Adding a little transplant surgery to the Central: The nation's first hand transplant

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It has been a privilege to serve as the 73rd President of the Central Surgical Association (CSA) this past year, and this unquestionably represents the highest honor of my academic surgical career. Before I start my address, I would like to thank those who mentored and guided me as a student, resident, fellow, and staff surgeon and to acknowledge my family who have always supported me and provided me with a wonderful and meaningful life away from the hospital.

Throughout my medical school, residency, and fellowship training, I was very fortunate to be at the right place at the right time, attending both SUNY Downstate and the University of Minnesota during their "heydays" in academic surgery. In 1979, one year after I started medical school at SUNY Downstate, Dr Bernard Jaffe came from Washington University, St. Louis, to be Chair of the Department of Surgery. Within one year's time, he had recruited 2 young surgeons just out of training to their first faculty positions, Drs Dana Andersen and Michael Zinner. I was fortunate to work in the laboratory with both of these individuals as a third- and fourth-year student and together, Drs Andersen, Zinner, and Jaffe introduced me to the fascinating world of academic surgery and surgical research.

My interest in transplantation was fostered by Dr Khalid Butt, a pioneer in renal transplantation, with whom I scrubbed on the 1,000th kidney transplant performed at Downstate, only the third transplant program in the nation to reach this milestone. Dr Butt was the protégé of Dr Samuel Kountz, the country's first African American transplant surgeon and second African American surgery department chair.

With a strong interest in pursuing an academic surgical career and transplantation, I was fortunate enough to match at the University of Minnesota, my first choice. Drs Henry Buchwald and William Gamble were instrumental in my development as a general surgeon, and I received strong clinical and research mentorship in transplant surgery from Drs John Najarian, Richard Simmons, and David Sutherland. I also would be remiss if I did not acknowledge my most recent mentors and advisers at Wayne State University, namely the 2 department chairs I have served under. Drs David Fromm and Donald Weaver have given me tremendous support and guidance over the last 15 years.

Moving to family, I would like to thank my 3 children: Marisa, who teaches children with special needs; Shoshana, a nurse; and Marc for all the joy they have given me. Finally, I could not have reached this stage without my wife Andrea's support, love, and sense of humor over the past 33 years of our marriage.

The CSA is very much a broad-based, general surgical organization, with the subspecialty of transplant surgery on the periphery of our Annual Meetings. Indeed, since 2011, at most 1 of the 36 or 40 main program presentations and 1 of the 6 or 9 Quick Shot presentations has dealt with clinical transplantation. As far as prior leadership of the Association is concerned, only 1 transplant surgeon has served as recorder, none as secretary, only me as treasurer, and 2 others as president, Drs Jeremiah Turcotte and Folkert Belzer. Interestingly,

Presented at the 73rd Annual Meeting of the Central Surgical Association, March 10–12, 2016, Montreal, Canada.

Accepted for publication February 9, 2016.

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Surgery 2016;160:823-7.

0039-6060/$ - see front matter

Published by Elsevier Inc.

http://dx.doi.org/10.1016/j.surg.2016.02.037

neither spoke about transplantation as part of their Presidential Address. I, too, have diverted from transplantation for the last 5 years, presenting basic science work on pancreatic cancer performed in collaboration with Dr Ramesh Batchu, a research scientist in the Department of Surgery whose lab is located at the Detroit VA. However, prior to this, during my years of clinical activity and maximal involvement in the program committee, my presentations were focused on clinical renal transplantation and dealt with global issues I felt would be of interest and relevance to the general surgeon: avoiding steroid immunosuppression, racial disparities, primary versus retransplantation, and cancer incidence.

In view of all this, I am going to take the liberty of devoting the remainder of my time to a transplant subject near and dear to my heart, namely, sharing with you the story behind—and my personal involvement in—the performance of the first hand transplant in the nation.[1] This bench-to-bedside success opened up the entire field of vascularized composite allografting, and I trust that this academic general surgical audience will find these events as exciting and fascinating as I do.

Unlike visceral solid-organ transplants, vascularized composite allografts (VCAs) are modules composed of various tissues of predominantly ectodermal and mesodermal derivation. Although VCAs have tremendous potential clinical application for functional and structural reconstruction of major congenital and acquired peripheral tissue defects, these transplants remained the last frontier in clinical organ transplantation because of concerns regarding their risk/benefit ratio. In particular, the lack of specific, safe, and effective immunosuppressive therapy to prevent rejection without producing unacceptable systemic- and drug-specific side effects was most problematic.

The first hand transplant was performed in Ecuador in 1964 using the only immunosuppressants available at the time, azathioprine and prednisone, and was lost to rejection in 2 weeks. Following the introduction of cyclosporine (CsA), primate studies of partial hand transplantation in the early 1990s still noted an unacceptable incidence of acute rejection despite maintenance of toxic systemic drug levels.[2] One possible approach to both effectively suppress rejection and diminish drug side effects is to administer appropriately chosen immunosuppressive agents directly into the allograft, termed local immunosuppression.[3,4]

I focused on this area of research during my 3 years in the laboratory while a general surgery resident at Minnesota (1986–1989). We developed a novel canine renal allograft model to study the pharmacology of intra-arterial (i.a.) infusion of immunosuppressive agents directly into the transplanted kidney via a programmable, implantable pump/catheter system with an access port for sampling the venous effluent.[5]

Autotransplant studies with i.a. 6-mercaptopurine (6-MP) infusion produced a 4-fold increase in local drug concentration and 80% decrease in systemic drug delivery as a result of first-pass elimination to create an overall renal-to-systemic concentration gradient of 30 fold.[6] Allograft studies with i.a. 6-MP demonstrated that 10-fold lower doses produced an antirejection effect equivalent or superior to that of intravenous therapy with reduced systemic drug exposure and toxicity.[7] These studies were the first to demonstrate the pharmacokinetic and pharmacodynamic advantages of local immunosuppressive therapy in a large-animal model.

In September 1991, just as I was starting my busy clinical transplant fellowship, the Rehabilitation Research and Development Service of the Department of Veterans Affairs held a 2-day workshop on VCAs, titled "Can limbs be transplanted in humans in five years?," to provide future directions, options, and recommendations regarding limb transplantation research. The consensus of the workshop was that the side effects associated with immunosuppression of VCAs would have to be minimal, while the effectiveness in preventing graft rejection and allowing biomechanical and physiologic functional return maximal, prior to clinical consideration.

The Chief of Plastic Surgery, Dr Bruce Cunningham, who attended the workshop, sent a letter to Dr Najarian suggesting that we apply for VA funds to adapt my model of locoregional infusion to limb transplantation, and Dr Najarian readily agreed to provide departmental funds for pilot studies in early 1992. Unfortunately, however, we never got these studies off the ground, and I soon left Minnesota for my first staff position at Albany Medical College in January 1993.

For the majority of the 1990s, VCAs remained one of the last frontiers in clinical organ transplantation despite refinements of microsurgical technique and replantation surgery; introduction of more potent immunosuppressive agents, such as tacrolimus (TAC) and mycophenolate mofetil (MMF); development of better techniques of organ preservation; expansion of extrarenal visceral organ transplantation; and improved understanding of the cellular mechanisms of allograft rejection.