uro

MDPI

Review

From the Triangulation Technique to the Use of the Donor Aorta and Vena Cava for Kidney Transplantation: Lessons from the Past and Path to the Future of Xenotransplantation

Dai D. Nghiem

Department of Surgery, Division of Transplantation, Allegheny General Hospital and Drexel University, Pittsburgh, PA 15212, USA; nghiem5000@gmail.com

Abstract: Revascularization of the kidney transplant is classically performed by anastomosing the renal vessels to the recipient iliac vessels. This technique is not applicable when the renal vessels are very small, numerous or anomalous and aberrant. In these instances, the donor aorta and the vena cava have to be used for vascular anastomosis. It would be useful to briefly review the development and the use of the donor aorta and cava in renal transplantation during the last century and discuss the potential clinical application of this technique in xenotransplantation of the porcine kidneys in humans at the dawn of the 21st century.

Keywords: triangulation technique; donor aorta and vena cava; en bloc donor nephrectomy; en bloc kidney transplantation; porcine kidneys xenotransplantation

Citation: Nghiem, D.D. From the Triangulation Technique to the Use of the Donor Aorta and Vena Cava for Kidney Transplantation: Lessons from the Past and Path to the Future of Xenotransplantation. *Uro* **2023**, *3*, 151–159. https://doi.org/10.3390/uro3020016

Academic Editor: Tommaso Cai

Received: 28 April 2023
Accepted: 18 May 2023
Published: 26 May 2023

1. Introduction

Revascularization of a kidney transplant is classically performed by anastomosing the renal vessels to the iliac vessels. This technique is not applicable when the renal vessels are very small as with small pediatric kidneys, or anomalous and aberrant, as with horseshoe kidneys, or multiple as in the case of en bloc adult marginal kidneys. In these instances, the donor aorta and the vena cava bearing the two kidneys are removed en bloc and anastomosed to the recipient iliac vessels. This model of "in mass transplantation", pioneered by Carrel, was also used in the first non-human primate xenograft kidneys in humans in the 1970s. This review briefly chronicles the historical development of this en bloc technique and discusses its potential application in xenotransplantation of the porcine kidneys in humans.

2. From Myths to Miracles: The Development of Neo-Circulation and Tissue Grafting

Saint Cosmos and Saint Damian were described by Jacobus de Voragine, the Archbishop of Genoa, in the 13th century, to have reattached a dead Moor's leg to a devout man whose leg had been cut off due to cancer. This most miraculous feat provided inspiration for a number of religious paintings and sculptures by Jaime Huguet, Fra Angelico, Andrea Mantegna, Ambrosius Francken and Pesellino. Thus, Saint Cosmos and Saint Damian, both physicians, became patrons of physicians and surgeons, standing guard over the doorways of many medical schools [1]. Duhamel Du Monceau was the first scientist to coin the term "animal grafting" in 1746 after "plant grafting", defined as the "growth of a plant fragment inserted into another plant". Up the 12th century, this technique was called "greife", which is derived from the Greek word for stylet, the tool used to perform the operation. In 1767, John Hunter (1728–1793), the father of British "scientific surgery", confirmed the success of grafting spurs of a young chicken onto the comb of another animal, and human cadaver teeth on a live human recipient. It was thought that tissue grafts grew only when they were "legitimate" and after the establishment of "neo circulation" between the two organs, as

demonstrated by the successful split-skin grafting in humans by Jacques Louis Reverdin (1842–1928) in 1869 [1].

3. The Dawn of Transplantation

Transplantation of an organ is much more sophisticated than tissue transplantation. It requires the removal of the organ from the host and reimplanting it into the recipient, with anastomosis of vessels to the recipient's. It was attempted by a number of surgeons, such as Potemsky (1886), Murphy (1896) and Payr (1900), who reported some success in joining blood vessels using metallic rings and buttons to temporarily maintain blood flow through the anastomosis. At the Vienna Medical Society meeting held in January 1902, Emerich Ullmann reported the first case of kidney autografting to the neck of a dog by means of Payr's prostheses. The ureter made "urine" in a period of five days [2]. Later in the same year, he presented a goat with a dog kidney transplanted into the neck to "one hundred members of the assembly to watch urine excretion." The kidney thrombosed the following day [3]. Ullmann continued to perform transplantation experiments but failed to solve the technical difficulties. Unaware of these works, Carrel (1875–1944) reported in the *Lyon Medical* in 1902 the transplantation of a kidney to the cervical area of a dog with anastomoses of the renal vessels to the carotid artery and the jugular vein by the method of triangulation: "After removing the clamp, the circulation in the kidney was restored immediately and the kidney made urine several hours later" [4]. In 1902, De Castello also reported experiments on the transplantation of the kidneys using prostheses [5]. The animal lived forty hours, during which time 1200 cc of urine rich in albumin and casts was secreted. von De Castello and Sturli subsequently reported on the fourth blood group AB, which is now recognized as the universal recipient blood type. In 1903, Karl Beck of Chicago performed a kidney transplantation using Murphy's method of anastomosing vessels [6]. In 1905, Floresco transplanted the kidneys to the cervical area and the inguinal region, "and in every case gangrene occurred" [7]. He chose later to transplant autoplastic kidneys (autografts) in the lumbar area, but all the animals died of septic shock. Stich, in 1907, opted for the iliac region with renal vessels anastomosed to the iliac vessels and the ureter grafted into the bladder [8]. The iliac approach was later popularized by Rene Kuss [1], and eventually became the preferred site for modern renal transplantation. Carrel and Guthrie also transplanted the kidneys in the lumbar position, but the experiments provided little information on the function of the kidneys [9,10]. All these efforts were short-lived technical trials since lethal infection was the norm. From 1896 to 1898, Mathieu Jaboulay (1860–1913), who hailed from Lyon, pioneered the technique of vascular anastomosis by "circular everting suture" in arterial transplantation, a technique used later by Blalock in the "blue baby" operation in 1944. He reported the first success of arterial suture of the carotid artery of a donkey with a follow-up of several months. He thought that this method could be applied to the treatment of aneurysms, but the anastomosis was imperfect, and thrombosis of the vascular segment occurred. In Berlin, Ernst Unger (1875–1938) performed over seventy "en bloc" homologous kidney transplants in animals (cats and dogs) with survivals lasting several weeks [1]. Carrel followed this with multiple publications on vascular suturing and transplantations [11–13].

The modern transplantation of organs only started after Carrel and Guthrie reported on the successful long-term transplantation of the kidneys during their work at the Physiological Laboratory of the University of Chicago in 1906 [9,14,15] and at the Rockefeller Institute in 1907. Carrel laid down the principles of transplantation in a series of fourteen "transplantations in mass of the kidneys" in cats performed from February to October 1907 [16]. This seminal paper requires careful scrutinization since it spells out all the steps required in organ transplantation as they are practiced today. First, the kidneys were dissected carefully with minimal trauma to the structures and removed en bloc, leaving 1.5 cm of aorta and vena cava above the renal vessels and 2 cm below the renal veins. The ureters were dissected to the bladder, which was excised, leaving 1 cm of the detrusor rim and mucosa bearing the ureteral implantations. Second, the aorta was flushed with

Ringer's solution at room temperature. Third, the en bloc kidneys were transferred to the native nephrectomy site and transplanted by interposition orthotopically with proximal and distal end to end "termino-terminale" anastomosis to the recipient aorta and vena cava using round, fine, preferentially straight (instead of curved) Kirby needles (No. 16 for small vessels and No. 12 for the larger ones) with continuous fine silk sutures boiled in Vaseline to avoid damage to the intima. Extreme care was undertaken to ensure that intima-to-intima contact be obtained with eversion of the vascular wall, avoiding inclusion of the thrombogenic adventitia in the anastomosis [17]. The intima was approximated under slight tension using three equidistant retaining sutures properly located on the circumference as described in the "triangulation method". The thin venous wall needed extra sutures, an important anatomical fact to remember when transplanting pig renal xenotransplants into humans. Fourth, once hemostasis was completed, the bladder dome was opened, and the rim of the detrusor bearing the ureters was sutured to the bladder in two layers, the mucosal and muscular layers. Hemostasis was checked again prior to closure of the abdomen with catgut.

The en bloc kidneys were transplanted after a period of ischemia of 35.7 (range 0–65) minutes, which is, by current standards, a technical feat since there were four vascular anastomoses to perform. All animals were kept in metabolic cages to follow urine output and albuminuria. The animals survived for 14.2 (range 3–35) days. At autopsy, the kidneys were found slightly hydronephrotic from compression by organized hematoma, adhesions, ureteral twisting and edema. In the arteries, "The anastomoses united by their endothelial surfaces were first covered with a very fine layer of fibrin, and little by little, the threads became invisible, and by the end of some months, no trace of the suture could be perceived". Sutures in the veins stayed prominent "as long as ten months after the kidney had been replanted". This was confirmed by histological examination and "explained the perfection of the clinical results" [18]. Carrel's technical prowess was duplicated by Richard H. Lawler (1896–1982), a surgeon at the Little Company of Mary Hospital in Chicago, a senior attending surgeon at Cook County Hospital and staff member at the Loyola Stritch School of Medicine, who made medical history by performing the first successful kidney transplant in the world, *before* the discovery of immunosuppressive drugs, on 17 June 1950 on Ruth Tucker, a 49-year-old woman who was dying of renal failure from polycystic kidney disease. The donor happened to pass away from liver cirrhosis after 5 weeks of searching. With roughly 40 other physicians looking on, Dr Lawler performed the transplant operation in 45 min. The patient did well during the next 60 days, and the kidney was removed 10 months later for rejection. She passed away 5 years later from coronary artery disease [19]. After this little-known story, Lawler never performed another kidney transplant, saying in 1979, "I just wanted to get it started". For this performance, he was nominated for the Nobel Prize. The next successful transplant was to be performed in 1954 by the Brigham hospital team, in a modified host and using immunosuppression.

After solving the technical aspect of en bloc kidney transplantation, Carrel described most importantly the microscopic examinations of the transplanted kidneys. He described acute tubular necrosis as renal "tubulopathy" with dilated tubules, sloughing of the epithelial cells and the presence of exudates in the lumen, which is called tubular casts today. The sub-acute "interstitial nephritis" process with infiltration by plasma cells of the interstitial tissue, "more marked in the cortex than in the medulla", blood clots, is nothing else but severe rejection in different phases that is accompanied by a decrease in urine output and presence of albuminuria [18].

The transplantation of the jugular vein onto the carotid artery of a dog was attempted by Gluckin in 1898, but the segment quickly thrombosed. Exner, Hoepner and Goynes attempted the same experiment but failed [1]. In 1905, Carrel and Guthrie succeeded in transplanting segments of the jugular vein and patches of the peritoneum of a dog onto the carotid artery, and segments of vena cava onto the abdominal aorta, the vena cava, and finally, the thoracic aorta. He demonstrated that the "autoplastic vein transplant" (autograft, autologous graft) wall became thicker and "arterialized" to accommodate the

higher arterial pressure. The thickening was the result of "augmentation of the connective tissue of the adventitia and the intima despite degeneration of the muscular fibers". Even at the two-year follow-up, the vein did not become aneurysmal. "Fusiform aneurysms only developed if tissues had been infected", wrote Carrel. Carrel anticipated that "the use of vein bypass grafts readily available would be easier than the use of arteries to reestablish the continuity of an artery" [18]. The auto-transplanted venous graft became the backbone material of modern cardiovascular arterial grafting and reconstruction with long-lasting clinical and histologic outcomes. Carrel also described achieving the uni-terminal, latero-terminal (end-to-side) anastomosis with the triangulation method currently used in human transplantation. He ultimately showed that a denervated auto-transplanted kidney worked as well as the original kidney and clearly defined the long-term pathology of the different vascular grafts. In "homoplastic" (homologous, allograft) transplantation, even when the vessels were preserved for weeks in cold storage, and the veins remained normal in appearance, the intima thickened and the muscular fibers completely disappeared. In "heteroplastic" (heterologous) transplantation (xenograft), the results were different. Obliteration of arteries often occurred, the graft became more dilated, the walls became thinner, and after weeks and months, not only did the muscular fibers degenerate, but the elastic framework also completely disappeared. However, the fibrous wall was resistant enough to last several years [18]. These important findings have yet to be confirmed or refuted by current non-human primate transplants since severe arterial thickening may affect the long-term function of the xenografts. During his thirty years of collaboration with C.C. Guthrie, Carrel published at least eighty-one communications on vessel transplantation, limb replantation, organ transplantation, Dakin solution and finally cell culture, as well as a prototype of a heart–lung pump in collaboration with the trans-Atlantic aviator Charles Lindberg. He was awarded the Nobel Prize in Medicine and Physiology in 1912 [1].

It is important to mention that, although these experiments showed "that it is technically feasible to revascularize an organ", they also established that "the transplant could not survive when it was removed from an individual of the same species or a different species", and it is necessary to "investigate the reciprocal influence of an organism and the new organ, and ascertain under what conditions an organ can be accepted by another individual, and identify the means of recognizing the individuals between whom organs can be interchanged with impunity" [18]. Ullmann recognized this individual specificity in 1914 when he said "there are just as many protoplasms as there are individuals" [1]. In this day and age, the timing of the destruction of the foreign organ, i.e., rejection, still needs to be diagnosed by molecular monitoring of the donor-derived cell-free DNA [20]. Indeed, in 1912, Schoene, Metchnikoff's student, attributed the phenomenon of the body's behavior to "transplantational immunology". B. Murphy, who performed experiments on tumor and tissue transplantation in 1912 and 1914, was convinced that "the rejection action was due to a function of the organism at a certain period of time to eliminate foreign tissue, which did not exist in the embryo" [1]. In 1923 and 1924, in the Mayo Clinic, Williamson suggested the importance of genetic factors [1] and emphasized the importance of blood group compatibilities with regard to blood groups A, B and O, as described in 1900 by Landsteiner [21], and later, in conjunction with Alexander Wiener, the Rhesus factor. In 1912, Carrel and Interbitzen mentioned the search for a serum reaction that should "be able to determine the reactions of the recipients serum and tissue to the donor" prior to transplantation [1], and which is the version of the currently used microcytotoxicity crossmatch described by P.I. Terasaki (1929–2016) in 1964 [22,23]. This test was conducted recently during a trial of porcine kidney xenotransplant in humans by the Birmingham group [24]. Between 1943 and 1944, Tom Gibson observed the advent of severe anaphylactic reactions and accelerated rejection of a second skin graft from the same donor, a phenomenon PB Medawar called "second set rejection" whereby the host was actively immunized and developed "immune competent cells" to the first skin graft [1]. From there, research led to the identification of humoral immunity and cell-mediated immunity, which require prevention and control with current immunosuppressive drugs such as prednisone,

azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, rapamycin, plasmapheresis, anti-lymphocyte preparations and monoclonal antibodies [1]. The only successful living donor kidney transplantation between dizygotic twins was performed by Murray, Merrill and Harrison at Brigham Hospital in Boston on 23 December 1954 after body irradiation with 460 rads in two sessions, on 29 June 1959 by Jean Hamburger's group at Necker Hospital, and in non-twin siblings by Rene Kuss at the Foch Hospital in Paris on 17 January 1960. Unfortunately, the last recipient died 2 months later from disseminated liver metastasis. Both former recipients lived up to 20 and 26 years, respectively. J.E. Murray was awarded the Nobel Prize in Medicine and Physiology in 1990 [1].

4. Renal Heterotransplantation in Man—The primate Xenograft Experience

In 1963–1964, several surgeons, encouraged by the results obtained with living donor homotransplantation and the availability of immunosuppressants, developed a renewed interest in heterotransplantation, especially as the results of cadaveric transplants were so disastrous and donors were scarce.

Keith Reemstma from the University of Tulane, New Orleans, reported six cases of transplantation in humans using chimpanzee kidneys [24]. The full-grown animals weighed 32–60 kg and were of blood groups A and O, and thus, may be considered universal donors from the stand-point of blood groups. Immunosuppressive regimens consisted of azathioprine, actinomycin C, steroids and local irradiation to the kidneys. The kidneys were removed en bloc after anticoagulation and the aorta was flushed. They were transplanted extra-peritoneally in the iliac fossa, with the donor distal aorta and vena cava anastomosed to the external iliac artery and vein, respectively, in an end-to-side fashion. The ureters were implanted separately into the bladder. All transplants functioned immediately. The BUN improved from an average of 119 (range 40–172) mg/dL to 33.2 (range 12–39) mg/dL, and creatinine levels decreased from a mean of 18.1(range 11.5–21) mg/dL to 0.94 (range 0.5–2.0) mg/dL. All patients succumbed to septicemia after a mean of 60 (range 11–195) days. Pathologic studies showed hypercellularity of the glomeruli, fibrin thrombi, extensive interstitial edema, tubular degeneration, marked perivascular cellular infiltration and fibrinoid necrosis of the blood vessels. It was concluded that "caution is urged in clinical hetero-transplantation". As a corollary of these xenotransplantation experiments, Reemtsma established a transplant registry of human kidney homotransplantation to further transplant research with support from the National Research Council and the Public Health Service [24].

Thomas Earl Starzl from the University of Denver, Colorado, followed this with six patients receiving baboon kidneys in 1964 [25]. Hypothermia at 28–30 °C was employed. For cases 2 to 6, Reemtsma's method of en bloc transplant to the iliac fossa was performed in an extra-peritoneal fashion. All transplants functioned, halving BUN levels from a mean of 95 mg/dL to 52 mg/dL at 64 h. Recipients lived for 19 to 98 days and succumbed to lethal infection resulting from the use of azathioprine, prednisone, actinomycin C and local irradiation to the kidneys, with anti-rejection therapy used repetitively. Pathology reports documented heavy infiltration with plasma cells, "heavier than that seen in any of the previous homografts performed at the University of Colorado, with disruption of peritubular capillaries, interstitial edema, widespread tubular damage, fibrinoid necrosis of arteries, focal infarcts and extensive interstitial hemorrhages. Pathologic changes were more severe than those observed by Reemstma in his series of chimpanzee-to-man heterotransplants". It was concluded that "unless improved management becomes available, further trials do not seem justified" [25]. Both series, using primate kidneys, showed that the kidneys were best transplanted en bloc to double the nephron mass and to allow the larger and thicker donor aorta and vena cava to be anastomosed safely to the external iliac vessels, instead of using the smaller renal vessels with thinner walls, a fact identified by Carrel in the 1902 experiments.

5. Clinical Experience with the Use of en Bloc Kidneys in Transplantation

5.1. Transplantation of the Pediatric en Bloc Kidneys

The first infant kidneys from an anencephalic baby were transplanted en bloc successfully into a 17 lb child in 1968 by Martin L.W. et al. [26]. The en bloc kidneys were transplanted in the right iliac fossa, and the distal aorta and vena cava were connected end-to-side to the external iliac vessels. Both ureters were implanted into an ileal loop. Both kidneys functioned immediately, and the recipient was reported to be doing well thirty years later. This en bloc model was popularized in 1991 by Nghiem, who used pediatric kidneys from donors under 15 kg [27]. Pelletier S.J., using data from the Scientific Registry of Transplant Recipients [28], compared 1301 en bloc kidneys transplants to 1175 single-kidney transplants. They reported that single kidneys are ten times more likely to be discarded than en bloc kidneys, and these patients had a 78% higher risk of graft failure than those in the en bloc group ($p < 0.0001$). At the 10-year follow-up, adjusted graft survival was 25% higher in the en bloc group than in the single-kidney group. Compared to 24,530 single kidneys from ideal kidney donors, the recipients of single kidneys from small pediatric donors had a significantly increased risk for graft loss ($p < 0.0001$). Another study comparing 149 en bloc kidneys from <20 kg donors to 581 matched non-en bloc standard criteria donors with similar characteristics showed that the 20-year death-censored graft survival was significantly higher in the en bloc recipients than the non-en bloc recipients with $p < 0.0011$ [29].

After transplantation, the en bloc kidneys demonstrated a rapid catch-up growth within a short period of time, as shown by the increase in the volume of both kidneys from 132 ± 69 cc to 209 ± 69 cc and to 325 ± 106 cc during the three study periods: 1–3 months, 3–6 months and over 6 months. At the same time, the total glomerular filtration rate of the en bloc kidneys rose significantly from 22.5 ± 14.2 mL/1.73/Mn/m^2 to 85.4 ± 52.3 mL/1.73/Mn/m^2 and to 120 ± 45 mL/1.73/Mn/m^2, with $p < 0.001$. For comparison, the volume of 1 kidney determined from 12 single standard criteria adult kidneys was 260 ± 110 cc, and the GFR was 67 ± 25 mL/1.73/Mn/m^2 [30]. Taken altogether, these findings suggest that small kidneys perform best when they are transplanted en bloc to maximize the nephron mass. Current techniques of ureteral reimplantation used in neonatal kidneys can be applied to the transplantation of xenografts [31].

5.2. Transplantation of the Horseshoe Kidney

The world literature search for the period 1975–2021 identified 131 pairs of horseshoe kidneys, of which 53 pairs were transplanted en bloc since multiple aberrant and anomalous renal arteries vessels were observed in 70% of the cases. Separating horseshoe kidneys will expose them to severe devascularization and also urinary leakage from division of the isthmus, as shown by the discarding of 18% of the grafts after splitting. Additionally, the use of the distal aorta and vena cava anastomosis to the recipient iliac artery and vein has never been reported to be a technical problem during the transplant procedure [32]. After a median follow-up time of 14 (range 1–26) months, the serum creatinine level was 90 (range 53–256) micromoles/L as opposed to 150 (range 65–400) micromoles/L for the split group. Graft survival was 87% after a follow-up of 22 months, which is equivalent to that of a control group of standard criteria kidney transplants [32,33].

5.3. Transplantation of the Marginal Adult Kidneys en Bloc

En bloc transplantation of dual adult kidneys with multiple vessels has been described recently as a universal approach to transplanting marginal kidneys since multiple arteries have been found in 30% of kidneys [34]. After bench reconstruction, the en bloc technique permits converting two complex vascular renal grafts into one en bloc graft with single arterial inflow and single venous outflow conduits. En bloc transplantation requires only two vascular anastomoses at the time of transplantation, instead of a minimum of four vascular anastomoses for single-artery and single-vein dual renal grafts. Thus, the en bloc technique halves the operative time to an average of 180 min, reducing the

morbidity of a prolonged operation and anesthesia exposure in elderly recipients. Patient and graft survival were 100%. At 36 months, serum creatinine levels averaged 1.8 (range 1.4–1.9) mg/dL [34].

6. The Gene-Edited Porcine Kidney Transplantations

The limited supply of donor organs remains the greatest barrier to transplantation. As of 11 January 2022, in the United States, there were over 100,000 patients on the waitlist for a kidney transplant, with only 20,402 kidney transplants performed in 2021 [35]. As a result of this severe organ shortage, patients have had to wait a median time of 3–6 years to receive a kidney transplant. Only 60% of patients on the waitlist survived 5 years, compared to 75% for recipients of deceased donor kidneys and 85% for recipients of live donor kidneys [36]. It appears that xenotransplantation has the potential to reduce the organ shortage, mostly since research efforts have been able to use the CRISPR-Cas 9 clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated (Cas proteins) technologies to edit out the unwanted genes from pigs to reduce the immunologic barriers and potential incompatibilities between pigs and humans, and to allow using their kidneys for transplantation in non-human primates and in humans. Currently, 10 or more gene-edited pigs are available for transplantation purposes. For the first time in the history of medicine, it is possible to *modify the donor* for transplantation, rather than treat the recipient as usual, with all the potential side effects of the immunosuppressive drugs [37,38].

Two groups in the US—the New York University Langone Health [39] and the University of Alabama at Birmingham [24]—have recently moved forward with short-term (54 and 74 h, respectively) trials using brain-dead human subjects transplanted with triple-knockout pig kidneys into the inguinal area to study hyperacute rejection, antibody-mediated rejection and porcine retrovirus transmission. In the first set of experiments, the native kidneys of the recipients were not removed, so "conclusions about isolated xenograft function cannot be made", although the creatinine levels, which had been at a steady state, decreased from 1.97 to 0.82 mL/dL in recipient 1, and from 1.10 to 0.57 mg/dL in recipient 2. In the second set of experiments in Birmingham, "the grafts did not work appropriately, and the study had to be terminated due to the decompensation of the recipient" from multiple organ failure and severe thrombotic microangiopathy [39]. In view of the extensive clinical research conducted on the use of the en bloc transplants, it would seem reasonable to use the en bloc model in xenotransplantation to double the nephron mass, and to make surgery safer by using the larger and thicker pig aorta and vena cava for anastomoses.

7. Conclusions

The development of gene-edited pigs has finally allowed the use of porcine renal grafts in non-human primates without the risk of hyperacute rejection. Since the first human experiments have shown that the kidneys may not be able to sustain normal renal function, it is strongly suggested that 1. both kidneys should be used to double the nephron mass, and 2. they should be transplanted en bloc to avoid technical problems associated with the use of small and thin-walled vessels. This procedure has stood the test of time since it was introduced successfully for human use over fifty years ago.

Funding: This research received no external funding.

Institutional Review Board Statement: This study did not involve any personal identifying data and did not require IRB approval.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The author declares no conflict of interest.

References and Notes

1. Kuss, R.; Bourget, P. *An Illustrated History of Organ Transplantation: The Great Adventures of the Century*; Sandoz: Basel, Switzerland, 1992.
2. Ullmann, Wien, Klin Woch 1902,xv,281. Cited by Carrel, A. Transplantation in mass of the kidneys. *J. Exp. Med.* **1908**, *1091*, 98–140. [CrossRef]
3. Ullmann. Ibid, 707. Cited by Carrel, A. Transplantation in mass of the kidneys. *J. Exp. Med.* **1908**, *1091*, 98–140. [CrossRef] [PubMed]
4. Carrel, A. The operating technique for Vascular Anastomoses and Transplantation. *Lyon Med.* **1902**, *98*, 859.
5. De Castello Wien klin Woch xv, 317. Cited by Carrel, A. Transplantation in mass of the kidneys. *J. Exp. Med.* **1908**, *1091*, 98–140. [CrossRef] [PubMed]
6. Back, K. Verbal Communication. Cited by Carrel, A. Transplantation in mass of the kidneys. *J. Exp. Med.* **1908**, *1091*, 98–140. [CrossRef] [PubMed]
7. Floresco, Jour, de Physio et de Path, générale,1905, vii, 27:47. Cited by Carrel, A. Transplantation in mass of the kidneys. *J. Exp. Med.* **1908**, *1091*, 98–140. [CrossRef] [PubMed]
8. Stich. Archiv f Klein Chirurgie 1907, Lxxxiii, 494. Cited by Carrel, A. Transplantation in mass of the kidneys. *J. Exp. Med.* **1908**, *1091*, 98–140. [CrossRef]
9. Carrel, A.; Guthrie, C.C. JAMA 1906, xlvii, 1948 and Science, xxiii, 304. Cited by Carrel, A. Transplantation in mass of the kidneys. *J. Exp. Med.* **1908**, *1091*, 98–140. [CrossRef]
10. Carrel, A. Science, xxii, 473. *C.R. Soc. Biol.* **1905**, *ii*, 669.
11. Carrel, A.; Guthrie, C.C. The transplantation of veins and arteries. *Am. Med.* **1905**, *10*, 1101–1102.
12. Carrel, A.; Guthrie, C.C. Uni-terminal and bi-terminal Venous Transplantations. *Surg. Gynecol. Obstet.* **1906**, *2*, 266–286.
13. Carrel, A. Results of the transplantation of blood vessels, organ limb. *JAMA* **1908**, *51*, 1662. [CrossRef]
14. Carrel, A.; Guthrie, C.C. *J. Am. Med. Assoc.* **1906**, *xlvil*, 1648. Cited by Carel, A. Transplantation in mass of the kidneys. *J. Exp. Med.* **1908**, *1091*, 98–140. [CrossRef] [PubMed]
15. Carrel, A. Science 1906; xxiii, 394. Cited by Carrel, A. Transplantation in mass of the kidneys. *J. Exp. Med.* **1908**, *1091*, 98–140. [CrossRef] [PubMed]
16. Carrel, A. Transplantation in mass of the kidneys. *J. Exp. Med.* **1908**, *1091*, 98–140. [CrossRef]
17. Saviana, A. Alexis Carrel, Father of Vascular Anastomosis and Organ Transplantation. Available online: http:www.indjvascsurg.org (accessed on 31 July 2017).
18. Carrel, A. Nobel Lecture, December 11, 1912. Available online: https://www.nobelprize.org/prizes/medicine/1912/carrel/lecture/ (accessed on 31 July 2017).
19. Lawler, R.H.; West, J.W.; McNulty, P.H.; Clancy, E.J.; Murphy, R.P. HOMOTRANSPLANTATION OF THE KIDNEY IN THE HUMAN. *J. Am. Med. Assoc.* **1951**, *147*, 45–46. [CrossRef]
20. Woodward, R.N. Donor-Derived Cell Free DNA (dd-cfDNA) for Detection of Antibody-Mediated Rejection in Kidney Transplantation. In Proceedings of the FDA Workshop: Antibody Mediated Rejection in Kidney Transplantation, Silver Spring, MD, USA, 12–13 April 2017.
21. Tan, S.Y.; Graham, C. Karl Landsteiner (1868–1943): Originator of ABO blood classification. *Singap. Med. J.* **2013**, *54*, 243–244. [CrossRef]
22. Terasaki, P.I. *Microcytotoxicity Crossmatch*; Wikipedia: San Francisco, CA, USA, 1964.
23. Porrett, P.M.; Orandi, B.J.; Kumar, V.; Houp, J.; Anderson, D.; Killian, A.C.; Hauptfeld-Dolejsek, V.; Martin, D.E.; Macedon, S.; Budd, N.; et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. *Am. J. Transplant.* **2022**, *22*, 1037–1053. [CrossRef]
24. Reemtsma, K.; McCracken, B.H.; Schlegel, J.U.; Pearl, M.A.; Peace, C.W.; DeWitt, C.W.; Smith, P.E.; Hewitt, R.L.; Flinner, R.L.; Creech, O. Renal heterotransplantation in Man. *Ann. Surg.* **1964**, *160*, 384–408. [CrossRef]
25. Starzl, T.E.; Marchioro, T.L.; Peter, G.N.; Kirkpatrick, C.H.; Wilson, W.E.C.; Porter, K.A.; Rifkin, D.; Ogden, C.A. Renal Heterotransplantation From Baboon To Man: Experience with 6 cases. *Transplantation* **1964**, *2*, 752–776. [CrossRef]
26. Martin, L.W.; Gonzalez, L.L.; West, C.D.; Swartz, R.A.; Sutorius, D.J. Homotransplantation of both kidneys from an anencephalic monster to a 17 pound boy with Eagle-Barrett syndrome. *Surgery* **1969**, *66*, 603–607. [CrossRef] [PubMed]
27. Nghiem, D.D. En-Bloc transplantation of kidneys from donors under 15 kg into adult recipients. *J. Urol.* **1991**, *145*, 14–16. [CrossRef] [PubMed]
28. Pelletier, S.J.; Guidinger, M.K.; Merrion, R.M.; Englesbe, M.J.; Wolf, R.A.; Magee, J.C. Recovery and Utilization of Deceased Donor Kidneys from Small Pediatric Donors. *Am. J. Transplant.* **2008**, *8*, 1646–1652.
29. Kizilbash, D.J.; Evan, M.D.; Chinnakotla, S.; Chavers, B.B. Survival Benefits of En-Bloc Transplantation of Small Pediatric Kidneys in Children. *Transplantation* **2020**, *104*, 2435–2449. [CrossRef] [PubMed]
30. Nghiem, D.D.; Hsia, S.; Schlosser, J.D. Growth and function of en bloc kidney transplants. A preliminary study. *J. Urol.* **1996**, *153*, 326–329. [CrossRef] [PubMed]
31. Nghiem, D.D. Pull-through Ureteroneocystostomy for Very Small En Bloc Kidney Transplants from Donors Weighing $\leq$ 5 kg. *Uro* **2022**, *2*, 102–108. [CrossRef]
32. Nghiem, D.D. Transplantation of the Horseshoe Kidneys: A Model for Dual Adult Kidney Transplantation. *Uro* **2022**, *2*, 157–165. [CrossRef]

33. Stroosma, O.D.; Shurink, G.W.; Smits, J.M.; Kootstra, G.J. Transplanting Horseshoe Kidneys. A Worldwide Survey. *J. Urol* **2001**, *166*, 196–199. [CrossRef]
34. Nghiem, D.D. Transplantation of Dual Adult Kidneys with Multiple Vessels. *Uro* **2021**, *1*, 274–280. [CrossRef]
35. United States Renal Data System. Available online: https://www.usrds.org/adr.aspx (accessed on 25 February 2023).
36. Cooper, D.K.C. Clinical Pig Kidney Xenotransplantation: How Close Are We? *JASN* **2020**, *31*, 12–21. [CrossRef]
37. Cooper, D.K.C. The Long and Winding Road to Clinical Xenotransplantation. A Personal Journey. *Eur. Res.* **2022**, *63*, 165–172. [CrossRef] [PubMed]
38. Montgomery, R.A.; Stern, J.M.; Lonze, B.E.; Tatapudi, V.S.; Mangiola, M.; Wu, M.; Weldon, E.; Lawson, N.; Deterville, C.; Dieter, R.A.; et al. Results of Two Cases of Pig-to-Human Kidney Xenotransplantation. *N. Engl. J. Med.* **2022**, *386*, 1889–1898. [CrossRef] [PubMed]
39. Ganchiku, Y.; Viella, L.V. Pig-to-human kidney transplantation using brain-dead donors as recipients. One giant leap, or only one small step for transplant kind? *Xenotransplantation* **2022**, *29*, e12748. [CrossRef] [PubMed]