The history of renal transplantation in Canada: A urologic perspective

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Abstract

While the urologist's involvement in kidney transplantation varies from center to center and country to country, urologists remain integral to many programs across Canada. From the early days of kidney transplant to contemporary times, the leadership, vision, and skillset of Canadian urologists have helped progress the field. In this review of Canadian urologists' role in kidney transplantation, the achievements of this professional group are highlighted and celebrated. Original contributors to the field, as well as notable achievements are highlighted, with a focus on the impact of Canadian urologists.

The early days of kidney transplantation

The role of the urologist in kidney transplantation parallels the history of the procedure itself. Dr. Hartwell Harrison was the urologist present at what is widely considered the first successful human kidney transplant between identical twins in 1954. In actual fact, it was a Canadian surgeon (Dr. Gordon Murray) who first performed a successful deceased donor transplant in 1952.[1] This recipient survived over 35 years after her transplant. Unfortunately, what Dr. Murray possessed in surgical genius was countered by a lack of planning for long-term followup, monitoring, and documentation of his surgical successes. This has led to questions about whether the transplant was successful or whether the patient's underlying disease improved, especially in the nascent years of immunosuppression.[1] Nonetheless, the technique of transplant performed by Dr. Murray in 1952 represents a technique nearly identical to that employed today.[2] Since this early period, urologists have played an important role in the development, dispersion, and advancement of transplant surgery in Canada.

The launch of Canada into the new era of kidney transplantation occurred in 1958 at McGill University, where a transplant team comprised of urologist Dr. Ken MacKinnon, vascular surgeon Dr. Joe Luke, and the team led by Dr. John Dossetor successfully transplanted the first living donor pair of identical twins in Canada.[3] This recipient survived another three decades. The first repeat transplant was performed in Saskatoon by a pioneering team in 1964 led by nephrologist Dr. Marc Baltzan, along with urologists Drs. Casamir Wolan and Manuel Ty. The urology team at The Hospital for Sick Children (Sick Kids, Toronto), led by Dr. Bernard Churchill and nephrologist Dr. Gerald Arbus, pioneered pediatric renal transplantation in the late 1960s and, by 1988, published factors influencing graft survival in their first 300 allografts.[4] Other triumphs of kidney transplant have come from urologists across the country. In 1972, Dr. Rex Boake from the University of Alberta performed a deceased donor transplant into a recipient who continues to enjoy a functioning allograft 48 years later, making

Fig. 1. (A) Dr. Rex Boake is photographed with former patient Freda Ainlay. Ainlay has had a functioning kidney graft for 48 years. ***(B)*** Dr. Boake's graduation portrait. Reprinted with permission by the University of Alberta.

this allograft one of the longest surviving transplants ever reported (Fig. 1).[5]

Urologists have helped launch successful kidney transplant programs in centers across the country. Many programs have recently celebrated their 50th anniversary of kidney transplant, including several with urologists as part of the foundation of these programs. These include the University of British Columbia (1968), University of Alberta (Dr. William Lakey, 1967) (Fig. 2), University of Saskatchewan (Drs. Casamir Wolan and Manuel Ty, 1964), St. Michael's Hospital in Toronto (Dr. Vince Colapinto, 1969), Queen's University (Dr. Andrew Bruce, 1968), McMaster University (Drs. Peter Knight and Art Shimazu, 1974), Western University (Drs. John Sharpe, Lloyd McAninchm and Nick Gergley, 1972), University of Ottawa (Drs. Alan Irvine and Bernd Koch, 1967), Dalhousie University (Drs. Allan MacDonald and Stan Lannon, 1969), Winnipeg Health Sciences Centre (Dr. Allan Downs, 1969), and L'Hôtel-Dieu de Québec (Drs. Roméo Charrois and Gilles Laroche, 1972). Table 1 summarizes the emergence of the kidney transplant programs around most of the major Canadian centers. The early foothold in kidney transplantation by several urology programs set the stage for transplant innovation by the urological community.

Fig. 2. Dr. William Lakey performs the first kidney transplant in Alberta at the University of Alberta, Edmonton, AB, in 1967. Reprinted with permission from Alberta Health Services. Original image supplied by AHS.

Advances in kidney donation

Despite success in living and neurologic death kidney donation, the imbalance between the number of kidney donors and recipients force thousands across Canada to remain on the waitlist for a kidney. Measures to increase the number of possible organ donors have included the re-emergence of donation after circulatory death (DCD) kidney donation, as well as innovations in living donor techniques.

After physicians at St. Michael's Hospital (Toronto) spearheaded donor withdrawal protocols for DCD donation, Dr. John Mahoney and the transplant group from the University

Table 1. List of Canadian kidney transplant programs and their first kidney transplant

First kidney transplant by center			
Year	**Transplant center**	**Type**	**Lead physicians**
1952	Toronto General Hospital, Toronto, ON	First successful deceased donor	Dr. Gordon Murray
1958	Royal Victoria Hospital, Montreal, QC	Living donor identical twins	Drs. Ken McKinnon, Joe Luke, and John Dossetor
1963	Royal University Hospital Saskatoon, SK	Repeat kidney transplant from deceased donor	Drs. Marc Baltzan, Casamir Wolan, Manuel Ty
1967	University of Alberta Hospital, Edmonton, AB	Deceased donor	Dr. William Lakey
1967	Ottawa Civic Hospital, Ottawa ON	Living related transplant	Drs. Alan Irvine and Bernd Koch
1968	Kingston General Hospital, Kingston, ON	Deceased donor	Dr. Andrew Bruce
1968	Vancouver General Hospital, Vancouver, BC	Deceased donor	Not available
1969	St. Michael's Hospital, Toronto, ON	Deceased donor	Dr. Vince Colapinto
1969	Hôpital Notre-Dame, Montreal, QC	Deceased donor	Dr. Pierre Daloze
1969	Victoria General Hospital, Halifax, NS	Deceased donor	Drs. Allan MacDonald and Stan Lannon
1969	Hôpital Maisonneuve, Montreal, QC	Deceased donor	Drs. Paul Dessureault, Michel Auger, Paul-Eugène Bertrand, Rolland Lévy, Jacques Brière
1969	Health Sciences Centre, Winnipeg, MB	Deceased donor	Dr. Allan Downs
1972	University Hospital, London, ON	Deceased donor	Drs. Cal Stiller, John Sharpe, Lloyd McAninch
1972	L'Hôtel-Dieu de Québec, Quebec City, QC	Living related transplant	Drs. Roméo Charrois and Gilles Laroche
1974	McMaster University, Hamilton, ON	Living donor	Drs. Peter Knight, Art Shimazu

The individuals and hospitals involved with the first transplants throughout Canada are incompletely represented in this table. However, the table provides a general outline of the date, individuals, and procedures performed during the early era of transplantation.

of Ottawa led the way with the first deceased donor transplant from a DCD donor in 2006. St. Michael's Hospital and University Hospital (Western University) transplant programs followed shortly with their first DCD donor transplants in the same year. Western University then performed the first pediatric DCD donor kidney transplant in 2008, and the first Canadian DCD combined kidney-pancreas transplantation in 2008.[6,7]

Following the first laparoscopic donor nephrectomy reported in 1995 by Dr. Lloyd Ratner and Dr. Louis Kavoussi, organ donors were finally offered a minimally invasive alternative to the painful flank or subcostal incision for live kidney donation.[8] Shortly after the first Canadian case was performed in Montreal, the St. Michael's team performed the first case in Ontario. Dr. Ken Pace and the St. Michael's team published a prospective case series outlining the advantages of laparoscopic donor nephrectomy, thereby establishing minimally invasive techniques as the standard of care for living donation in the early 2000s.[9-11] By 2009, Dr. Anil Kapoor published an illustrative guide to right-sided laparoscopic donor nephrectomy, helping advance the field toward access to minimally invasive donation regardless of kidney laterality.[7] In 2013, Drs. Alp Sener and Patrick Luke at Western University performed the first robotic single-site (R-LESS) donor nephrectomy in Canada. The same team would go on to publish a series of R-LESS donation compared to laparoscopic donation, demonstrating improved cosmesis and patient satisfaction.[12] Laparoscopic living kidney donation is now offered at all Canadian transplant centers with urologists consistently advancing the field.

The criteria for accepting living donors has been further developed through the work of Canadian urologists. During his time in Winnipeg, Dr. Tom McGregor published outcomes from a series of living donor kidneys where ex-vivo renal surgery was employed to manage issues that historically would have caused potential donors to be ineligible to donate.[13] In this series, 11% of consecutive kidney donors at a single institution were managed with "back table" ex-vivo surgery, including ureteroscopy, partial nephrectomy for angiomyolipoma, open nephrolithotomy, and calyceal diverticulum ablation (Fig. 3). While at Maryland, Dr. Alp Sener published a series of patients who underwent ex-vivo partial nephrectomy for renal masses (3/5 with renal cell carcinoma) prior to living donor renal transplantation.[14] Dr. Neal Rowe and the urology group in Ottawa followed this up by performing a systematic review of transplanted kidneys from donors with small renal masses and confirmed the safety of this practice.[15] Given that these procedures are uniquely within the armamentarium of most, if not all urologists, our participation in kidney transplantation has had a significant impact on increasing the donor pool.

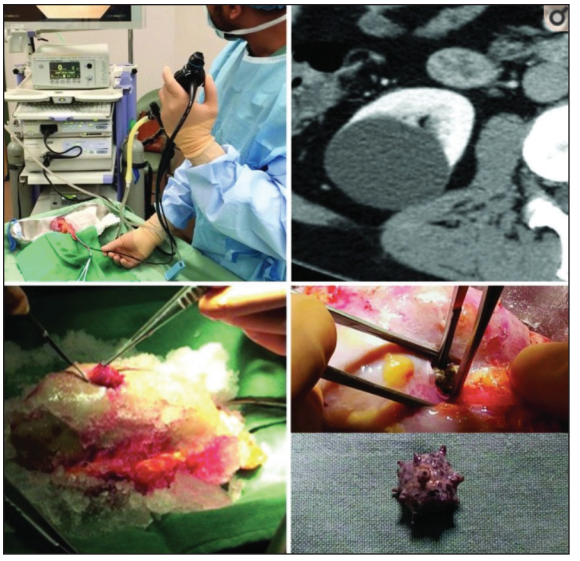

Fig. 3. Ex-vivo urological surgery on kidney grafts. McGregor TB, Rampersad C, Patel P. Expanding living kidney donor criteria with ex-vivo surgery for renal anomalies. *Can Urol Assoc J* 2016;10:301-5.

Live donor paired exchange

In 2003, Dr. Bill Gourlay and the transplant group from St. Paul's Hospital in Vancouver published a seminal paper documenting various psychosocial profiles of potential anonymous living kidney donors and created a framework for developing ethical and safe policies around accepting anonymous donors.[16] This Canadian led publication set the groundwork for living donor paired exchanges (LDPE) to take place across North America. Further work by Dr. Tom McGregor from Queen's University assessed the hardships in transporting organs across a country as large as Canada.[17]

The very first paired exchange of living donor kidneys in Canada took place in 2004 between St. Michael's Hospital in Toronto and University Hospital Network (Toronto).[18] By 2009, Canada performed the first multi-donor long-distance kidney paired exchange involving a "swap" between Toronto, Edmonton, and Vancouver.[19] This achievement speaks to the cohesiveness and tenacity of the Canadian transplant community, overcoming the great distance between our centers to come together to help save lives. Dr. Jeff Veale, a Canadian urologist at UCLA, has orchestrated many of the largest paired exchanges in the world, including a 30-pair chain in 2012.[20] One of the greatest successes in organized transplantation medicine worldwide is the Canadian Blood Service driven LDPE and Highly Sensitized Patient Program, which provides matching of organs to highly sensitized patients across Canada. Together, these programs have led to over 1000 transplants that otherwise would never have occurred.

Immunosuppression

Prior to modern-day immunotherapy, donor-specific blood transfusions were used to accompany the kidney transplant procedure. Dr. Calvin Stiller, a nephrologist from Western University, along with urologists Drs. Eric Shepherd, Jack Sharpe, and Phil Hayman, showed that transfusion of donor blood on the same day of transplant improved graft survival.[21] This beneficial effect persisted in practice until the discovery of cyclosporine in the early 1980s by Dr. Jean Francois Borel in Switzerland. Cyclosporine was the first calcineurin inhibitor used in clinical practice and became the backbone of immunosuppressive protocols for decades. Dr. Stiller served as the principal investigator in the landmark randomized, controlled, multicenter trial comparing cyclosporine to azathioprine in Canada. This launched cyclosporine into the forefront of kidney, and all solid organ transplant immunosuppression.[22] Canadian urologists Dr. Phil Belitsky, Dr. Joe Lawen, and colleagues at Dalhousie University further refined the use of cyclosporine. Their research demonstrated improved performance of the two-hour concentration (C2 level) as a superior marker of cyclosporine exposure compared to trough levels, improving the efficacy of this vital drug.[23] Cyclosporine was a "game-changer" in the world of transplant, and the calcineurin inhibitor remains the cornerstone of transplant immunosuppression regimens. Dr. Andrew Lazarovits from Ottawa and London discovered a monoclonal antibody called anti-CD45RB.[24] Subsequently, Dr. Luke and his research group showed that this antibody shifted the T cell subsets from effector CD45RB^{hi} to CD45RB^{lo}, a tolerogenic T cell phenotype.[25,26] In fact, a team of scientists, physicians, and surgeons from Western University (Drs. Robert Zhong, Anthony Jevnikar, and Patrick Luke) showed that this antibody could induce tolerance in mice and in primates (indefinite graft survival with a limited induction course).[27,28] Two primates continue to survive and remain off immunosuppression over a decade later. This was a remarkable achievement, but the efficacy was unpredictable, and it was never clear which animals would reject early and which developed tolerance.

Techniques

Around the time that microvascular reconstruction for kidneys with complex branch renal artery arrangements was first described by Canadian-born urologist Dr. Andrew Novick at the Cleveland Clinic in the early 1980s,[29,30] Dr. Joseph Chin incorporated preoperative, ex-vivo microvascular reconstruction into the surgical algorithm for renal allografts.[31,32] Kidneys with multiple arteries and/or veins, and those with certain vascular anomalies (e.g., aneurysms) or injuries during procurement were reconstructed in an ice-water basin with 2.5–10 X magnification (with optical loupes or microscope), with the objective of minimizing the number of in situ vascular anastomoses. Side-to-side or end-to-side anastomosis, or a combination thereof, was performed, depending on the initial vascular arrangement (Fig. 4).[33,34] Ex-vivo microvascular reconstruction was performed by Dr. Chin on 104 allografts (83 deceased donor, 21 living donor).[35] While 74 kidneys underwent a single microreconstruction, 30 kidneys with three or more arteries or previously deemed unsuitable for transplant were salvaged with extensive preoperative microvascular reconstruction.

Due to limited graft survival or high risk of complication, kidneys from older or young pediatric donors are often discarded. Kidneys conventionally considered too old or too young for transplant are now able to be used since the concept of transplanting two kidneys into a single patient took hold. Urologist Dr. Yves Caumartin and the Laval group published one of the largest series of dual transplant procedures at the time, using kidneys that were deemed too old for solitary transplantation.[36] They showed that although ureteral complications may be higher, dual transplants from expanded-criteria (older) donors had function and graft survival similar to transplants from younger, standard-criteria kidney donors. Taking this further, the Western University team published a series of 30 dual en bloc transplants from older donors, which used ex-vivo vascular reconstruction techniques to facilitate solitary arterial and venous anastomoses during the in-vivo transplant procedure.[37] While in Cleveland, Drs. Michael Hobart and Anil Kapoor characterized excellent early technical results in transplanting pediatric en bloc kidneys.[38] In the following years, in a collaborative effort between the Dalhousie and Western groups, the dual en bloc technique was shown to have excellent results in pediatric donors under the age of two years.[39]

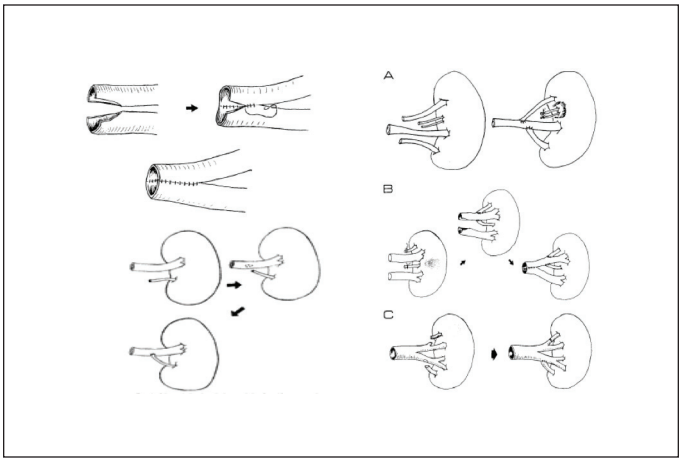

Fig. 4. Arterial reconstruction techniques pioneered by Dr. Chin and colleagues. Chin JL, Stiller, CR. Microvascular surgery as an adjunctive tool in renal transplantation. *Can J Surg* 1986;29:263. Chin JL, Stiller, CR. Microvascular reconstructive "bench" surgery for donor kidneys before transplantation: Techniques and results. *J Urol* 1989;142. Reprinted with permission.

By 2019, the Western group extended this microvascular technique to transplant kidneys from donors as young as two weeks of age.[40]

Transplantation of kidneys into the dysfunctional lower urinary tract has been an area that has specifically called for urological expertise. Dr. Phil Belitsky from Dalhousie University first described ureteral dynamics in human transplants using a cineradiographic study in 1972. Dr. Joe Lawen, from the same center, performed one of the first randomized studies that compared the use of the ureteral stent vs. no stent during ureteral implantation in renal transplantation, and concluded that routine stenting may not be necessary.[41] However, despite the results of this study, the majority of Canadian transplant surgeons continue to use stents routinely.[42] With regards to transplantation into the hostile lower urinary tract, Dr. Marie Dion, while at Western University, described a predictive algorithm that determined postoperative lower urinary dysfunction post-transplant.[43] Early successful transplants into urinary conduits provided eligibility for children with dysfunctional lower urinary tracts to receive kidney transplants.[44] Dr. Luke, while training at the University of Pittsburgh under Canadian urologist Dr. Mark Jordan, demonstrated equivalent allograft outcomes in pediatric patients with dysfunctional lower urinary tracts compared to those with normal bladders, provided that adequate lower urinary tract assessment had been performed.[45] Accordingly, Drs. Belitsky and Chin individually showed good outcomes in adults with diversions and defunctionalized bladders.[46,47] Furthermore, if the bladder or intestinal reservoir were inappropriate urinary reservoirs, Dr. Kapoor and his group showed that they could be excluded by creation of a terminal loop cutaneous ureterostomy from the transplant ureter.[48] In addition to complex implantation of the ureter, Canadian urologists have described algorithms to optimally repair ureteral strictures, as well as provide descriptions and assessments of repair techniques.[49-51]

Renal protection

The discovery of cold perfusate solutions, such as University of Wisconsin Belzer solution, and use of hypothermic machine perfusion devices have been shown to protect kidneys against deterioration during prolonged cold storage.[52,53] In a donor-matched, prospective study, Dr. Chris Nguan, while at Western University, showed that the calcium channel blocker verapamil further protects the allograft when injected into cold perfusate solution.[54] Dr. Nguan's group at Vancouver General have also assessed modification of Belzer solution with hyperbranched polyglycerol.[55] Additionally, Drs. Sener and Luke have shown that small endogenous molecules, such as carbon monoxide and hydrogen sulfide, reduce ischemia reperfusion injury, improve vascular compliance, and reduce cell death when administered to kidney donors, recipients, and even directly to the kidney ex-vivo.[56-59] Dr. Sener further explored the ability of H_2S in creating a hibernation-like state for transplantable organs.[60] The Western team have created a device that can deliver oxygen to the organs through a blood-free hemoglobin carrier under conditions that avoids hypothermic injury to the organs, with superior outcomes to hypothermic machine perfusion[61] (Fig. 5). In a pre-clinical, large, animal model, this pump has been shown to be superior to hypothermic machine perfusion in the prevention of ischemia reperfusion injury.[62] Furthermore, addition of anti-inflammatory agents, such as H_2S or CO, can be performed ex-vivo to further protect the organ from reperfusion injury.[63-66]

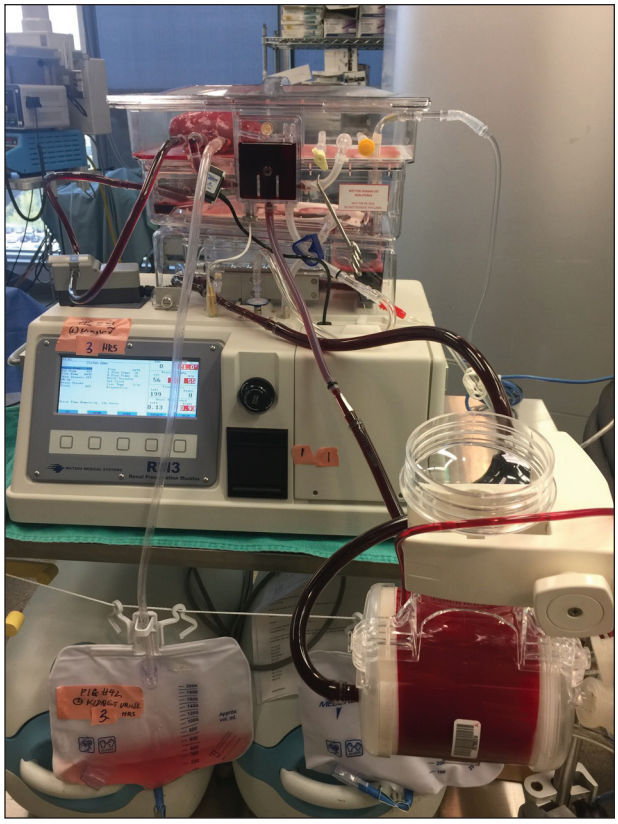

Fig. 5. Renal perfusion pump from the Luke Laboratory at Western University, London, ON.

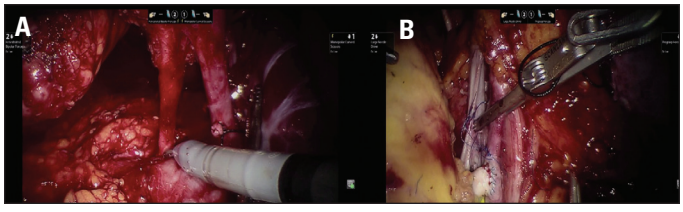

Fig. 6. Selected images from completely intracoporeal autotransplant performed by Dr. Jason Lee. ***(A)*** View of hilar dissection during the nephrectomy. ***(B)*** Completed vascular anastomosis prior to unclamping. Lee JY, Alzahrani T, Ordon M. Intra-corporeal robotic renal auto-transplantation. *Can Urol Assoc J* 2015;9:E748-9.

Auto-transplantation

Renal auto-transplantation is a surgical procedure firmly in the realm of the urologist since the 1960s. It represents a treatment option for those with complex/large ureteric strictures, as well as loin pain hematuria syndrome. Dr. Chin published the largest North American series in 1992, with updates in 1998, demonstrating the durable results in freeing patients of loin pain hematuria syndrome from narcotic dependency.[67,68] Further advancement of the auto-transplant procedure was performed by Dr. Jason Lee from the University of Toronto, who reported the first purely intracorporeal robotic renal auto-transplant in 2015[69] (Fig. 6).

Renal vascular surgery

The skillset of the transplant urologist lends aptitude to other complex renal surgery, such as renal vascular cases. Drs. Kapoor and Luke presented the largest known series of minimally invasive repair of renal artery aneurysms (RAA). In 2006, Kapoor and Luke demonstrated a series of three patients with RAA, managed in two cases[70] with a laparoscopic and one with a robotic approach.[71] The integration of vascular surgical principles and practice of the transplant urologist lends capability to tackling these challenging cases.

Transplant training

Surgical training in renal transplant has continued to evolve as the field matured in contemporary times. The early days saw urologists drawn to the field of transplant entering the practice directly, but as with many subspecialties, formal fellowships have shaped the training for most transplant urologists. The American Society of Transplant Surgeons (ASTS) educational committee has served as the benchmark for establishing the standards of transplant surgical training since 1980.[72] ASTS certification in kidney transplantation has been granted to several Canadian institutions involving urologists, including the University of Alberta, Western University, and Dalhousie University. As a critical mass of Canadian contributors to the field of solid organ transplant grew over the years, the development of Canadian credentials emerged. The Royal College of Physicians and Surgeons has created an Area of Focused Competence designation in several subspecialties, including Solid Organ Transplant.[73] Currently, two programs in Canada are accredited under this emerging framework (University of Ottawa, Western University), with a third in the process of becoming accredited. This evolving form of accreditation will serve to set national benchmarks for training quality while improving the recognition and access to transplant training for urology trainees across Canada.

Summary

Urologists in Canada have provided leadership roles in renal transplantation since its inception and continue to do so in the current era. Urologists' early and ongoing participation in renal transplant have afforded the current generation the opportunity to establish Canadian urology as a significant player in the transplant field and has set the stage for the next generation of urologists to continue this important work for years to come.

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