The answer to the ultimate question, “What is the meaning of life, the universe and everything?” was, as you may recall, “42.” The answer to the question posed in the title of this article is on one level yes and both, but is also a call for greater recognition of how much we have yet to learn.

ACKNOWLEDGEMENTS

Support: None.

Financial Disclosure: The author declares that he has no relevant financial interests.

Peer Review: Evaluated by 3 external peer reviewers, Feature Editor Winerals, Education Editor Gilbert, and Editor-in-Chief Levey.

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ACKNOWLEDGEMENTS

Support: None.

Financial Disclosure: The author declares that he has no relevant financial interests.

Peer Review: Evaluated by 3 external peer reviewers, Feature Editor Winerals, Education Editor Gilbert, and Editor-in-Chief Levey.

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