The Ripple Effect of Transplantation

Ripple effect:

"A spreading effect or series of consequences caused by a single action or event."

My dear friends and colleagues,

It has been an enormous privilege and honor to serve as your President for the past year. I stand at this podium as a consequence of the support and inspiration of my teachers and colleagues. These include my mentors Drs. Elmo Cerise, the late Ted Drapanas, James Fisher, William George, Louis Ignarro, and Dr. William P. Longmire. Dr. Thomas Starzl, our first President, taught me the art and craft of liver transplantation. The friendship and guidance of Nancy Ascher, Josh Miller, Milton Benjamin, Gail Durant, the ASTS Council, and all of our members have been essential. I wish also to recognize my transplant fellows, who have made me a better surgeon and scientist, and my wonderful transplant team at UCLA. Finally, to my wife, JoAnn and our daughters, Amber and Ashley – your unwavering support, understanding and love mean more than you can imagine.

In choosing a topic for this Presidential Address, I could not help but reflect upon the way that I entered the field of transplantation, as my route was certainly unconventional by current standards. Those standards were developed by Dr. Najarian during his presidency and appropriately require formalized fellowship training for a career in transplantation, reflecting maturation of the discipline into a full-fledged surgical specialty. But 17 years ago it was possible to simply hop the fence, and I did that -- I became a student of transplant surgery after six years of academic practice as a vascular and liver surgeon with a particular interest in the surgical treatment of portal hypertension and end-stage liver disease. My research at the time was focused upon mechanisms of host defense and ischemic injury, and while the clinical applications that we studied were related to infectious processes in the surgical patient rather than allograft rejection or acceptance, the relevance to transplantation is obvious. Coming to a

career in transplant surgery from a background in general and vascular surgery, critical care, and pharmacology, my personal journey perhaps mirrored the way that a series of nontransplant disciplines formed the foundation for the field of transplantation.

Today I intend to rotate the prism and reflect on the reverse process – the effect of transplantation and of transplant surgeons on the practice of surgery and allied disciplines, the refinement and expansion of existing disciplines because of the influence of transplantation, and the creation of new disciplines for which transplantation may take credit. I hope to show you that this ripple effect is quite extensive. I also wish to speak about the multi-disciplinary team approach, another product of transplantation. I will describe its importance to my year as ASTS President, to our Society, to our profession and the way in which we are viewed.

Basic Scientific Discovery

The field of clinical organ transplantation from its birth has been irrevocably intertwined with scientific discovery in the areas of immunology, pharmacology, histocompatibility matching and genetics.

The seminal observations which propelled transplantation from an experimental to a clinical discipline were the demonstration by Medawar in 1943 that allograft rejection was an immunologic event and ten years later in 1953 that tolerance could be induced in neonatal mice by injection of immunocompetent cells from adult animals. One year later, in 1954, the first successful transplant between twins was performed by Murray, Merrill and Harrison. Despite their success, it was soon recognized that genetic incompatibility would preclude allografting unless the body's natural defense to foreign antigens could be inhibited. Investigative study of rejection phenomena led to the development of an entirely new field, known today as transplantation biology, which has been responsible for enormous progress in our understanding of tolerance, allograft and xenograft rejection, use of immunosuppressive drugs, ischemia-reperfusion injury, T-cell activation, and molecular signaling. These fundamental advances have greatly improved patient outcomes after transplantation.

But they have also led to critical discoveries in other areas. Among them are included the identification of auto-antibodies in the pathogenesis of a number of diseases such as thyroditis, scleroderma, and rheumatoid arthritis; the treatment of hematologic malignancies with cytoablation and bone marrow transplantation; and the development of new anti-neoplastic agents. The application of principles gained from organ preservation research has spawned strategies used in the treatment of vascular thrombosis and myocardial infarction. The deciphering of genetic defects causing in-born metabolic errors successfully treated by solid organ transplantation has paved the way for gene therapy protocols attacking the fundamental molecular defects themselves. Furthermore, with a better understanding of the mechanisms of action and intracellular molecular effects of the calcineurin inhibitors cyclosporine and tacrolimus, a whole new set of indications for these drugs has been established.

Cytokine Research

Our understanding of molecular cytokines expanded dramatically after early observations in the field of transplantation. The initial era of cytokine research, extending from the 1950s through 1970s, involved the description of multiple protein factors that were thought to be immune mediators and discovery of fever-producing pyrogens and macrophage associated factors. Transplant immunologists led the golden era of cytokine research in the 1980s with a tremendous avalanche of information about the individual cytokines as well as discovery of new ones.

During the past decade, transplant research has paved the way for investigations which have categorized cytokines in the induction and maintenance of inflammatory responses, antiproliferative stimuli, and ischemia - reperfusion injury. This work has stimulated others to explore the role of immune mediators in a wide variety of pathological conditions, including hematologic disorders, immune deficiency syndromes, sepsis, catabolism, wound healing, pancreatitis, ARDS, angiogenesis and burns.

Kidney Transplantation

Kidney transplantation is duly recognized as the pioneer discipline in solid organ transplantation -- the stimulus for the development of transplantation immunobiology and a model for discovery and evaluation of many immunosuppressive drugs and strategies. The procedure also has influenced development of vascular reconstructive techniques.

At the outset, kidney transplantation provided a strong impetus to further improve and refine dialysis techniques for support of patients with acute and chronic renal failure. The new therapy gave rise to the field of nephrology, a new medical specialty. Early on the nephrologist viewed the transplant surgeon with ambivalence. But in time a synergistic relationship was forged, and it is that relationship which has served as the model for multidisciplinary team care of the transplant patient, with profound effects on many other disciplines.

HLA Antigens

With the discovery of the first HLA antigen by Dausset and the demonstration of HLA antibodies in pregnant women by Van Rood and Payne, histocompatibility matching of kidney donors and recipients using HLA identification became a new tool that would have far reaching implications in other fields of medicine, forensics, and anthropology.

In medicine, the further discovery of HLA associations with numerous disease states has been a major advance in our understanding of the genetics of these diseases. Although these associations have failed to provide hoped-for breakthroughs in etiology and treatment, there are now over 500 diseases associated with HLA, which have been confirmed in tens of thousands of patients.

In forensics, HLA haplotypes as markers of biological individuality have changed paternity testing over the past 25 years and replaced blood testing procedures, which

are far less accurate. Newer techniques utilize monoclonal antibodies to the HLA molecule, as well as DNA testing.

In anthropology, HLA has been used for genetic analysis of populations and their relationships and helps to verify Nei's hypothesis of the origin of man in Africa. Additionally, the HLA system can tell us about man's global wanderings -- indeed quite a far-reaching influence of transplantation research.

Bioethical Considerations

As the kidney is a paired organ, the concept of live donation, of which the first is shown here, became a reality and provided the framework for many of the medical and ethical guidelines which have been established for other solid organs and for bone marrow transplantation. The envelope has been pushed further with current use of adult-to-adult living donor liver transplantation, about which the ASTS has taken a leadership position and developed a white paper, and will be pushed further still with use of xenografts in the future.

And then there's Dolly, the first cloned mammal. Ethical questions regarding cloning have particular immediacy because of transplantation, which provides a potentially immediate use for cloned organs. What are the long-term consequences to humans who receive cloned animal organs? Are we headed toward human cloning? Should industry be permitted to patent genes and DNA, the basis of life? Transplant surgery has helped to generate these tough questions, and we have an obligation to continue to provide leadership in the search for answers.

Pancreas Transplantation

The discovery of insulin by Banting and Best in 1922 radically changed diabetes from a uniformly fatal disease to one that could be managed. Pancreas transplantation evolved as a means to achieve physiologic glucose control which would substantially prevent the long-term complications of diabetes.

Despite the benefit of whole organ pancreas transplantation, there is significant morbidity with the procedure, and the search for alternatives has stimulated development of a new field -- cellular transplantation, which has demonstrated putative advantages over whole organ replacement. Evolving technology for cellular transplantation has been applied to a variety of unrelated diseases including acute hepatic failure, atherosclerosis, Parkinson's disease, and spinal cord injury. Moreover, pancreas islet cell transplantation has paved the way for the development of new cellular encapsulation technologies.

Cardiac Transplantation

The first human heart transplant was performed by Barnard in Capetown on December 3, 1967. One month later, the second recipient became a long-term survivor, although repeated success with the procedure was still 15 years in the future. In recent years a crucial shortage of heart donors has produced a need to develop alternative therapies for end-stage cardiac disease, in particular ventricular assist devices. These devices now play an important role in the treatment of patients with a variety of severe cardiac conditions, including myocardial infarction, myocarditis, and advanced heart failure.

With these devices, which would not likely have been available without heart transplantation, approximately 90% of patients with Class IV CHF leave the hospital and can be returned to an improved status often without the need for a heart transplant -- hence the concept of a "bridge to myocardial recovery".

Endocardial biopsy and intra-coronary ultrasound imaging are two additional techniques which were developed for evaluation of heart grafts and have found major applications in treatment of non-transplant cardiac disorders. Intra-coronary ultrasound imaging, developed for evaluation of heart grafts, provides clear images of the layers of the coronary wall and permits quantitation of internal thickening which has been shown to be highly predictive of subsequent luminal stenosis and death from coronary artery

disease. This technique has direct applicability to non-transplant coronary atherosclerosis.

Transplant cardiology is a discipline fueled by cardiac transplantation. Its practitioners have provided novel insights into the pathogenesis and treatment of diverse non-transplant cardiac diseases and have collaborated with heart transplant surgeons on the development of the artificial heart which will soon be in clinical trials.

Liver Transplantation

Since Tom Starzl performed the first liver transplant in 1963, liver replacement has had a widespread impact on the surgical disciplines from which it has grown.

Liver Growth and Regeneration

Experimental studies in liver transplantation were essential to our understanding of liver growth and regeneration. Discovery of the first hepatotrophic factors derived from the splanchnic venous circulation demonstrated the absolute necessity for portal perfusion of the liver.

More recent investigations have identified gene expression of other hepatotrophic factors produced within hepatocytes as well as the effects of calcineurin blockers on liver regeneration. The field of segmental and lobar transplantation has stimulated investigation of the mechanisms involved in liver remodeling. This is research driven by liver transplantation which has already shown potential applicability to treatment of patients with loss of liver substance from a wide variety of causes, including cirrhosis, trauma, and surgical resection.

Operative Techniques and Liver Resection

The principles of total hepatectomy and implantation of the hepatic allograft have taught the general surgeon that total exposure of the upper abdomen may be achieved via a transverse upper abdominal incision with substernal extension. Through this incision, the most complex liver resection can be accomplished without utilizing the highly morbid right thoracotomy, which in the past was considered essential for major hepatic resections.

During the past 25 years, developments in liver resection and liver transplantation have been intertwined. The transplant surgeon's intimate familiarity with segmental liver anatomy was further strengthened by the use of lobar and segmental transplantation, which in turn has facilitated liver resection for benign and malignant processes. For example, surgical treatment of caudate lobe lesions, once considered extremely complex and hazardous, is now performed with ease, the consequence of lessons learned from exposure through the gastrohepatic ligament, hepatectomy with caval preservation, and use of segment II, III grafts in pediatric transplantation.

Extensive hepatic resections, in the past fraught with the potential to precipitate postoperative liver failure, are now performed successfully after a volumetric assessment shows sufficient residual liver mass. Derived from its use in partial liver transplantation, volumetric assessment has given us a parameter by which to judge the extent of safe hepatic resection in patients with normal livers and as well as those with cirrhosis. Moreover, new resection techniques and novel technical refinements borrowed from liver transplantation have improved the surgical approach to challenging liver tumors. These include use of portal clamping with or without caval occlusion to decrease blood loss and ex-situ or extra-corporeal bench procedures for resection of tumors otherwise deemed untreatable by conventional means.

Liver Trauma

Experience in liver transplantation has greatly facilitated the surgical approach to major liver trauma. Retrohepatic vena caval and hepatic venous injuries are devastating in part because of the difficulty in gaining rapid access to the privileged portion of the inferior vena cava between the renal and hepatic veins. Both donor and recipient operations illustrate the proper approach with rapid and complete mobilization of the right lobe and dissection posterior to the retrohepatic vena cava, allowing control of the supra and infra hepatic vena caval segments. Although these maneuvers are conceptually simple, many surgeons are unfamiliar with them and may be reluctant to perform them or only do so partially. In certain situations, veno-venous bypass, born from liver transplantation, may be employed to provide adequate preload for patients who cannot tolerate clamping.

Anesthetic Management

Principles of anesthetic management required for rapid volume resuscitation in the coagulopathic liver failure patient with portal hypertension have direct application to patients with major hepatic, multi-visceral, and vascular trauma and have contributed significantly to the improved outcomes now seen in these difficult circumstances. Finally, for major liver injuries with massive parenchymal destruction or uncontrollable porta hepatis injuries, total hepatectomy with

orthotopic liver transplantation can be lifesaving. Clearly, a collaborative relationship with the liver transplant team provides the trauma service with a valuable resource.

Hepatology

As with kidney and heart transplantation, liver transplantation has contributed to the growth of a major medical subspecialty . Hepatology has now undergone a metamorphosis to encompass not only the diagnosis and pathogenesis of liver disease, but also molecular characterization and epidemiologic assessment of liver disorders and analysis of long-term outcomes following liver replacement.

Surgical Education

Experience on a liver transplant service is a crucial component of surgical education. The multi-organ procurement procedure exposes the student to key relationships of the foregut, visceral vasculature, kidneys, aorta and vena cava. Lessons learned have direct application not only to liver surgery, but also to such varied operations as esophageal procedures, aortic aneurysm resection, and pancreatectomy. The value of this single operation is so substantial that it should be an absolute requirement for completion of the general surgery residency.

With the current application of minimally invasive surgical techniques to many general surgical procedures, most common biliary operations are performed laparoscopically, and training of open biliary surgery is in jeopardy. Rotation on a hepatobiliary service which performs liver resection, complex biliary reconstruction, and liver transplantation provides a balance between open biliary surgery and the laparoscopic methods. Finally, education in surgical critical care through management of liver failure patients is unmatched. These patients demonstrate the widest spectrum of multi-system organ dysfunction, and their care demands an extensive theoretical and practical knowledge of all target organ systems which are affected by hepatic insufficiency.

Multidisciplinary Team

Perhaps transplantation's most profound and far-reaching contribution is the emphasis on a multi-disciplinary team approach both to patient care and to research. The team model, a virtual prerequisite to creation of a successful transplant program, has been applied in some form by virtually every clinical and investigative specialty. The ultimate goal of the team approach, simply stated, is "the best" in patient care, scientific discovery, and education. It is a mandatory goal for our profession and one that has been emphasized repeatedly in prior presidential addresses by Starzl, Belzer, Najarian, Corry, MacDonald, and others.

And that leads me to the final portion of my address. I wish to provide a brief review of my personal experiences as President over the past year and to show you how teamwork has been essential to our accomplishments.

ASTS 1999-2000

Upon assuming the Presidency, I set three goals for the society and myself. Let me give you a brief progress report and a few editorial comments on each of these in turn.

Recruitment and Enfranchisement of Young Members

The first goal was to fully integrate the younger members of our profession and society into our activities, direction, and vision. To accomplish this, we initiated a focused campaign to recruit younger members into the society, and we created a new standing committee, the Vanguard Committee, comprised of members who had been in the ASTS for less than three years.

Under the leadership of Ken Drazan, with mentorship by Jim Schulak and Dick Thistlethwaite, this Committee has provided a much-needed dose of Geritol (some would say Viagra) for the ASTS. Its members have articulated a direction for the society; doubled the number of young surgical recruits and basic scientists; planned the first ASTS Winter Symposium on living donor transplantation (slated for February 2001); and begun an analysis of the academic and clinical activities of our junior members which will guide future educational and training activities for the ASTS. By all measures the Vanguard Committee has been a winner.

Relationship with AST

The second goal was to re-establish a relationship with the AST, with the aim of moving towards a new joint society in the future. I have been fortunate this year to have had the opportunity to work with Jack Lake, the AST President, on this and other issues. Together we made substantial progress on a number of cooperative initiatives and important ventures. We have agreed on a joint scientific meeting through 2005, of which the current one is the first. We have established "The American Journal of Transplantation", a new official journal of our two societies. We have endeavored to foster a sense of inclusivity and camaraderie among our respective members.

But these measures are not enough. If we are to realize our full potential, we must reach beyond the artificial boundaries that differentiate us as surgeons, medical specialists, and research scientists. We must shed any mantle of parochialism, embrace our common goals, and speak with a unified voice on the many contentious issues of public policy that we face today. Separate and divergent, we will struggle and falter and almost certainly we will fail.

Transplant Politics

The third goal was to continue my prior efforts as President-elect to broker a consensus between DHHS and the transplant community on the thorny issue of organ allocation. For the past 20 months, I have been actively involved in deliberations with various Congressional and DHHS Committees on behalf of the ASTS. The aim of my efforts was to support a balanced organ allocation policy which kept medical decision making in the hands of transplant doctors. The results of these discussions could best be characterized as bipolar – at times encouraging and hopeful and at other times disappointing and frustrating.

Despite our eleventh hour attempt for a compromise with DHHS on the issue of Secretarial authority and the composition and functions of the Independent Review Board as proposed by the IOM, we were unable to reach a final written agreement – hence the frustration. Just the same, I am convinced that our discussions and negotiations demonstrated the absolute need for ASTS involvement in transplant policy formulation, and furthermore that our efforts helped to ensure DHHS support for a bill to reauthorize NOTA which was drafted by Senators Frist and

Kennedy. As you know, this role of the ASTS -- immersion in the governmental politics of transplantation -- has always been a part of our history.

The ASTS was born in response to the US Department of Health, Education and Welfare, which sought input from the transplant surgeons regarding Medicare reimbursement for end-stage kidney disease in 1974. In 1978, ASTS members were involved in the establishment of a national computerized registry of transplant recipients called UNOS. In 1984, NOTA was enacted to create a national system for donor organ distribution and allocation. ASTS provided strong commentary on this legislation, and many important contributions were made by past Presidents Belzer, Ferguson, Kahan, Monaco, Starzl and Williams. The 1990s were no less fractious politically.

Organ Allocation

By 1995, transplant recipients on the waiting list far outnumbered the available donors; this, coupled with the proliferation of transplant centers, ignited the allocation war, which has continued to rage, pitting colleague against colleague, center against center, and, unfortunately even patient against physician, so that the trust, the mutual respect, the teamwork which are the cornerstones of our profession, have been injured severely. Furthermore, the contentious public displays of divisiveness within our ranks have very likely decreased organ donation, which is dependent on a spirit of trust, sharing and altruism. Talk about counterproductive!

For me this was drawn into such stark relief just two months ago, when Mrs. Julia Fernandez lost her son on the liver waiting list. Mrs. Fernandez is a petite, endearing woman with unwavering faith in her doctors. How severely that faith must have been challenged for her to ask me, "Is it true that my son did not get a liver in time because doctors are fighting over donors?"

Let Mrs. Fernandez's painful query be our wakeup call. The fighting and bickering have got to stop, because the chaos created by factional support of competitive pieces of allocation law, coupled with states' rights initiatives to lock organs within state lines, are confusing to patients, destructive of collegiality among physicians, and demeaning to our profession. Let's cool the

rhetoric, amalgamate the best of evidence-based options on organ allocation, apply these to set a uniform policy, and make that policy work. We are on the right track with our support of the Frist-Kennedy bill to reauthorize NOTA. This legislation may not be perfect, and it may have to be modified. The same is true of current organ allocation policies, which may need revision as new outcome data become available. All of that we will address in due time. For the present, let's focus our attention where it belongs – to heal the rifts which divide us and to rekindle our team spirit, which we must do if we are to increase organ donation, advance scientific inquiry, and provide the finest in patient care.

How else to sustain the tradition of unique accomplishment derived from transplantation about which I have spoken today? How else to push forward with work which will have profound and far-reaching influence, not on transplantation alone, but on all of medicine? Is that not what we strive to contribute? By the quality of that contribution -- that's how we will be remembered. That's how we will be measured. And that's how we should be measured.

Respectfully submitted,

Ronald W. Busuttil, M.D., Ph.D.

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