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Editorial

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El trasplante renal pionero y motor de los trasplantes de órganos

Pioneer kidney transplant and driving force of organ transplantations

Organ transplantations (OTs) were among the greatest milestones in medicine in the 20th century. It was possibly the greatest milestone because of the complexity of their development, requiring a number of findings and advances in different fields of medicine. Examples of such advances included understanding of immunology and organ rejection, indispensable to achieve an effective outcome.

Although each organ has its own characteristics, OTs share a number of common aspects: transplantation surgery, immunosuppression to prevent and/or treat recipient rejection, and immunological aspects to study organ histocompatibility. The objective is to achieve excellence in treatment, resulting in an optimum organ and patient survival to allow patients to lead a normal life.

Apart from these common aspects, there are other specific questions arising during the historical evolution of each type of transplantation which clearly differentiate them. Kidney transplantation (KT) was the pioneering and basic procedure because it served as a driving force for all other OTs. It is therefore necessary to recall the steps taken during KT history.

Relevant historical facts about KT

In the first decade of the 20th century, a significant number of French, German, and Austrian surgeons started to practice transplantation of virtually all organs in experimental animals, particularly dogs. The kidney was rapidly selected as a model and continued to be the test bench in animals, and later in humans, until transplantations were successfully performed 50 years later. The kidney was selected because of its morphological characteristics (vascular pedicles, excretory route) and its bilaterality. Kidney self-transplantations were performed, and graft function was achieved in many cases. Particular mention should be made to the vascular anastomosis techniques devised by the French physicians Mathieu Jabulay and, particularly, his disciple Alexis Carrel. Such procedures are still used. In 1911, Alexis Carrel reported to the French Medicine School a kidney self-transplantation in a dog with a two-year survival. Carrel noted that when the kidney was transplanted to another dog, organ self-destruction events similar to those seen in vascular necrosis occurred. He wrote: *"The surgical part of OTs is now complete, as we are able to perform them comfortably and with excellent anatomical results, but the procedures cannot yet be applied to human surgery… All of our efforts should now be aimed at finding a biological method that foresees the reaction of the body to foreign tissue and allows for adapting the homologous organs to their hosts"*. Alexis Carrel was describing the rejection crises, which have been and will continue to be the subject of many research studies.[1]

After this exciting start, there were no advances in KT until the 40s, except for the first transplantation from a cadaver to a recipient, performed by the Russian physician Voronoy in 1933. The recipient died at four days. There were two facts which had a marked influence on KT. During World War Two, an English plastic surgeon, Sir Peter Medaward, discovered the basic laws of transplant immunology, describing the concepts of incompatibility and tolerance. Virtually at the same time, Dr. Kolff, in The Netherlands, was able to operate the first artificial kidney and to perform the first hemodialysis procedures. Both discoveries were essential for KT. The first one because of an improved donor-recipient immunology. The second, because it provided for effective treatment of patients with end-stage renal disease that would allow for saving their lives if they lost a transplanted kidney. However, hemodialysis could not be implemented until after 1963.[2]

Dramatic results were achieved in the 50s in both Hospital Necker in Paris and Peter Bent Brigham Hospital in Boston. On December 23, 1954 Murray and his colleagues performed in Boston the first KT between homozygous twins with good function and survival. These two major hospitals made for a

decade continuous advances in living donor transplantation, not only between twins, but also between unrelated donors. In 1960, René Kuus performed in France two transplantations from unrelated donors with survivals of 17 and 18 months. KT from living donors was thus achieved. This dramatic achievement consecrated the kidney as the first transplanted organ and prompted attempts at transplantation of other organs such as the liver. Jack Cannon performed in 1955 the first liver transplantation between two animals with a survival of four days.[2]

Achievement of the first KT from a living donor led to more intensive work in cadaveric donor transplantation in the 60s, but results were poor. There was criticism, sometimes merciless, by a minority of the medical class, associated to wide coverage in communication media.[1] This is reflected by the words of Dr. Kolff, to whom millions of renal patients owe their lives, who wrote in 1965: *"When kidney transplantation is discussed, why are temporary results so despised? If everybody agrees that a patient with stomach cancer should undergo palliative surgery, which will not prolong his life for longer than six months, why is it criticized that a patient with renal failure is offered a life as long and comfortable?"*. Similarly, Dr. José María Gil Vernet, who pioneered KT in Spain and worldwide, wrote the following in the preface to our paper "Surgical complications of kidney transplantation", presented to the 1992 CAU Congress in Madrid; *"The main two obstacles we face in the dawn of transplantations are: the merciless criticism by a medical sector for which transplants were an act of pride that was against the nature of man, against the essence itself of human beings… The other great problem was deficient organ preservation and the severe complications from sepsis due to immunosuppressant treatment, with local radiation, azathioprine, and prednisone. The poor results accounted for the fact that in 1963 there were only six centers in the world with an active KT program"*.[1]

Once the euphoria caused by the early KTs from genetically identical living donors faded away, the 60s was a very hard decade for professionals working in KT, as shown by the 1963 International Congress in Washington,[2] which was attended by fewer than 30 physicians from different specialties with an interest in KT. Those present reported the results achieved in the total 244 transplantations performed by them. Early failure rate was very high. Forty-five percent of transplants had been performed between relatives (49 parents, 39 siblings), and 85% between unrelated people (volunteer donors, available kidneys, and cadaveric kidneys). Nine grafts had been functioning for one year, six of them from relatives, two from unrelated people, and one from a cadaver. However, among monozygotic twins not prepared with immunosuppressants and irradiated dizygotic twins (28 of the 244), early graft failure occurred in only 10%, and 60% survived for longer than one year and up to seven years in some cases.

There were also positive reports at this meeting. Two young surgeons, T. Starz and Marchioro, reported 27 KTs performed in the past 10 months using azathioprine alone and treating rejection with prednisone and actinomycin D. Twenty-five of the kidneys came from voluntary related living donors, and only two from cadaveric donors; the latter two did not function. Of the remaining transplant recipients, 18 were alive and had a good renal function. Results were better when donor and recipient were related (approximately 85%). T. Starz concluded that: *"While KT raises great hopes, this procedure should continue to be a very limited and highly experimental indication and may not be widely used"*. He could not imagine that several of these patients undergoing surgery at the beginning of 1963 would be living with their grafts almost 30 years later. This contribution represented a great stimulus for older professionals at a time when all efforts performed were being questioned.[2]

A further interesting contribution by D. Hume "was that cadaveric kidneys preserved by cold fluid perfusion showed more rapid urine output, which advised use of such fluid". This procedure represented a critical step in organ preservation for transplantation. Some years later, in 1966, Geoffrey Collins and Folker O. Belzer reported two infusion fluids with a different composition but achieving the same objective of decreasing cell energy metabolism and oxygen consumption. Cold was thus found to be the best ally for transplanting physicians. Haste and fight against the clock in the 50s to remove organs allowed physicians to perform an elective procedure that benefited from biochemical and histological studies. Once again, KT did all the donkey work for all other organ transplants, some of which were already in their experimental period.

The Human Kidney Transplant reported in 1968 survivals of 45% at one year and 38% at two years with cadaveric kidneys. Despite these poor results, hard work continued on three aspects that would soon bear fruit: immunology, immunosuppression, and the concept of brain death. Both humoral and cell immunology are involved in the pathogenesis of rejection, and researchers focused on the study of antigens that stimulate rejection. In 1958, Jean Dausset first reported a leukocyte antigen. Additional antigens present in leukocytes, members of what was subsequently called human leukocyte antigen (HLA) system, continued to be discovered. Progress in immunosuppression continued to be applied to transplantation recipients. In addition to the abovementioned, antilymphocyte serum and globulins (ALS and ALG) started to be used and improved graft survival. All of these agents and their combinations were only used in kidney transplant, and based on their results they were used or not in other types of transplant. KT thus contributed to progress in all other transplants. In 1972, Dr. Borrel showed in Basle the immunosuppressant properties of cyclosporin A, discovered two years before. This drug was shown to be much more active than the previously used immunosuppressants, as documented by Sir Roy Caine. The third essential contribution to improve transplant results emerged from the studies conducted by the French neurophysiologists Mallaret and Goulon, who reported the occurrence in certain patients of a transient clinical status from which "there was no return" and which they called "status beyond coma".[3] This led to the concept of brain death. The concept was established in 1968 by the Harvard University Committee and subsequently accepted by most countries, and made it possible to remove the kidney while the heart was still beating and, thus, in optimum hemodynamic conditions.

Together, all of these advances reported in the 50s and 60s made kidney transplant a true therapeutic model of renal failure and led to approval of a number of legal provisions to regulate its use and insertion into society.

In the 70s, KT survival was 66% at one year and 56% at three years. According to data from our own transplant team at Hospital Universitario Virgen del Rocío, based on 333 KTs performed from 1978 to 1984, patient survival rates were 94% at one year and 92% at three years.[1] Cyclosporin A was introduced in the protocols of the transplanting hospital from 1982, resulting in a dramatic increase in graft survival. At our hospital, in the 1986-1989 period, kidney survival rates in a population of 733 transplant recipients were 83% at one year and 75% at three years. Patients' survival rates were 98% and 93% at one and three years respectively.

As shown by the above data, KT is a total success as treatment. However, we cannot forget the long period of agonies suffered by multiple surgeons, clinicians, and researchers, interspersed with exciting findings that encouraged physicians to continue working despite the drawbacks.

If we analyze this historical review, we see that the rigor of biological laws governing evolution of species is changed by the first time by enabling an individual to live thanks to an organ removed from another individual.[2] It may be stated with absolute certainty that KT pioneered transplants and opened the way to other organ transplants (liver, heart, pancreas, bowel, lung).

A short review of the history of at least the two types of transplant closest to KT in time (liver and heart transplants) is required to support our contention.[2] The work of professionals who achieved liver and heart transplant has of course the same value as that of surgeons and urologists who developed KT. However, things happened as discussed here, and this should be recognized.

The most relevant historical events in liver transplant (LT)

As noted above, Jack Cannon transplanted in 1995 a liver from one animal to another, which survived four days. Thomas Star, an American surgeon from Iowa, reported in 1960 his experience with animals. Seven of the 31 animals reported survived for longer than four days. This same author performed in February 1963 the first liver transplant in humans to a three-year-old child with biliary atresia. In his own words, *"the procedure started with an atmosphere of confidence, but ended in tragedy. Five hours of survival"*. Two months later, Thomas performed another transplant in a patient who, after surgical success, died at 22 days from pulmonary embolism and with an intact liver. Dr. Thomas, subsequently called the father of liver transplants, continued his program of LT from living donors and achieved similar or superior results to those reported by the Necker Hospital in Paris or the Brigham Hospital in Boston. This great surgeon had excellent experience in KT from living and cadaveric donors, which was undoubtedly useful for the advances he made in LT.[2]

In England, Roy Caine started his LT program in 1970. However, in 1975 results were still very poor. Worldwide, 20 teams achieved survival of only 20 out of 228 LT recipients. At the end of the decade, Thomas Star reported discouraging results, with 30% survival in a series of 100 LTs. An analysis of results shows that deaths were due to sepsis from severe infection, severe peroperative and postoperative bleeding, and inadequate indications. KT was at the time already an established procedure which continuously provided information to all other transplant procedures being developed.

From 1980, all deficiencies were resolved and a time of splendor started in Pittsburgh with Thomas and in England with Roy Caine. The latter started to use a combination of cyclosporin and corticosteroids to prevent rejection. In 1983, the worldwide scientific community considered LT as the best method to manage patients with end-stage liver disease. In 1990, LT survival rates were 69% at one year and 62% at two years.[2]

The most relevant historical events in heart transplant (HT)

At Cape Town, on December 3, 1967, at 5:52, Christian Neetling Barnard, leaning over the chest of his patient, watched the beating of the heart he had just implanted to Louis Wahkansky, a 54-year-old recipient. The patient was administered immunosuppressants: azathioprine, prednisone, and local irradiation. The patient died on December 21 from bilateral pneumonitis induced by pseudomonas. As occurred with cadaveric KT first and with LT, sepsis was the leading cause of failure in HT.[2]

In 1978, disappointment was widespread among surgeons and clinicians because of the poor results. However, some of them still clung to some isolated reports of survival for one year (5 patients) and up to nine years (one patient).

Improved surgical procedures, review of adequate indications, and improved immunosuppression with the advent of cyclosporin started to change results. It was not until 1985 that the International HT Congress established the great impact of the type of cardiomyopathy and recipient age on survival. Three-year survival rates are 75% for patients aged 0-19 years, 59% for those aged 20-29 years, 51% in the group aged 30-39 years, and 30% in patients over 50 years of age.[2]

Pancreas, lung, and bowel transplants followed a similar evolution to that reported for KT and LT.

A review of the history of OTs from their beginning in both experimental animals and humans and of their surgical and medical evolution (and, of course, their survival rates) shows that KT was undoubtedly the pioneering procedure and acted as a driving force for all other transplants, setting the adequate pace until it became the optimum treatment. The keys to this leadership may be summarized as follows:

1. The anatomical morphology of the kidney and its size and consistency, bilaterality, vascular components, and excretory route "invite" surgeons to perform this surgery.

2. Many great surgeons achieved at the beginning of the 20th century spectacular surgical and functional results, achieving self-transplants in dogs with survivals longer than two years. However, such results were not seen when the kidney was transplanted to another dog.
3. Implementation of the first artificial kidney in the 50s was essential and probably definitive for the future of KT because it allowed many transplant recipients to enter hemodialysis and continue with their previous status, thus surviving even if kidney function stopped. This was achieved from 1963. All knowledge and advances achieved in the field of immunology and immunosuppression were first applied to human KT from cadaveric donors and subsequently to all other OTs.
4. As a double organ, the kidney allowed for the first transplants between twins. Survival results in such cases were spectacular because of organ tolerance by the recipient due to the immunological similarity between donor and recipient.
5. KT served as a warning for all other transplants that sepsis was the leading cause of death in transplant patients. This was partly promoted by the impairment in defenses caused by administration of some immunosuppressants.
6. Kidney preservation by perfusion with fluid solutions at low temperature was another discovery that was helpful for all other OTs. The marked decrease in cell suffering[4,5] allowed for programming procedures and performed the biochemical and histological tests required.
7. Finally, the possibility of removing the kidney from a heart beating donor after discovery of brain death and the advent of cyclosporin led to dramatic improvements in kidney survival, which also had an impact on all other OTs.

When one checks the dates of all discoveries previously listed, there is not the least doubt that development of KT was essential for the dramatic and incredible advance in medicine represented by OTs in humans. KT was undoubtedly the pioneering procedure in organ transplant and motivated professionals to achieve optimal results in all other transplants.

In addition to this great achievement, KT surgery made a decisive contribution to the development of urology as a surgical specialty because in the 60s and 70s urologists made great efforts to increase their experience in management of large vessel surgery and their understanding of the different surgical approaches to the peritoneal cavity and retroperitoneum. Such knowledge was required for en bloc kidney removal following in situ perfusion of renal units. As a result of this, KT remained, at least in Spain, in the hands of urologists, which raised urology to a top level surgical specialty.

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