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The History of Kidney Transplantation: Past, Present and Future (With special references to the Belgian History)

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1. Introduction

The history of kidney transplantation is thought to have originated at the early beginning of the previous century with several attempts of Xenografting, and experimental works on vascular sutures (Küss & Bourget, 1992)[1]. But it really started more than 60 years ago with first attempts of deceased donor transplantation (DCD) and the first successful kidney transplantation of homozygote twins in Boston (Toledo-Pereyra et al, 2008)[2]. Belgian surgeons contributed to that field of medicine by performing in the early sixties the first ever organ procurement on a brain dead heart beating donor (DBD) (June 1963) (Squifflet, 2003)[3]. Later on, in the eighties, they published a first series of living unrelated donor (LURD) transplantations, as well as ABO-Incompatible living donor (ABO-Inc LD) transplantations. With the advent of Cyclosporine A, and later other calcineurin inhibitors such as Tacrolimus, with the advent of more potent immunosuppressive drugs (IS), the gap between the number of renal transplant candidates and the number of transplanted recipients was and is continuously increasing in Belgium and most countries. It opened the search for other sources of organs such as donors after cardiac death (DCD) defined with the Maastricht conference and the extended criteria donors (ECD) compared to standard criteria donors (SCD). In Belgium another source of DCD was identified after the promulgation in 2002 of a law on euthanasia. The Belgian example and all its historical measures could help others to fight against organ shortage and its consequences, organ trafficking, commercialization and tourism.

2. The prehistory of transplantation

Already in old civilizations, the Egyptians, the Greeks, the Romans, were dreaming and expecting morphological changes in the structure and behavior of the human body. Old mythologies with their sculptures and art offer many examples such as gods, heroes, sirens, tritons, centaurs which are "prefiguration" of the xenotransplantation era (Küss & Bourget, 1992)[1].

The real transplantation story started with Saints COSMAS and DAMIAN during the fourth century: the extraordinary influence of these physicians extended far beyond the Middle Ages and even into modern times (Squifflet, 2003)[4]. After learning the medical art, these legendary early Christian brothers were said to have earned so much grace through the

Holy Spirit that they were able to banish all diseases from man and beast. Therefore, in the fourth century, they transplanted a Moor's leg to their Sacristan (Fig. 1). In Rome, the healing brothers were venerated, but they were also martyred under Diocletian (Fig. 2) and subsequently canonized. Today, they are acknowledged as the patron Saints of Surgery.

Oil on wood. Württembergisches Landesmuseum, Stuttgart, Germany.
Fig. 1. Transplantation of the Moor's leg by the brothers Cosmas and Damian.

Sint-Jacobskerk, Brugge, Belgium.
Fig. 2. Lancelot Blondeel'stritych on canvas. The martyrdom of the twin brothers Cosmas and Damian.

At the beginning of the twentieth century (Table 1), the kidney became the pilot organ in the field of transplantation development with Emerich Ullmann (Vienna, Austria, 1902) who successfully transplanted a dog kidney into the animal neck. In parallel, the Lyon School with Mathieu Jaboulay described the circular suture of the arteries, a first step towards transplanting in 1906 a pig kidney and shortly after, a goat kidney in the inner elbow of end-stage renal failure patients. Both kidneys rapidly thrombosed, while Mathieu Jaboulay was erroneously blaming his suture technique!
An indelible mark on the pages of the transplantation history was made by one of Jaboulay's pupil, Alexis Carrel who immigrated to the United States and got, later on, the 1912 Nobel price. For vascular sutures, he moved to another technique, the so-called

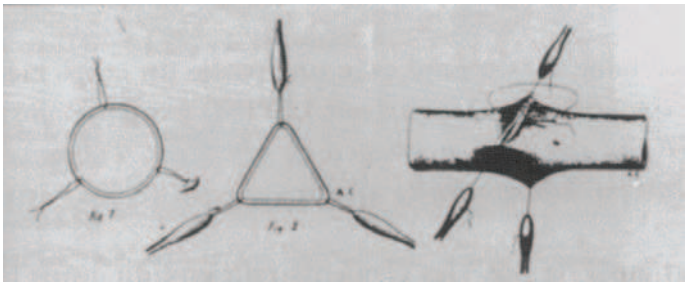
"triangulation" while using and exchanging dog legs in order to prove its efficiency (Fig. 3). Even if the procedure was effective for vascular anastomosis and organ revascularization, Carrel mis-recognized that transplanted organ allografts were not permanently accepted. Indeed he did not recognize the immunological reaction and the existence of the immune system. Nevertheless, his surgical technique for vascular suturing is still valid and persists today, with several modifications introduced for microsurgery like the eccentric biangulation technique proposed by Cobett in the Sixties (Fig. 4) (Squifflet et al. 1993)[5].

Year	Author	Dicovery or application
1902	Ullmann	Dog kidney into the neck
1902	Carrel	Developed vascular anastomotic techniques
1906	Jaboulay	Pig and goat kidneys to the elbow
1909	Unger	En bloc Maccacus kidneys
1912	Carrel	Nobel price
1928	Voronoff	Testis transplantation
1936	Voronoy	First deceased donor kidney transplantation
1951	Küss	Free kidneys from guillotined donors transplanted with surgical techniques still in use today
1952	Hamburger	First use of living related donor kidney (mother to son)
1954	Hume	First transplantation of identical twin kidney
	Murray	(+ first post-transplant pregnancy)
	Merril	(+ TBI: total body irradiation)
1962	Hamburger	Successful transplantations of two living related but non-twin kidney allografts (TBI-Steroids)
1962	Küss	Successful transplantations of two non-related kidney Allografts (TBI-Steroids-6-Mercaptopurine)
1962	to 1964	Xenograft period:
	Remtsma	5 en-bloc kidneys from chimpanzees
	Starzl	6 baboon kidneys and 1 liver
	Hume	1 baboon kidney (54 Liters of urine)
1963	Starzl	First three attempts at orthotopic liver transplantation in humans 25/27 successful renal transplantations with 6-MP
1966	Kelly Lillehei	First human pancreas transplantation at the University of
	Barnard	Minnesota
1967		First transplantation of a human heart in Cape Town

Table 1. A timeline in organ transplantation.

In 1909, Ernst Unger used en-bloc Macaccus kidneys in humans which rapidly failed, due to the unknown hyperacute vascular rejection. By contrast, the success of dog autografts at the Mayo Clinic in Rochester helped the transplant physicians to suspect the rejection phenomena; it was also the open door for human kidney homografting.
In 1928, Serge Voronoff at the Collège de France in Paris, who was well-known for his monkey to human testis transplantations, was ready to transplant a young girl with renal tuberculosis. The candidate for the organ donation was a murderer condemned to be beheaded, but willing to offer his organs after death. Unfortunately, the Prosecutor of the Republic took a wrong decision and opposed his veto. That's why, only 5 years later, in 1933, another Russian Surgeon, Voronoy, underwent in Kherson, the first ever renal

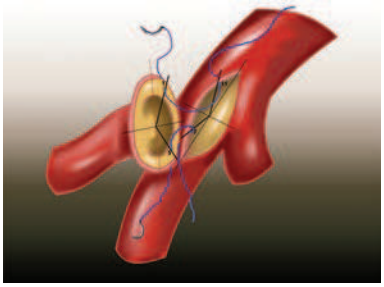
a.



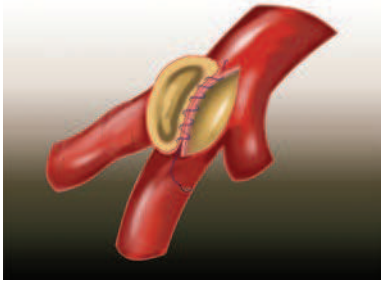
b.

c.

Fig. 3. Alexis Carrel (a) and his surgical technique of vascular sutures (b) exchanging dog legs to prove its efficiency (c). (Küss & Bourget, 1992)[1].



a.



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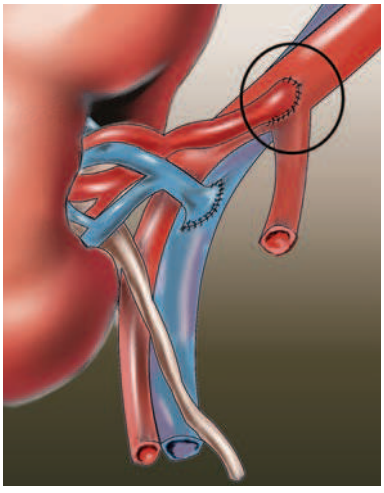


c.

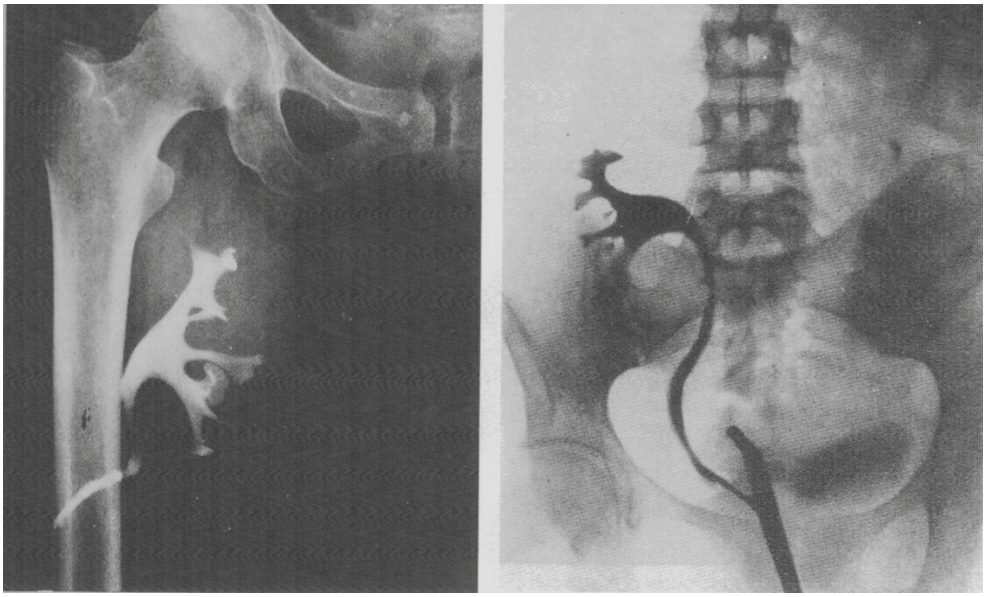
a: two stitches are place on both sides at 1 hour and 11 hour, at 5 hour and 7 hour, in order to correctly tackle the posterior ridge of the vessels, while opening the anterior wall.
b: the posterior running suture is placed from the inside.
c: the anterior running suture.
(Meurisse M., drawings).
Fig. 4. The eccentric biangulation technique for end-to-side vascular anastomosis

homotransplantation in human using a kidney from a deceased–brain trauma, 60-years-old donor (DCD) (Blood group B). The recipient was a 26-years-old woman (Blood group O), who was dying from acute renal failure due to mercury intoxication. The kidney was placed into the groin (Fig. 5). Despite the ABO incompatibility, the urine output remained on 5 ml per hour until PO day 2 while the recipient died on PO day 4 with no vascular thrombosis of graft vessels.

(Küss & Bourget, 1992)[1].
Fig. 5. First renal homotransplantation by Voronoy in 1933. Implantation in the groin of the recipient.

Later on, David Hume in Boston (1947) and Lawler in Chicago (1950), using again DCD kidney did not encounter better success; they used the Voronoy surgical technique for implantation. In 1951, a further and definitive step was taken in the surgical technique of kidney transplantation, by the French School in Paris. Dubost, Œconomos, Servelle and Rougeulle were using kidneys procured in guillotined murderers; Küss, Teinturier and Millez, used also the Matson kidney (nephrectomy of a normal kidney for ventriculo-peritoneal shunt placement to treat hydrocephalia). All kidneys were implanted with the French technique: in the right iliac fossa with vascular anastomosis on the iliac vessels (Fig. 6). That technique was used at the Necker Hospital in Paris on Christmas Eve 1952, to transplant Marius Renard with his mother kidney (Fig. 7). Marius had a single kidney, which had to be removed following a trauma (ladder fall). The mother kidney functioned well without any IS therapy during 3 weeks until rejection occurred, followed by recipient death.

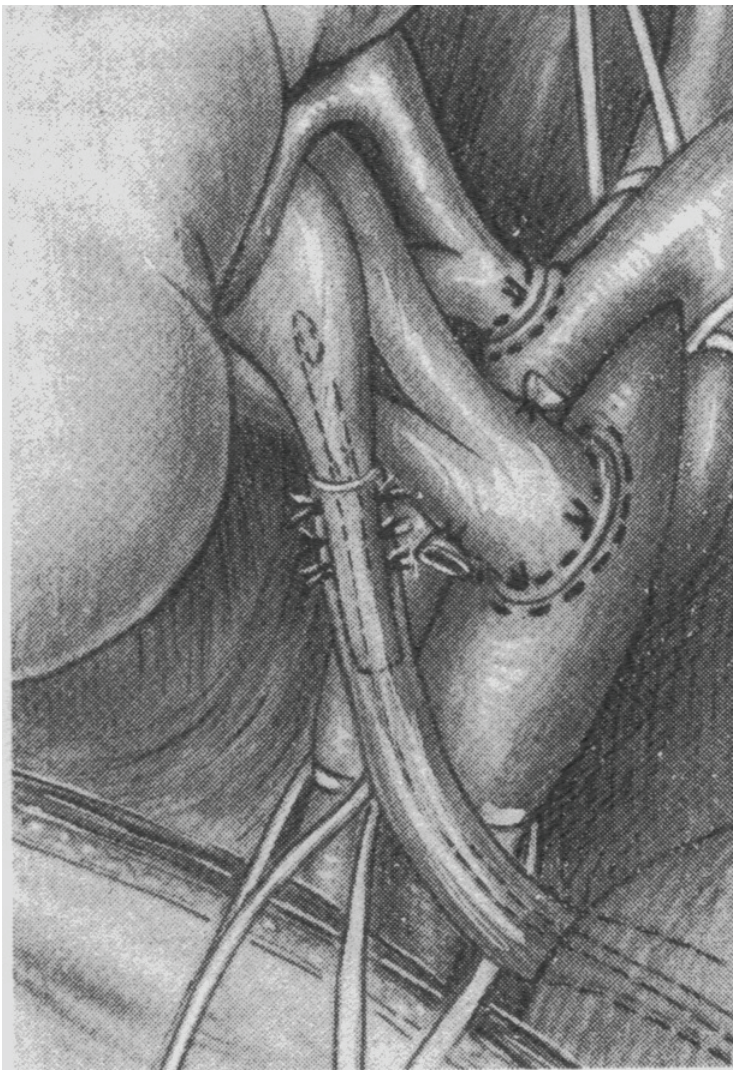
The procedure developed by Küss and the other French surgeons is currently widely used: it inspired Joseph E. Murray, John Merril and their associates at the Peter Bent Brigham Hospital in Boston with their identical monozygotic twin transplantation, which was first attempted two days before Christmas 1954. The US surgeons proved without any IS agents that living renal transplantation could be safely performed for either the recipient who survived eight years, but also, for the donor (Fig. 8) who recently died at the age of 79 years (Murray, 2011)[6]. Following that attempt, other 19 twin transplantations were successfully performed until 1956 with a 30% recurrence rate of chronic glomerulonephritis (CGN). At that time, the principal ingredients of organ transplantation – immunosuppression, tissue matching, organ procurement and preservation – were still unknown or undeveloped. Therefore, the failure of all other types of grafts, usually resulting in the death of the patient, left little room for optimism (Groth & Longmire, 2000)[7].



a. b.

(Küss & Bourget, 1992)[1].

Fig. 6. Surgical techniques for kidneys implantation. a. The groin technique (Voronoy). b. The French technique



(Küss & Bourget, 1992) [1].
Fig. 7. The French technique used for transplanting Mr. Marius Renard at Necker Hospital (1952).

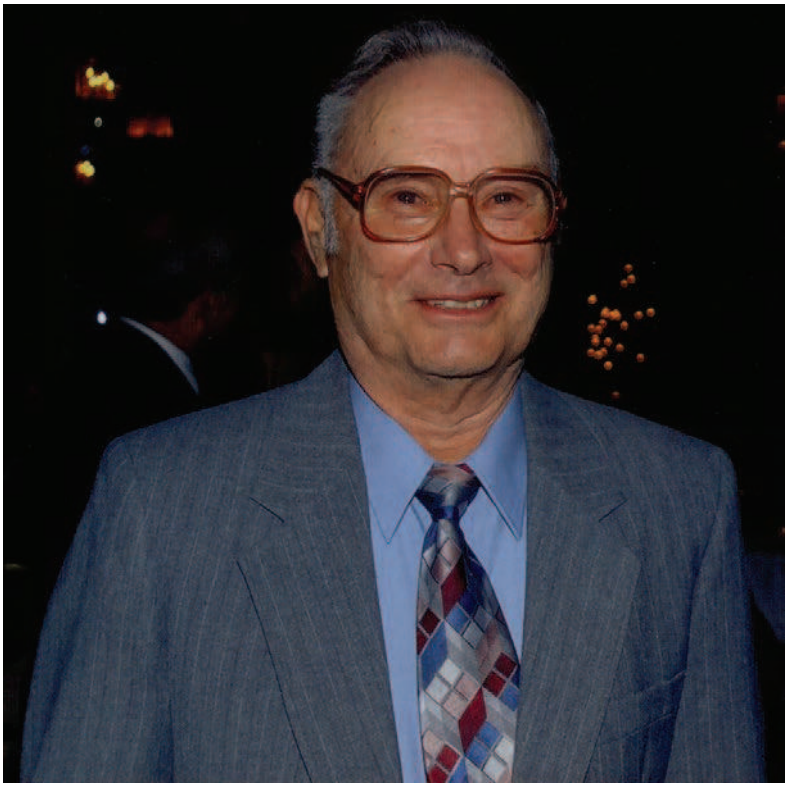


Fig. 8. Ronald Lee Herrick: first living donor for his twin brother, in December 1954 (Murray, 2011) [6].

3. Organ procurement and preservation

The sudden arrival of clinical kidney transplantation during 1962-1963 was so unexpected that little collateral research on the preservation of organs had been done. Kidney transplantation was accomplished at first with total body hypothermia of living volunteer kidney donors using methods developed by cardiac surgeons for open heart operations. In the experimental laboratory, Lillehei et al. simply immersed excised intestine and pancreas in iced saline before its autotransplantation. Thus the principle of hypothermia was understood at an early time, although not efficiently applied (Squifflet et al., 2008)[9].

Today, intravascular cooling is the first step in the preservation of all whole organ grafts. The practice was introduced in 1963 of infusing chilled lactated Ringer's or low-molecular-weight dextran solutions into the renal artery of kidney grafts immediately after their removal. By late 1981, however, it had become obvious that pancreas, liver and thoracic organ transplant procedures were going to be widely used. Methods of multiple organ procurement were required by which the kidneys, pancreas, liver, heart and lungs or various combinations of these organs could be removed without jeopardizing any of the individual organs (Squifflet et al., 1990)[10]. With these methods, all organs to be transplanted are cooled in situ, rapidly removed in a bloodless field, and dissected on a back table (Fig.

9). Fluids of differing osmotic, oncotic, and electrolyte composition are infused into the allografts before placing them in a refrigerated container. The solution described by Collins et al. or modifications of it (Eurocollins®) were used for almost two decades. Renal allograft preservation was feasible for 1 to 2 days, long enough to allow tissue matching and sharing of organs over a wide geographic area (Squifflet et al., 1981)[8]. The introduction of the University of Wisconsin (UW) solution to pancreas, firstly, and then, liver transplantation in 1988 by Belzer, Jamieson and Kalayoglu was the first major development in static preservation since the Collins solution. The superiority of the UW solution for preservation of kidneys and other organs was promptly demonstrated and confirmed in clinical trials.

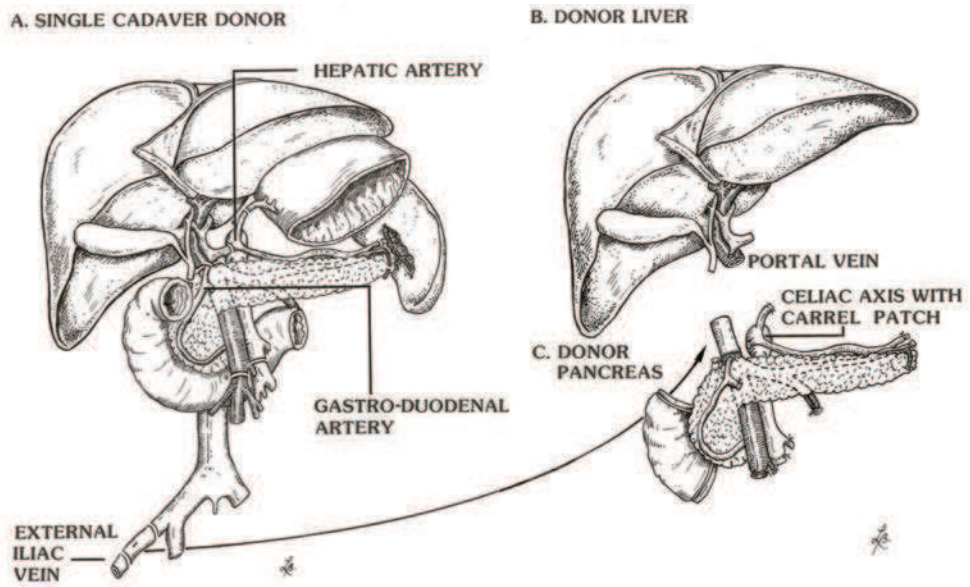


Fig. 9. Maneuvers for en-bloc removal of a whole pancreas and a liver from a cadaver donor with normal vascular anatomy. The gastroduodenal artery must be divided so that the common and proper hepatic arteries can remain in continuity and be retained with the liver. The portal vein is divided just superior to the entrance of the splenic vein. Then, the pancreatic portion is lengthened by an iliac vein graft. The celiac and superior mesenteric arteries can remain with the pancreas with a Carrel aortic patch (Squifflet et al., 1990)[10].

The ex-vivo perfusion technique also permitted good preservation of kidney or liver allografts. However, the complexity of the method precluded its general use. Thus, it was firstly abandoned in most European kidney transplant centers. A renewal of interest in the perfusion technique resulted from the lack of brain-dead cadaveric donors and the search for other sources such as the non-heart beating donors, or extended criteria donors (ECD). In these types of DCD kidneys, agonic ischemic damages are happening. They could be evaluated by a period of re-conditioning on machine perfusion prior to implantation (Moers et al., 2009)[11].

4. The concept of immunosuppression and need for pharmacological agents in transplantation

After Medawar's demonstration in 1944 that rejection was an immunological event, a logical and inevitable question was how to protect the organ allograft by weakening the immune system (Table 2).

Firstly Owen, Medawar and Billingham discovered the phenomena of neonatal tolerance, demonstrating that it was possible to prevent immune responses to allo-antigens. Secondly, works by Dausset and others (Payne, Van Rood, Bodmer, Amos, Ceppellini, Terasaki, Bach and Batchelor) defined what allo-antigens were, namely the major histocompatibility complex (MHC), which in humans is called HLA. Finally, an explosion of information about how the immune system works and further studies on the MHC have led to the concept of tissue typing, histocompatibility and cross-matching. Studies in the early 1960s defined the function of lymphocytes and identified separate roles for T cells (cellular immunity) and B cells (humoral immunity). The T cell receptor and immunoglobulins were discovered, and the role of HLA proteins in presenting antigens to T cells was elucidated (Turka, 2001)[12] (Halloran & Gourishankar, 2001)[13]. Thus, to interfere with that complex reaction, pharmacological agents were introduced for controlling rejection.

Year	Author	Discovery or application
1901	Landsteiner	Discovery of ABO blood groups
1944	Medawar	Rejection as an immunological event
1952	Dausset	Discovered first HLA antigens using antiserum from
1958	Van Rood	transfused patients
1964	Starzl	Demonstrated HLA antibodies in pregnant women
1964	Terasaki	Hyper-acute rejection of ABO-incompatible kidneys
1964	Bach	Description of microcytoxicity test
1966	Terasaki	Described mixed lymphocyte culture test
	Kissmeyer-Nielsen	Hyper-acute kidney rejection with antigraft
1967	Van Rood	lymphocytotoxic antibodies
		First international organ exchange organization (Eurotransplant)

Table 2. A timeline in tissue matching and transplant immunology.

Based upon the demonstration in 1950 that inflammatory diseases could be treated by adrenal steroids, it was natural to apply glucocorticoids to prevent or reserve the severe inflammation of graft rejection.

By the late 1950s, the first attempts to use whole body irradiation to prolong transplant survival were also reported (Halloran & Gourishankar, 2001)[13]. But the real IS options that would allow for successful cadaveric transplantation emerged at the end of the 1950s. During that period, Elion and Hitchings developed 6-mercapto-purine (6-MP) and azathioprine (AZA) (Table 3). By the early 1960s, the practice of using glucocorticoids in conjunction with AZA had been initiated with high-dose steroid used to reverse rejection. The first application of antilymphocyte globulin (ALG) took place in the 1960s. Efforts at immune cell depletion included thoracic duct drainage, irradiation, thymectomy and splenectomy.

In 1963, during a first International Transplantation Congress in Washington, 244 renal allografts were reported. Among them, 28 identical twin transplants. Starlz reported also the first three attempts at orthotopic liver transplantation in humans as well as 25 over 27 successful renal transplantations using 6-MP (Table 1).
With the emerging IS therapy, it was also a period in which attempts of xenografting took place and quickly abandoned.
By the late 1970s, the centers that had access to ALG were reporting improved survival rates in kidney transplantation. However, many patients experienced severe steroid side effects. Graft survival remained poor and only kidney transplants were performed in significant numbers with good success (Squifflet et al. 1981)[8].
The discovery of cyclosporine (CsA) and its first clinical use in 1978 changed transplantation. Results also improved with widespread access to effective ALG - polyclonal antibodies (Ab) therapy and later with the first monoclonal Ab therapy muromonab-CD3 - , which can reduce reliance on high-dose steroids. Many improvements in medical, surgical, anesthetic, and intensive care management improved clinical results. The growth in transplanting hearts, livers, pancreases and lungs, has created the transplantation programs of the present day. CsA, which blocks the transcriptional activation of IL-2 and others cytokines in T cells, made a significant contribution to the basic science of T cell activation.
Tacrolimus (Tac) differed from other drugs in that much that its early development occurred in liver transplants, rather than in kidneys. Acting by the same mechanism as CsA, Tac binds to abundant intracellular protein to create a complex that inhibits the enzyme calcineurin. By the late 1980s, Tac was introduced for use in organ transplants. Today, it is the most common and largely used IS drug.
Mycophenolate mofetil (MMF) is an agent derived from the older drug, mycophenolic acid, which is a potent inhibitor of de novo purine synthesis in lymphocytes and highly effective in combination with CsA and Tac in preventing acute rejection in humans.
Rapamycin (or Sirolimus-Sir) had been discovered in the 1970s as an antifungal, but the potential of its IS properties for commercial development was not recognized until the late 1980s. Large-scale trials have demonstrated its potential and have led to its recent approval for use in kidney transplantation (Table 3).

Year	Immunosuppressive milestones
1950	Glucocorticoid therapy in immune diseases
1959	6-mercaptopurine and azathioprine (AZA)
1968	Polyclonal antilymphocyte globulin (ALG)
1978	First clinical use of cyclosporine (CsA)
1981	Introduction of murine monoclonal anti-CD3 to reverse rejection
1989	First clinical results with tacrolimus (Tac)
1991	First report of clinical use of mycophenolate mofetil (MMF)
1998	First report of clinical use of rapamycin (Sirolimus-Sir)

Table 3. A timeline in transplant immunosuppression.

As the third millennium begins, new humanized or chimeric protein products are becoming available (anti-Il2 receptors; anti-CD2; anti-CTL4 Ig; anti-CD3; anti-CD40 ligand; …). Gene therapy and new classes of agents such as FTY720, FK778, peptides and antisense oligonucleotides are currently being evaluated to determine their potential. The new priority

is reduction in toxicity with equivalent efficacy. However, immunosuppression would be tailored by better laboratory measurements of the immunological status, ischemic reperfusion injuries, and stability (Halloran & Gourishankar, 2001)[13].

5. The history of Deceased Donor (DCD) transplantation in Belgium

5.1. The first cadaver – Heart Beating Donor (HBD) – kidney transplant in Belgium

In 1962, Professor G.P.J. Alexandre obtained a fellowship for a year of surgical research to be spent in the laboratory of the Harvard Medical School in Boston, under the direction of Professor Joseph Murray, in the Department of Surgery of the Peter Bent Brigham Hospital directed by Professor Francis D. Moore (Squifflet, 2003)[14]. His initial U.S. contact in Boston was with Professor Roy Calne who was packing to return to England, in whom he put his trust to look at the surviving dogs from his experiments. The dogs were receiving the BW – 57322 – the actual Azathioprine (AZA) – as well as other drug combinations including Azaserine and Actinomycin D. The later drug combination was considered good enough to be used in clinical practice (Fig. 10).

CLINICAL CONGRESS NEWS

American College of Surgeons

Founded by Surgeons of the United States and Canada, 1913

ATLANTIC CITY, N. J., TUESDAY, OCTOBER 16, 1962

Azaserine-Imuran Gives 20-Day, 100% Survival In Canine Homografts

Azaserine plus imuran is the best combination tested thus far in the prolongation of functional survival of canine renal homografts, Guy P. J. Alexandre, M.D. and Joseph E. Murray, M.D., F.A.C.S., of Peter Bent Brigham Hospital and Harvard Medical School, Boston, told the Forum on Fundamental Surgical Problems Monday. A 20-day survival in 100 per cent of animals indicates the drug has at least a minimal beneficial effect in all animals.

Maung M. Than, M.D., Peter R. C. Bina, B.A., Carlos Martinez, M.D., and Karel B. Absolon, M.D., of the University of Minnesota, Minneapolis, reported studies demonstrating that immaturity, genetic relationships and thymectomy play a role in rejection of skin homografts in dogs.

Methotrexate in doses of 0.15 to 0.5 mg./kg. prolonged skin graft survival in the dog, it was shown in a study by Herbert B. Hechtman, M.D., David A. Blumenstock, M.D., E. Donnall Thomas, M.D., and Joseph W. Ferrebee, M.D., of Mary Imogene Bassett Hospital, Cooperstown, N. Y. BW-57-322, an analogue of 6-mercaptopurine, was less effective. Combined treatment pro-

(Continued on Page 6)

Too Many General Surgeons In Their Communities, Say General Surgeons In New College Survey

Dr. Reed M. Nesbit points to reporter at Sunday press conference on surgical practices survey made by College. Dr. Nesbit is chairman of committee which planned survey. Seated to his right is Dr. Loyal Davis and standing behind them is Dr. Robert S. Myers. Wearing spectacles, Director John Paul North looks on.

General surgeons in the College typically feel that there are too many much surgery is done by physicians not recognized as specialists? Where? Are

Fig. 10. Proceedings of the Meeting of the American College of Surgeons, Atlantic City, October 16, 1962.

Azathioprine plus Imuran is the best combination tested; a 20-day survival in 100% of animals. Therefore, Professor G.P.J. Alexandre returned to Belgium with both drugs in his luggage. Since no chronic dialysis apparatus was available in the Department of Surgery at Saint Pierre Hospital in Louvain where Professor G.P.J. Alexandre was completing his surgical

training, first candidates for renal transplantation were maintained on peritoneal dialysis, performed by medical students on a voluntary basis, in 24-hour rotation.
On June 3, 1963, a patient was brought in the Emergency Department with a head injury and a profound coma. Despite active resuscitation and vasopressive drugs administration, the patient presented all the signs of what Mollaret had previously described and named "coma dépassé" (Mollaret & Goulon)[15]. Professor Jean Morelle, who was the Chief of the Department of Surgery and also experienced in neurosurgery, took the most important decision of his career: to remove a kidney from that patient while the heart was still beating. Moreover, and by contrast to Professor Hamburger's donor management (Legendre & Kreis, 2010)[16], they stopped the mechanical ventilation, immediately after kidney procurement, waiting for the heart beat stop in the OR. No preservation fluid was used; the blood contained in the transplant was not even washed away; the graft functioned immediately without any tubular necrosis (Delayed Graft Function) and the patient's serum creatinine normalized in a few days. The patient died on day 87 from sepsis; at that time of death, three other patients had been transplanted with that effective drug IS regimen. The third patient was transplanted with a living donor kidney (patient's uncle) while the fourth, with a cadaver kidney: both had long term function, more than six years. In this way the kidney transplant program of Professor Alexandre was launched. From then on, the number of transplants performed annually has increased progressively and reached a mean stable number of 100 transplants per year in 1978 when the Department moved to Unit 22 of the Clinic Saint-Luc in Brussels and Professor Jean-Paul Squifflet joined the team. Professor Alexandre left in January 1992 while Professor Squifflet moved to Liege, CHU Sart Tilman in October 2005. From 1963 to 2005, during 42 years, 3.355 renal transplants have been performed (Table 4 and Table 5) (Squifflet J.P., 2007)[17].

Organ	First transplant	Number	
		Total	Live donor
Kidney (Total)	June 3, 1963	3.355	501
Kidney + liver	February 2, 1987	23	
Kidney + heart	February 23, 1986	8	
Pancreas (Total)	November 10, 1982	89	
Pancreas + kidney (SPK)	November 10, 1982	83 (in 82 recipients)	
Pancreas alone (PTA)	February 5, 1983	3	
Pancreas + liver	September 22, 1988	1	
Pancreas after liver	April 4, 1998	1	
Pancreas after failed Kd (SPK)	May 11, 1999	1	
(Islets after kidney)	(October 13, 2002)	(2)	

(Squifflet J.P., 2007)[17].
Table 4. Total number of Organ (Kidney and Pancreas) Transplantations at Saint Pierre Hospital in Louvain (June 3, 1963 to October 30, 1977) and Saint-Luc Hospital in Brussels (November 1, 1977 to September 30, 2005) by G.P.J. Alexandre (June 1963 to October 1991) and J.P. Squifflet (January 1978 to September 30, 2005)

Year	Application
June 3, 1963	First cadaver kidney transplant First heart beating donor First use of AZA and steroids
August 24, 1963	First living related donor renal transplant
January 20, 1965	First haemodialysis
January 20, 1966	First living unrelated donor renal transplant with thoracic duct
June 10, 1966	drainage preparation
1967	First birth of baby from mother kidney recipient
November 8,	Creation of Eurotransplant Foundation
1967	Use of home-made ALG (antilymphocytic globulins) for rejection
March 31, 1971	treatment
September 1976	First pediatric kidney transplantation
November 1977	Use of Eurocollins solution for kidney preservation
January 1978	Move from Saint Pierre Hospital in Louvain to Unit 22 Saint-Luc
	Hospital in Brussels
June 30, 1978	Induction therapy with ALG vs ATGAM
October 1982	AZA and steroids
November 10,	First ABO-incompatible living related donor transplantation
1982	Introduction of cyclosporine A (CsA)
February 5, 1983	First simultaneous kidney and pancreas transplantation in Belgium
March 1985	First pancreas transplant alone in Belgium
March 1985	Introduction of OKT3 for treating acute rejections
February 23,	Honoris Causa: Professor D.E.R. Sutherland, Professor T. Starzl,
1986	Professor J. Van Rood
June 13, 1986	First simultaneous heart and kidney transplantation
February 2, 1987	Belgian law on organ donation and transplantation (presumed
	consent)
July 15, 1987	First simultaneous liver and kidney transplantation
November 7,	Birth of (the 3rd world) baby girl after SPK transplantation
1989	Introduction of bone marrow infusion after kidney transplantation
September 23,	Introduction of deoxyspergualin in kidney transplantation

1992	First use of LoCD2a/BTI-322/MEDI-507 monoclonal Ab in a human
October 12, 1993	kidney recipient
October 18, 1993	Introduction of mycophenolate mofetil (MMF) in kidney
February 17,	transplantation
1997	Introduction of tacrolimus (Tac) in kidney transplantation
March 2, 1997	First video assisted live donor nephrectomy in Belgium
January 1998	Introduction of sirolimus (Sir) in kidney transplantation
December 1998	Start of the EURO-SPK 001 trial
January 31, 2001	Implementation of N.H.B.D. program
June 25, 2001	Introduction of FTY 720 in kidney transplantation
January 2002	Introduction of FK 778 in kidney transplantation
October 13, 2002	Start of the EURO-SPK 002 trial
	First human islet grafting

Table 5. A timeline of the kidney and pancreas transplantation Program at Saint Pierre Hospital in Louvain (June 3, 1963 to October 30, 1977) and Saint-Luc Hospital in Brussels (November 1, 1977 to September 30, 2005) by G.P.J. Alexandre (June 1963 to October 1991) and J.P. Squifflet (January 1978 to September 30, 2005).

5.2 From the brain death concept to the Belgian law on organ donation and transplantation

In November 1957, Pope Pius XII released an important statement for the Catholic Church: he defined death as the "*complete and definitive separation of the soul and the body*" and distinguished "*human life from the mere life of the organs*". He stated also that a Christian "*has to accept the necessary treatments to preserve life and health*" but that "*usually this duty…requires only the use of ordinary means*". The Pope declared furthermore that the treatment of a patient in deep coma without any hope of recovery may be stopped even if this provokes cardiac arrest: "*the interruption of resuscitation attempts is only indirectly the cause of cessation of life*". For deciding when exactly the soul leaves the body, if it is when the brain is destroyed or when the heart stops beating, the Pontiff avoided to answer the question: "*the answer cannot inferred from any religious or moral principle and from that angle is not within the competence of the church*". On the contrary, he charged the clinicians "*to give a clear and precise definition of death and the moment of death of a patient who dies in a state of unconsciousness*" (Kinnaert, 2009)[18]. It was also the period during which Mollaret and Goulon proposed the term "coma dépassé" to describe the absence and complete destruction of cerebral functions in order to stop prolonging futile resuscitation (Mollaret & Goulon, 1959)[15]. Even if the concept was admitted in the transplant community, most of the surgeons were waiting for the heart beat stop before starting the procurement (Legendre & Kreis, 2010)[16]. The further step, taken by Professor Alexandre, in disconnecting the body in the OR after the kidney procurement was eventually more difficult to accept. Indeed, even T. Starzl who had performed the first

cadaver liver transplantations in 1963 did not apply it before his participation to the Ciba symposium in London in 1966 on Ethics in Medical Progress (Squifflet 2003)[3] (Kinnaert, 2009)[18], (Ethics in Medical progress, 1966)[19]. The discussions he had with Professor Alexandre illustrate well all doubts that people had during that period.

Alexandre:"*Dr. Gierts spoke about taking organs from a dying person. I would like to make it clear that, in my opinion, there has never been and there never will be any question of taking organs from a dying person who has "non reasonable chance of getting better or resuming consciousness". The question is of taking organs from a dead person, and the point is that I do not accept the cessation of heart beats as the indication of death. We are as much concerned with the preservation of life in a dying person as with the preservation of life in a fœtus: but I think irreversible damage to the central nervous system is an indication of physiological death that permits us to take an organ from a body that is already a cadaver.*"

Starzl: "*Dr. Giertz has drawn a distinction between the Stockholm case and the practice in Belgium which seems to me to be largely quantitative. I assume that when kidneys are removed from "living cadavers" in Louvain, only one organ is removed, so that the patient is not thereby killed. How long did your patients continue to be heart-lung preparations, Dr. Alexandre? Were there any specific differences in the subsequent care of your cases and of the Stockholm patient? The Swedish patient continued to be on the respirator after the kidney was removed. If, in your practice, the respirators is turned off immediately after the kidney is removed this could very easily explain the different survival times of less than one hour in Belgium, and 48 hours in Stockholm.*"

Alexandre: "*In our nine cases we switched off the respirator immediately after the kidneys were removed. The heart beats of all the patients ceased within two or three minutes. In my opinion it is irrelevant whether a heart-lung preparation goes on for two days or even for weeks: it is still a heart-lung preparation and for us it is still a dead person.*"

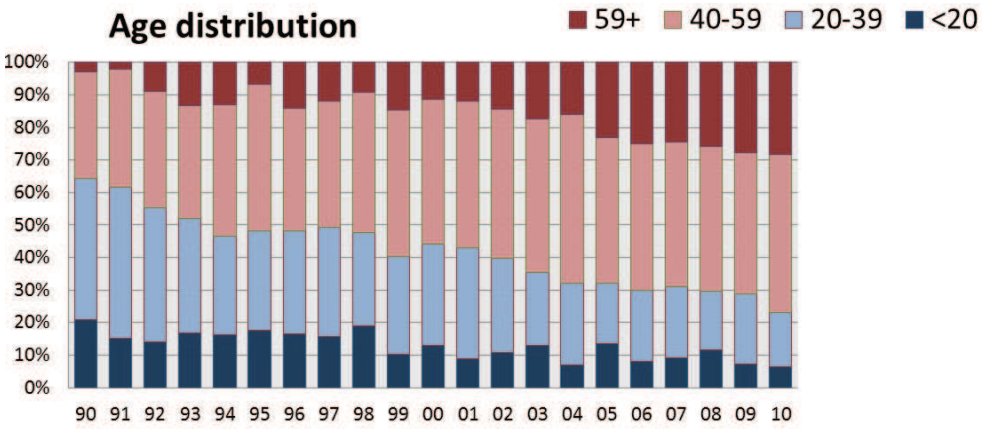
Starzl: "*The notion of permitting removal of our organs while we still have a circulation is an important one. Personally I would agree to this for myself, but I could not permit this to be done to a member of my family.*"

Nevertheless, that example was followed by other teams in Belgium and in most countries. In 1968, the French Heath Authorities published the "circulaire Jeanneney" following the Ad Hoc Committee of the Harvard School of Medecine (Ad Hoc Communitie, 1968)[20]. It opened the door for the first world pancreas transplantation by Kelley and Lillehei (1966), the first heart transplantation by Christian Barnard (1967) and the first heart transplantation in France by Cabrol (1968).

In Belgium, the first lung transplantation was performed by Fritz Derom (1968), the first adult liver transplantation by P.J. Kestens (1969) and soon later (1970) in children by J.B. Otte, the first heart transplantation by G. Primo (1973) and the first pancreas transplantation by J.P. Squifflet (1982).

Finally, the Belgian Transplantation community had to wait until June 1986 to get a law on Organ Donation and Transplantation. It includes an opting out system. Indeed, the transplant surgeon cannot start any organ procurement if the donor has expressed opposition at the National Registry, or if opposition is communicated in any way to the surgeon. Until 2007, it has been a soft version of the presumed consent principle because a first degree relative could oppose the procurement. A new step was taken in 2007 by suppressing this possibility and therefore turning the presumed consent principle into a strong version. Other important elements of the Belgian Act are that death is not defined – it could be brain death or cardiac death – but must be reported by 3 physicians and violent death must be also reported to the Public prosecutor (Squifflet A.C., 2011)[21]. Like other

European countries with presumed consent laws, Belgium was, in 2007 – and is still - , one of the leading countries for Multiple Organ Donors, with 27.5 cadaver donors by million inhabitants (pmi) and 86.5 cadaver organ transplants pmi (43.0 kidneys; 22.7 livers; 8.7 lungs; 6.7 hearts; 5.3 pancreases/islets). As others, Belgium is also facing challenges such as aging donors, the use of extended criteria donors (ECD) and donors with cerebral bleeding as the main cause of death (Fig. 11) (Roels & Rahmel, 2011) [22]. That's why the Eurotransplant (ET) organization had developed its ET Senior Program (ESP) and the use of non-heart beating donors (NHBD), the so-called deceased after cardiac death donors (DCD) by opposition to the brain death donors (DBD).



Average age 2010 effective donors: 50 yrs.
Youngest donor: 1 year – Oldest donor: 89 years.
46% women/54% men in 2010.
Fig. 11. Age distribution of (effective) donors between 1990 and 2010 in Belgium.

5.3 The first cadaver pancreas transplant in Belgium

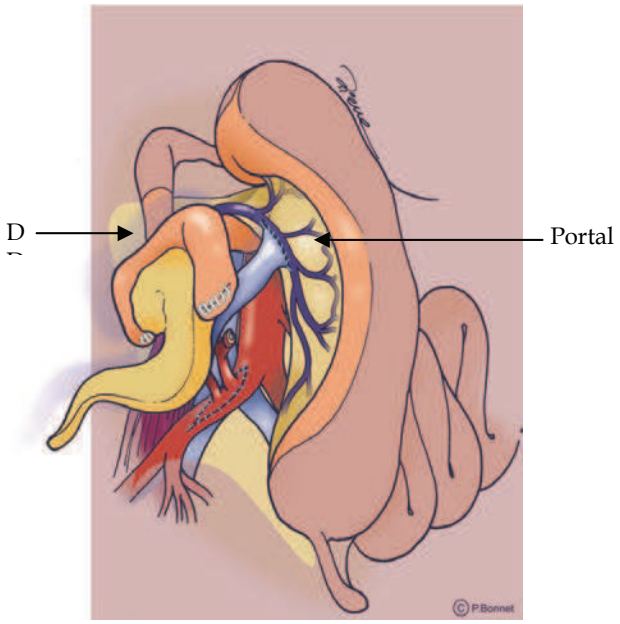
Professor J.P. Squifflet joined Professor G.P.J. Alexandre staff in 1978. After a research fellowship in transplantation at the University of Minnesota in Professor J.S. Najarian department, under Professor D.E.R. Sutherland's supervision, he started a program in pancreatic transplantation in Brussels and performed the first Belgian simultaneous pancreas and kidney transplantation (SPK) in November 10, 1986 (Tables 4 and 5). The women recipient was also one of the first who received cyclosporine A (CsA) as the basic drug in the IS regimen. CsA was used at the dose of 14 mg/kg/day, considered today as a toxic dosage but also in combination with low doses of steroids. The second pancreas transplant was a segmental pancreas transplant alone (PTA). It was performed on a diabetic recipient with pre-end-stage renal failure, in January 1983. Unfortunately, it never functioned due to ischemic damage, pancreatitis and vascular thrombosis. It was promptly removed. By contrast, the first patient rapidly recovered from her double operation; that led to a series of 10 SPK procedures in 10 patients using a segment of pancreas anastomosed to a Roux-en-Y loop. SPK patient number 9 was transplanted in January 86 after chronic rejection of a first cadaver kidney graft. One year later, she delivered a baby girl: she was the third woman ever in the world to enjoy a successful pregnancy after pancreas

transplantation. Despite her nephrologist's "disapprobation" she gave birth to a second baby boy in December 1990.

On September 22, 1989, with Professor B. de Hemptinne, J.P. Squifflet performed the first simultaneous liver and pancreas transplant on a 34-years-old man with a type 1 diabetes and a cryptogenic liver cirrhosis. One year later, the patient was back on insulin therapy with a well functioning liver graft. He asked for a second cadaveric pancreas graft that he received on April 4, 1998. Unfortunately, it stopped functioning after several months. A high level of anti-islet antibodies was demonstrated, confirming the recurrence of the type 1 diabetes auto-immune disease (Squifflet, 2007)[17].

The human islet program started in October 2002. The program benefited from the Edmonton experience but it did not succeed in reaching insulin independency with only one pancreatic organ for islet preparation. Therefore that activity remained marginal.

While moving the pancreas transplantation program to the University of Liege, a new surgical technique was implemented (De Roover et al., 2007)[23] and developed with mechanical sutures (De Roover et al., 2008)[24]. It consists in implanting the whole pancreas with a duodenal segment, with portal drainage (into the superior mesenteric vein) of the venous effluent of the pancreatic graft and exocrine diversion to the recipient duodenum. The latero-lateral duodeno-duodenostomy could be done using running sutures or mechanical staplers (Fig. 12). The advantage of that new technique is to allow pancreatic graft monitoring, and duodenal mucosa biopsy through serial endoscopy (Squifflet et al., 2008)[11].



DD: latero-lateral duodeno-duodenal anastomosis.
Portal: portal venous drainage in superior mesenteric vein (De Roover et al., 2007)[23].
Fig. 12. Whole pancreas transplantation technique with enteric drainage and portal drainage.

5.4 Current challenges in Donation after Cardiac Death (DCD)

Like in Austria and Spain which have a huge activity in DBD organ procurement, in Belgium it took almost 40 years to start with DCD organ procurement (Squifflet, 2006)[25]. The main reasons are multiple.

In 1995, the first international workshop on DCD – during that period, one was speaking of Non-Heart-Beating Donors (NHBD) – took place in Maastricht (The Netherlands) where the 4 categories of DCD were defined and published with 12 statements and recommendations (Kootstra et al., 1995)[26]. That was eventually approved by the European Council.

"1. The fact that NHBD organs have to be considered for transplantation is a direct result of the shortage of donor organs in view of the fact that the waiting list continues to increase. The use of NHBD organs can be valuable way to enlarge the number of organs for transplantation.

2. Only sparse data are available on the potential number of NHBDs and the cost of the procedure. More information should be collected to evaluate the efficiency of the procedure.

3. The concept of NHBD is evolving. Therefore, it is important to show that the results are good. Inclusion of NHBD data in registries is necessary.

4. For flush out and preservation methods, one should use solutions that are state of the art. Machine perfusion for kidneys should be considered.

5. No NHBD program should be started without a written protocol approved by the local medical ethical committee.

6. For better understanding and consistency, future reports on analysis concerning procurement and transplantation of NHBD organs should refer to the "Maastricht Categories".

I	*dead on arrival*
II	*unsuccessful resuscitation*
III	*awaiting cardiac arrest*
IV	*cardiac arrest in a brain-dead donor*

7. Category II and III NHBD procedure should only be started 10 minutes after cessation of cardiac massage and artificial ventilation to ensure the "dead-donor rule".

8. Warm ischemia time in NHBDs should be counted from the moment of cardiac arrest until the start of hypothermic flush out, irrespective of the period of cardiopulmonary resuscitation.

9. Better methods for viability testing of NHBD organs should be developed.

10. As in HBD procedures, the diagnosis of death in a NHBD has to me made by (a) physician (s) independent of the procurement team.

11. Public education and openness concerning NHBD are mandatory to keep public trust and to prevent backfiring on the HBD programs.

12. Opting-out or presumed consent systems allow placement of a preservation device before contact with the family. In countries with opting-in legislation, legal approval for placement of such devices should be sought."

Between 1995 and 2003, the Belgian National Council of Physicians established rules for implementing the DCD program according to the local law. Moreover, all 7 transplant centers had to get a formal approval from their own local Ethical Committee.

Finally, it was obvious that such a DCD program could not start without having access to machine perfusion for kidney preservation and re-conditioning. With the help of ET, a large international multicentric study was set up, comparing cold storage and machine perfusion for kidney preservation. In brief, the study demonstrated that 1 year kidney graft survival was 12% higher in recipient of a machine perfused graft which presented a PO delayed graft function (DGF) compared to recipients of a cold storage preserved graft. The length of DGF

was also significantly shorter as well as the time for GFR recovery (Moers et al., 2009)[13] (Jochmans et al., 2010)[27]. That study helped the Belgian Centers to implement the use of DCD without jeopardizing the DBD procurement rate (Fig. 13).

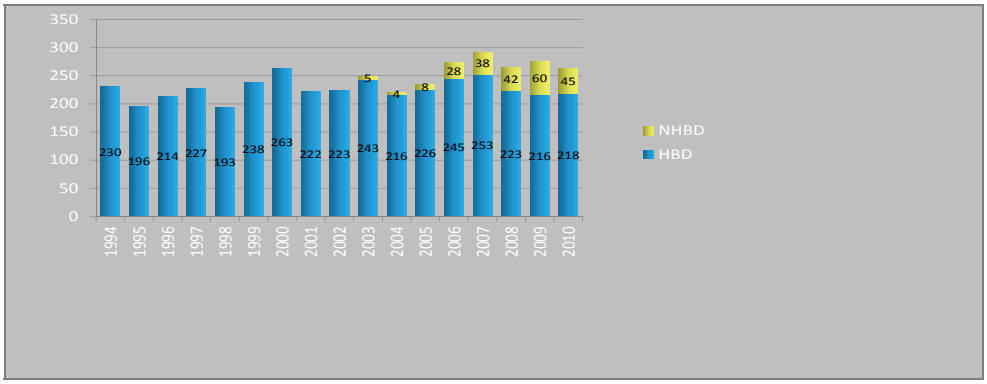


Fig. 13. Effective donor number in Belgium between 1994-2010.
In 2009: 44% University Hospitals – 56% collaborative Hospitals.

At the University of Liege (Le Dinh et al., 2011)[28], the use of DCD had as consequence to double the number of donors (Fig. 14 a), to double the number of kidney transplants (Fig. 14 b), and to 1 ½ time increase the number of liver transplants (Fig. 14 c). But it remains several issues to be solved.

5.4.1 The length of the « no touch » period

The Maastricht statement/recommendation n°7 is proposing a 10 min no-touch period after cessation of cardiac massage for Categories II and III. Indeed Category IV does not need a no-touch period as the cardiac arrest is occurring in a DBD. By contrast, 10 min might be too long if one considers that in categories II and III, the brain has already suffered from irreversible injuries. Then, the Pittsburgh School of Medicine protocol proposes a 2 min waiting time (Institute of Medicine, 1997)[29]. Today, there is a national consensus between all Belgian Centers to declare that a no-touch period of 5 minutes could be enough, but it has not been formally set up yet.

5.4.2 The comfort therapy

Even if intensivists are respecting and protecting all dying patients, they agree to avoid futile sufferances while accompanying the patient in his agonic phase. By contrast, others (Feng S., 2010)[30] think that obstacle against administration of drugs could be the logistics of individual and institutional informed consent for the donor and the potential organ recipients. For the above reason, most intensivists are administering what they call a comfort therapy, while withdrawing the unnecessary support. Therefore improved education of health care professionals and providers on the early recognition and special needs of this DCD population i.e. comfort therapy and implementation of clinical protocol should improve the yield of transplantable organs. Aggressive donor protocols will include early aggressive clinical management of DCD donors including comfort therapy. It requires the help of dedicated health care specialists.

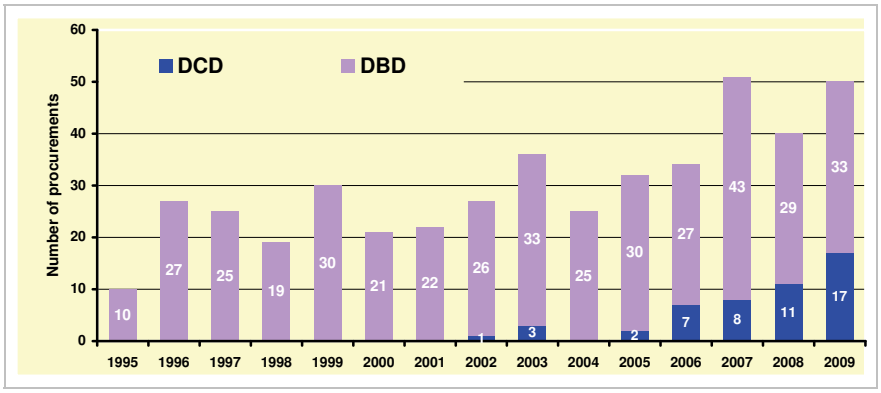


Fig. 14a

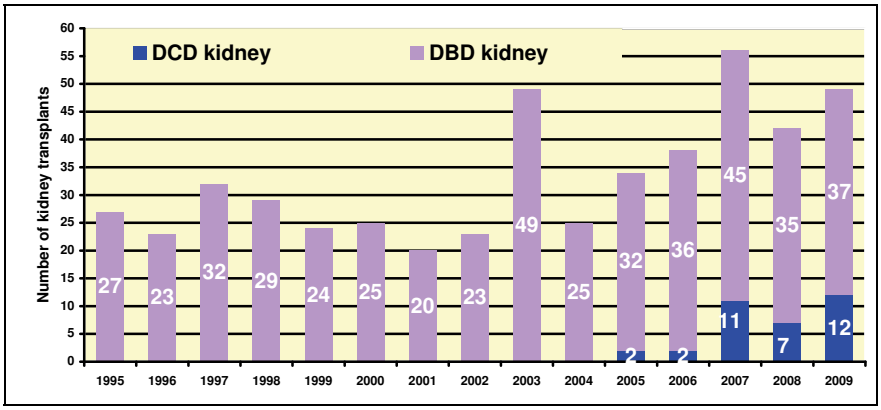


Fig. 14b

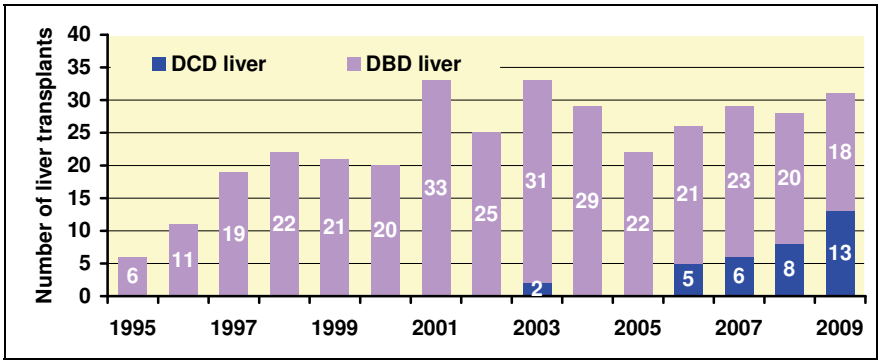


Fig. 14c

Fig. 14. Proportion of DCD/DBD donors (a), kidney (b) and liver (c) transplantations between 1995 and 2009 at the University of Liege (Hieu et al, 2011)[28].

5.4.3 The DCD management: Monitoring awaiting cardiac arrest and drug administration

Unfortunately, today DCD management varies from hospitals to organ procurement organizations, from physicians, nurses, administration and institutional review boards along with donor families (Feng S., 2010)[30]. It is worth remembering that donors are not concentrated in a few hospitals but rather scattered throughout the community. Therefore, a primary barrier to donor management is the need to reach consensus across a broad coalition of parties that stem from distinctive spheres.

A second obstacle for making uniform DCD management and drug intervention is the logistics of individual and institutional informed consent for the donor and the potential organ recipients. The definition of human subjects does not encompass DCD after they are legally dead but there is a grey shade period between the decision of stopping futile reanimation with family consent and the recognition of cardiac death, during which DCD management with drug administration takes an important place. That should require the intervention of independent well trained teams working according to ethical consensus and guidelines. The decision of stopping futile reanimation should be taken by 3 physicians, knowing that a small proportion of patients in a vegetative or minimally conscious state have brain activation reflecting some awareness and cognition. Careful clinical examination will result in reclassification of the state of consciousness in some of these patients, in order to avoid subsequent unuseless prolonged warm ischemic time which contra-indicaties DCD organ procurement (Monti et al., 2010)[31]. That should be done according to family wishes. Thereafter, and only thereafter, the DCD organ procurement procedure should be proposed, discussed with the next-of-skin, and informed consent should be obtained. After administration of the comfort therapy (5.4.2.), mechanical ventilation support is withdrawn with or without the endotracheal tube. If extubation is taking place, the tube must be replaced during organ procurement for lungs recovery. Arterial blood pressure is measured via a femoral – better than radial – artery catheter, along with peripheral oxygen saturation (Spo_2) and Fio_2. Systolic blood pressure should decrease lower than 30 mmHg, the heart rate down to zero, along without any Spo_2 waveform. The patient is pronounced dead by the physical examination 5 minutes after the absence of any systemic anterograde blood flow (through the femoral artery catheter) (DuBose and Salim, 2008)[32]. Drug administration, like heparin, is following Ethics guidelines for research with the recently dead (Pentz et al., 2005)[33].

5.4.4 Brain Death monitoring while waiting cardiac arrest

Current DCD organ procurement procedures make DCD heart graft not suitable for transplantation. Usually, cardiac valves are prepared for homografting. Research is also ongoing and consists in putting the heart graft on normothermic machine perfusion system in order to re-condition the graft during several hours before implantation. Nevertheless, if one could monitor for BD during the DCD procurement procedure, it will allow heart and other organs recovery before waiting for cardiac arrest and the end of the no-touch period, while decreasing the warm ischemic time.

The first attempt to monitor a DCD category III, controlled case for BD was done by J.M. Guerit in 2005, using the somatosensory evoked potentials (Guerit et al., 1999)[34]. By the left median nerve monitoring, he observed the disappearance of the P14 wave, while the dropping blood pressure reached the 51/27 mmHg value (Fig. 15).

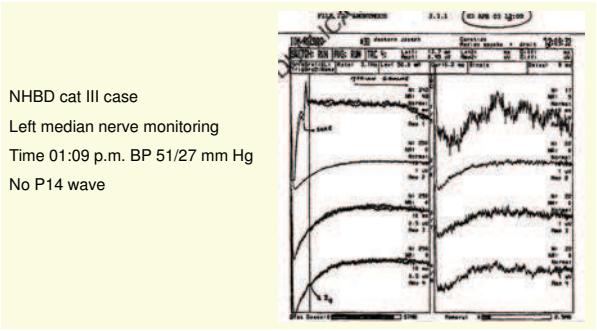


Fig. 15. The brain death (BD) monitoring during the DCD organ procurement procedure (Guerit, 2006)[36]. Disappearance of the P14 wave of somatosensory (left median nerve) evoked potentials with dropping blood pressure.

Another tool, proposed by Auyong et al. is following the bisprectal index (BIS). They presented a case series of increased BIS values during DCD procedure. If these increased BIS values could be a consequence of the catecholamic storm, which could represent a new monitoring tool of BD with the disappearance of BIS. But, limitations of BIS and electroencephelography are well known, the last one being the worst traditionally recommended tool for BD confirmation (Guerit, 2004)[35] (Guerit, 2006)[36]. Nevertheless, if these observed changes were not due to artefact, dosing of hypnotic or anaesthetic drugs might be warranted (Auyong et al., 2010)[37]. Moreover, it will open doors for recovering more DCD organs including hearts for transplantation. But it will need further manipulations to counteract the agonic phase lesions and ischemic injuries, like the intermediate use of machine perfusion for re-conditioning all grafts.

6. The living donor (LD) renal transplantation

The first attempt to LD renal transplantation took place as early as 1962 when no IS drugs were available in Belgium. Indeed, it was a first unrelated LD (LURD) kidney graft which rapidly failed (Kinnaert, 2009)[18]. Soon later, Professor Alexandre was more fortunate in performing living donor renal transplantation (LRD) using the Boston IS regimen. In 1968, he added to the IS armentorium the use of homemade antilymphocyte serum. Horses of the Belgian Police Corps and Army, disqualified for duty, were brought to the Hospital laboratories and injected with thoracic duct lymphocytes. These lymphocytes were being collected from recipients of LD kidneys who, in that period of time, were prepared, during 5 days before the operation, with drainage of the thoracic duct (TDD). After immunization, the horses were bled for extracting the antilymphocyte globulins, for injection into the recipients. Later on, Behringwerke Pharmaceuticals (Germany) took over this preparation known as the Behring horse antihuman ALG (Pressimmum ®) which was still in use until the eighties and from which thousands of patients had benefited. Initially ALG was used to treat steroid resistant acute cellular rejections. Since 1976, it had been used as induction therapy along with Aza and steroids. Moreover in LD recipients, a TDD was added to that protocol along with a per-tranplant splenectomy. In October 1982, CsA was combined to that basic IS regimen: that quadruple drug therapy was the reference treatment for more than 10 years. It allowed using low doses of each IS drug, avoiding toxic side-effects, while

hoping an IS synergistic effect (Squifflet et al., 1982)[38]. During the CsA period, for LD transplantation, TDD and splenectomy were abandoned.

6.1 The pediatric renal transplantation

The real advantages of using LD kidneys over DBD during the pre CsA era became obvious with the first results obtained in the pediatric population comparing parental to cadaver donation (Fig. 16) (Squifflet et al., 1981)[39].

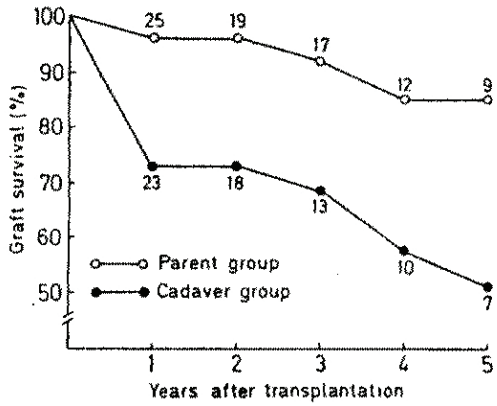


Fig. 16. **Renal Transplantation in Children.**
Graft survival in 32 parental and 35 cadaver graft in pediatric recipients during the pre CsA era (1971-1981). Numbers beside survival curses refer to the number of graft at risk. Difference between the two curses is significant ($P < 0.02$) and reaches > 30% at 5 years (Squifflet et al., 1981)[39].

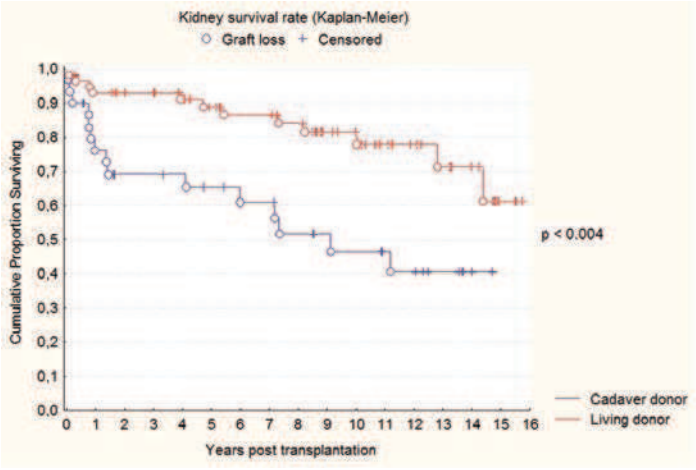


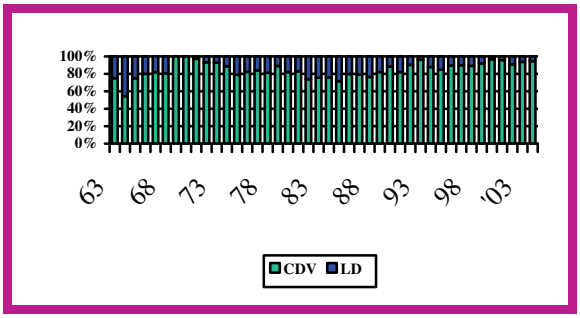
Fig. 17. **Renal Transplantation.** Kidney survival in 56 parental and 26 cadaver graft in pediatric recipients during the CsA era (1983-1994). Difference between the two curves reaches > 30% at 10 years (Malaise et al., 1995)[40].

Twenty years later during the CsA era, that was confirmed in the same pediatric population. Surprisingly, the difference in functional survival rates between the 2 subgroups remained similar but it was more than 30% at 10 years, instead of 5 years (Fig. 17). Even if one year results improved with the CsA use, the slope of the curves were parallel (Malaise et al., 1995)[40].

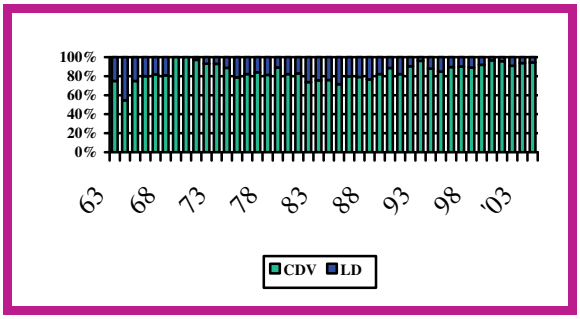
The children experience underlined the advantages of LD over the DBD renal transplantation. It allows donor selection according to strict medical, serological and anatomical criteria. It insures the quality of the grafts and can help for selection of potential live donors according to the HLA matching (twins, HLA identical siblings, parental…). Moreover the procedure can be programmed without any waiting on dialyse i.e. pre emptive procedure. The recipient can also be prepared by donor specific transfusions and/or pre-transplant IS therapy and/or bone marrow infusion or others. Working in 2 separate operating rooms, it can reduce ischemic injuries with a hemodynamically stable donor. Finally it increases donor self-esteem and the cadaver donor pool.

6.2 The Living Unrelated Renal Transplantation (LURD)

In looking at our LD activity (Table.5 and Fig. 18 a and b) the proportion of LD/DBD was globally 18%, but decreased slowly during the last decade, despite LD promotion.



a.

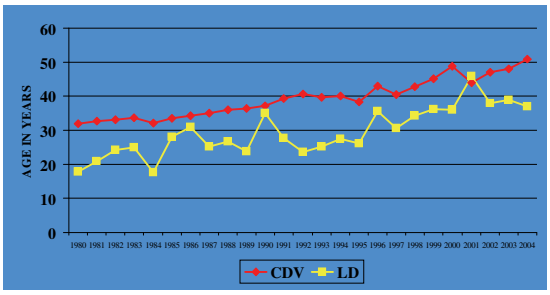


b.

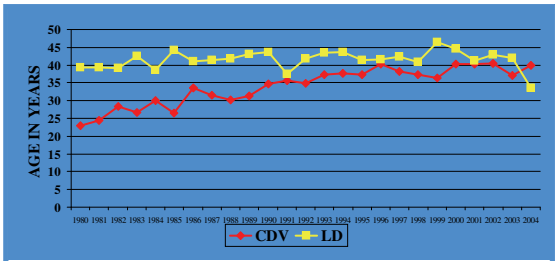
a.: numbers; b.: proportion in %.

Fig. 18. LD/CDV renal transplantation (Prof. G.P.J. Alexandre and J.P. Squifflet activity) from 06/1963 to 12/2004.

The explanation of the phenomena is to be found in looking at mean ages of recipients and donors: for the recipients, it increased from 30 to 50 years and 20 to 40 years for DBD and LD respectively (Fig. 19 a); for the donors, it increased only for DBD from 25 to 40 years but remains stable for LD, around 40 years of age (Fig. 19 b). One can conclude that our selection criteria for the LD did not change over time; for the aging population of recipients, most of their LRD candidates are not fulfilling the donation criteria. Thus, LURD could be another source for renal transplantation; that source in our program, increased slowly over time (Fig. 20).



a.



b.

Fig. 19. evolution of mean ages of recipients (a) and donors (b) from 1980 to 2004 according to donor sources: DBD red curves and LD yellow curves.

The LURD program started in 1966. During the pre CsA era, 17 were performed under AZA and Steroids as the basic therapy, plus ALG for induction, TDD and splenectomy (Squifflet et al., 1990)[41]. With the advent of CsA, 41 new LURD were performed between 1983 and 1996, and were compared to paired 82 DBD renal transplantations (Fig. 21) (Malaise et al., 1997)[42].

It is interesting to note that the donor-to-recipient relationship was 22 wife-to-husband, 9 husband-to-wife, 1 aunt-in-law, 1 brother-in-law, 1 wife's niece, 1 mother-in-law, 4 close friends and 2 family's friends. In that series, LURD renal transplantation offered similar results (Fig. 21 a and b) than DBD, despite poorer HLA-A, B and Dr matching and older donor age. The waiting time on dialysis was shorter; early better graft function was encountered in relation to the reduced total ischemia time and better preparation (conditioning) of both donors and recipients. Moreover the video-assisted donor

nephrectomy technique introduced for the late cases did not increase the incentive to LD (Berney et al. 2000)[43].

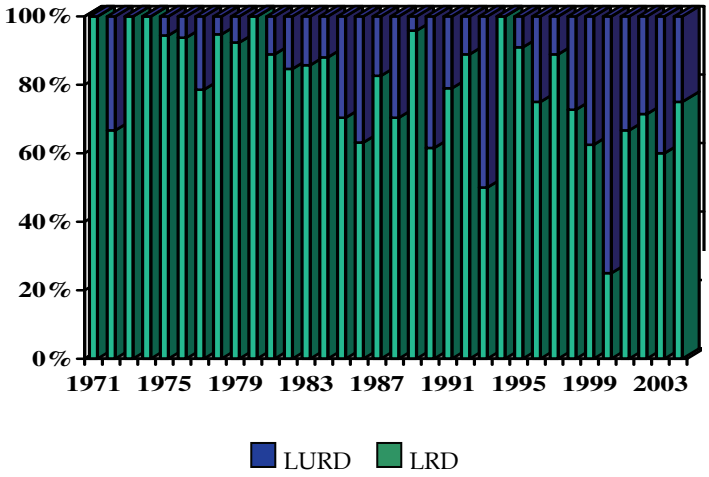
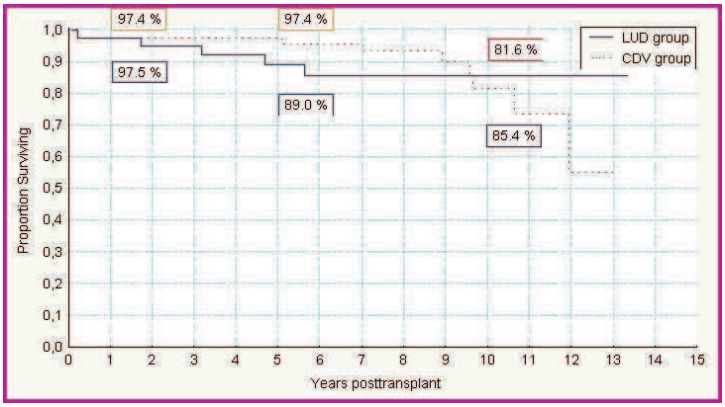
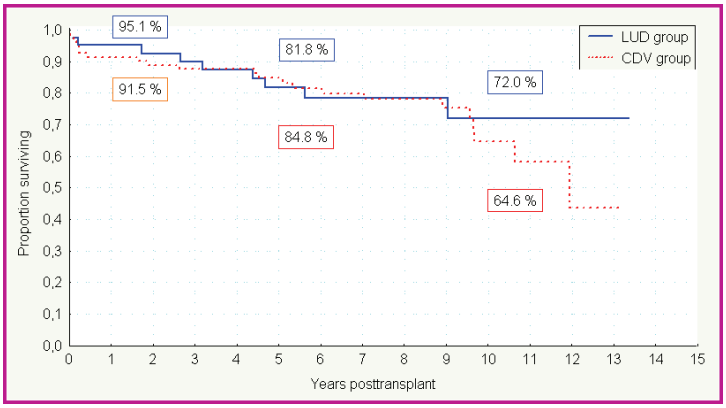


Fig. 20. Proportion LRD/LURD (Squifflet et al., 1990)[41] ; (Malaise et al., 1997)[42].



a.



b.

Fig. 21. Comparison of LURD and DBD kidney transplantations under CsA therapy: similar actuarial patient (a.) and renal graft (b.) survival rates (Malaise et al., 1997)[42].

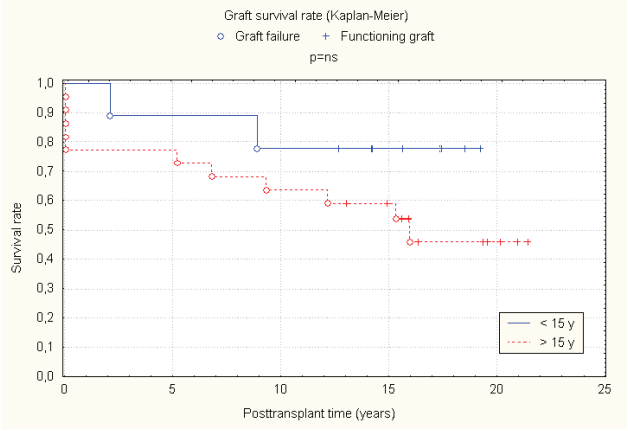
6.3 The ABO-incompatible (ABO-Inc) living donor renal transplantation

Early in 1981, an ABO-Inc cadaver kidney transplant was accidentally performed (blood group A1 into an O recipient). Despite a rejection crisis on the third week with a sharp increase of the anti-A iso-agglutinins, the renal function completely recovered. The patient survived more than 25 years post-transplantation with a functioning kidney graft.

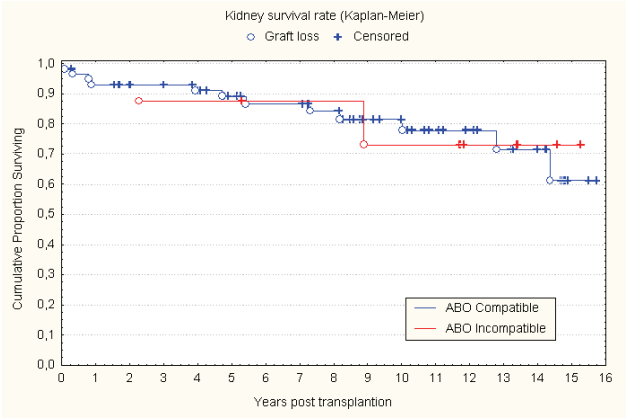
Using a similar approach to that used for achieving ABO-Inc bone marrow transplantation, a series of 39 ABO-Inc live donor kidney transplants (31 related and 8 unrelated donors) was successfully performed (Table 6). The recipients received donor-specific platelet transfusions, 3 to 5 plasmapheresis to get rid of the anti-donor iso-agglutinins and underwent splenectomy at the time of transplantation (Alexandre et al., 1985)[44]. Twenty years graft survival is as high as 76% in the youngest recipients (< 15 years) (Squifflet et al., 2004)[45]. It compares favorably with ABO-compatible LD renal transplantation (Fig. 22 a. and b.).

	N :	Mean age	No RRT Before TP	Death	Graft losses		Functioning graft		
		M ± SD	%		HA Rejection	Chronic Rejection	N :	FU (year) m + sd	Creatinine (mg/dl) m + sd (Median)
Related	**31**	**20 ± 7**	**35**	**0**	**5**	**8**	**18**	**17 ± 3**	**1.9 ± 1.3 (1.5)**
Time to graft loss					11 ± 3 days	9.5 ± 4.8 yrs			
< 15 years	9	11 ± 2	55	0	0	2	7	16 ± 2	1.8 ± 0.6 (1.7)
Time to graft loss						5.5 ± 4.8 yrs			
> 15 years	22	23 ± 6	28	0	5	6	11	18 ± 3	2.0 ± 1.6 (1.4)
Time to graft loss					11 ± 3 days	11 ± 4 yrs			
Unrelated	**8**	**37 ± 9**	**12**	**2**	**4**	**3**	**1**	**20**	**1.0**

Table 6. Outcome of 39 ABO-Inc related and unrelated living donor (LD) kidney transplantations.



a.



b.

a. Kidney graft survival in recipients < 15 years (n=9) and > 15 years (n=22) of ABO-Inc LRD.
b. Kidney graft survival in recipients < 15 years (n=9) of ABO-Inc LRD compared to a group of recipients < 15 years (n=58) of ABO-Comp LRD (Malaise et al., 1995)[40].
Fig. 22. ABO-Inc LRD: 20 years later (Squifflet et al. 2004)[45].

More surprising is the fact that some patients may carry very high levels of iso-agglutinins with the disappearance of all ABO blood group antigens on the endothelial cells of the transplanted kidney. Later on, Fritz Bach (Bach et al., 1997)[46] proposed the word "accommodation" to name this phenomena; probably there exists a critical period, before the third postoperative week, during which the ABO-Inc transplant is at risk for acute humoral vascular rejection. That is followed by a period of adaptation.
Today, more than 20 years later, each part of the original protocol has been further assessed or modified by different groups. Indeed, plasmapheresis was replaced by immuno adsorption columns. For deleting the last circulating iso-agglutinins, high doses of

intravenous immunoglobulins are communally used. Pre-transplant IS includes Rituximab ®, as well as at the time of transplantation, in order to avoid the splenectomy. In general, the PO IS therapy combines Tacrolimus and Mycophenolate Mofetil with r-ATG induction (Squifflet et al., 2004)[45].

Today, excellent results can be achieved: it is the demonstration that crossing the ABO barrier in LD kidneys transplantation is feasible. The same heavy protocol pertains and can also be applied for hyper immunized recipients with positive crossmatch against potential donors. Others, as well as the Belgian transplant community,

have proposed LD exchange programs (LDEP). Currently, in the Netherlands, that LDEP is very successful in helping numerous pairs of D and R from blood group O, while solving impossibilities (Fig. 23) by incorporating donations from good samaritans.

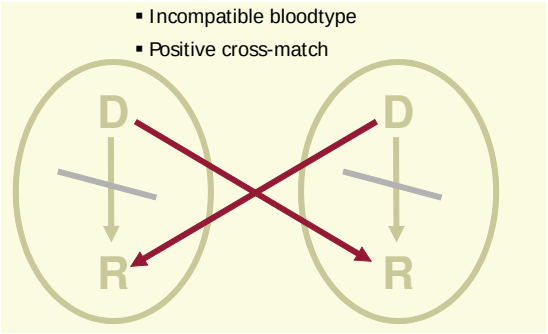


Fig. 23. Solving impossibilities with LDEP.

Based on that human experience and using the same preparation, a dozen pig-to-baboon renal xenografts were achieved in the mid-eighties. Three animal recipients survived 10, 22 and 23 days respectively. The baboon who lived for 10 days died of a pulmonary infection: the renal function was normal at the time of death and histology of the xenograft was remarkably normal. Two baboons, who lived for over three weeks, presented an acute rejection crisis at the end of the first week, vascular in nature for the first animal and cellular in the second one. This demonstrated that, together with an appropriate preparation of the donor animal and the recipient, xenotransplantation could be feasible using new potent immunosuppressive drugs.

7. Present and future perspectives

On May 28, 2002 Belgium adopted the Belgian act on Euthanasia after several months of intensive discussions (Squifflet A.C., 2011)[21]. Euthanasia is described as '*an act on purpose, performed by a third person, in order to end the life of a person who has requested for this act*'. The rules are the following:

The patient must be an adult or an emancipated minor, capable and conscious at the time of his / her request. The request is made voluntarily, is well thought out and reiterated, and is not the result of outside pressure.

The patient is in a hopeless medical condition and complains of constant and unbearable physical or mental pain which cannot be relieved.

If the person is not in the terminal phase of his illness, the 2 doctors must consult with a third doctor, either a psychiatrist or a specialist in the disease concerned.
At least one month must pass between the written request and carrying out the act.
Every euthanasia must be reported to a federal commission that regulate the practice and bring prosecutions when necessary.
Current statistics demonstrate more than 2 acts per day in Belgium and 7 per day in the Netherlands (Fig.24).

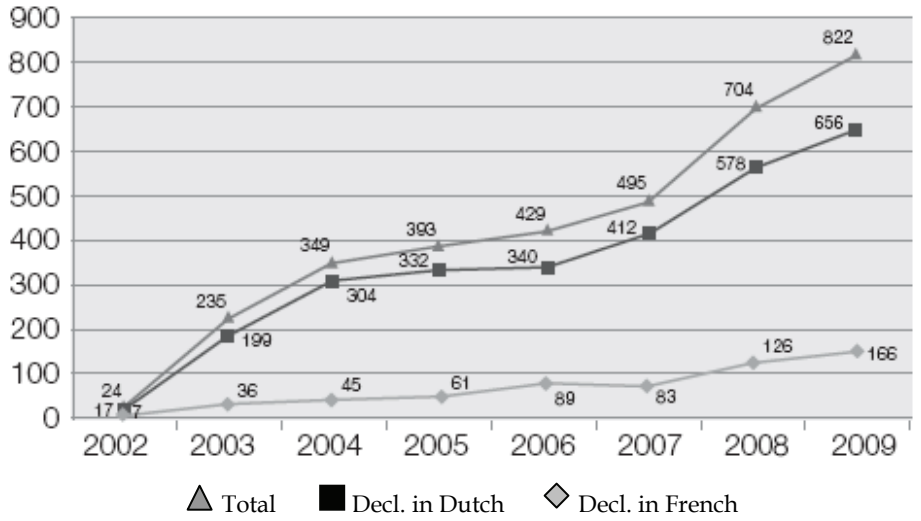


Fig. 24. Annual numbers of legal euthanasia acts in Belgium.

In January 2005, a first woman who was following the procedure of mercy killing asked for organ donation after death (Ysebaert et al., 2009)[47], (Detry et al., 2008)[48]. She was followed by 7 others persons so far. Data concerning the 4 patients are summarised in table 7 and 8 (Ysebaert et al., 2009)[47].
The organ procurement procedure which was adopted after euthanasia was as follow:

- Extensive written informed consent of donor - if possible (see patient 2) - and relatives.
- Strict separation between euthanasia request, euthanasia procedure and organ procurement.
- Euthanasia performed by 2 physicians + neurologist.
- Euthanasia in wheelchair (patients 1, 3, 4) or bed (patient 2), in a special room in the OR, in presence of the family.
- Organ retrieval after clinical diagnosis of cardiac death by 3 physicians.
- Procedures performed by senior staff members and nursing staff on a voluntary basis.
- Euthanasia procedure induced by overdose barbiturates, muscle relaxation and analgesia.
- Heparine given after euthanasia kit.
- The surgical procedure:
  - 3 times femoral vessels cannulation using the DBTL catheter (double balloons triple lumen) followed by a quick laparotomy for topical cooling (patients 1, 3 and 4).

Location	Age	Condition	Date of Euthanasia
1. UZA	44	**CVA** since 6 years, fixed hemliplegia, cortical blindness, special disorientation and dyspraxia.	01/2005
2. U of Lg	43	**CVA** since 4 years, locked-in syndrome, no motor recovery, central hyperthermia episodes, communication only by the eyes.	06/2006
3. UZA	47	**Multiple sclerosis** since 10 years, wheel chair dependent, depending on third parties for personal care, no quality of life, large decubitus wounds.	07/2007
4. UZA	50	**Multiple sclerosis** since 16 years, wheel chair dependent, depending on third parties for personal care, no quality of life.	10/2007

UZA: Universiteit Ziekenhuis Antwerpen
U of Lg: University of Liege, CHU Sart Tilman
Table 7. demographic data of the first 4 Belgian donors who requested organ donation after euthanasia (Ysebaert et al., 2009)[47].

- 1 time a quick laparotomy for insertion of the aortic and inferior vena cava canule, and topical cooling (patient 2).
- Organ allocation via Eurotransplant (for DCD kidneys, allocation is allowed 4 hrs before).
- Transplant centers informed about the nature of the case and the elements of organ procurement.

Based on that protocol, the first 4 patients donated 8 kidneys, 4 livers, 3 pancreases for islet preparation and 4 lungs. All those organs were successfully transplanted without delayed graft function and need for P.O. dialysis for the kidneys (table 8).

Patient	First warm ischemic times				Outcome			
	Start – Asystoly	Asystoly – Incision	Incision – flush	Total	Kidneys	Liver	Islets	Lungs
1	12′	9′	5′	26′	2	Yes	Yes	No
2	9′	3′	5′	17′	2	Yes	No	No
3	21′	8′	5′	34′	2	Yes	Yes	2
4	6′	5′	3′	14′	2	yes	yes	2

Table 8. First warm ischemic times and outcomes of the organs procured in the first 4 Belgian donors who requested organ donation after euthanasia (Ysebaert et al., 2009)[47].

The potential number of patients asking for euthanasia who fulfilled criteria for organ donation will remain limited and was estimated to be between 5 and 10% (table 9).
That first series demonstrates that organ donation after euthanasia is feasible. It allows respecting strong patient's wish to donate that cannot be denied. The proposed procedure clearly separates euthanasia request, euthanasia procedure and organ procurement. It ensures high quality of DCD organs which might enter in a so-called Fifth Category of Maastricht, of controlled NHBD.
A step further was undertaken by a Pediatric Heart Transplantation team from Denver, Colorado (Boucek et al., 2008)[49] who procured 3 pediatric DCD hearts after a no-touch

	2003	2004	2005	2006	2007	2008	2009
Euthanasia	235	349	393	429	495	704	822
Neuromuscular disorders	22	27	16	33	48	51	58
%	9,5	7,7	4,1	7,6	9,6	7,2	7,0

Table 9. Potential number of patients fulfilling organ donation criteria among Belgian patients requesting euthanasia (Squifflet A.C., 2011)[21].

period of 3, 1.25 and 1.25 minutes. All 3 hearts were successfully transplanted into 3 children. Therefore, the Denver procedure extends the boundaries of organ donation after circulatory death, and perhaps, will require ethical discussions and revisions of the definition of death. Currently the definition of brain death requires the complete absence of all functions of the entire brain (higher-brain definition). The cardiac definition of death requires the irreversible cessation of cardiac function (impossible to reverse). Based on the Denver procedure, the last definition is not valid anymore. It means also, that in DCD organ procurement, with a neuromonitoring of brain death, and adequate analgesic drug management, cessation of cardiac beats could not be waited for, even without any no-touch period. It will also allow heart procurement, reconditioning on artificial device before implantation.
That will necessitate the revision of the dead donor rule and the endorsement of the DCD procedure by separate well trained teams.
The Belgian initiatives in the field of cadaver organ procurement have paid off in terms of number of organs available for allocation. But it remains, like in other countries, that the number of suboptimal organs is increasing for recipients of increasing age and associated morbidities. That will impair the short – and long-term graft and patient outcome.
If there is an urgent need for those centers performing living donor transplantation to turn toward cadaveric organ transplantation, there is also an urgent need for those centers which have DCD programs to turn toward living donor transplantation which offers better results.
Current situation prevails: many persons are willing to offer their organs after death in hoping to help their neighbours. Many patients with end-stage renal disease are turning to live donor kidney transplantation to improve survival and quality of life. Many healthy adults are eager and willing to accept the risk of donor nephrectomy to help their loved ones. Therefore, the responsibility is within the medical community to quantify the risks as best as possible and make the information available to those considering donation. That should be considered and will help for avoiding organ trafficking, tourism and commercialisation in the field of renal transplantation.

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To Professor G.P.J. Alexandre, a pioneer in the field of transplantation
To Professor J. Malaise who initiated most data analysis.
Present address: University of Montreal, Quebec, Canada
Notre Dame Hospital

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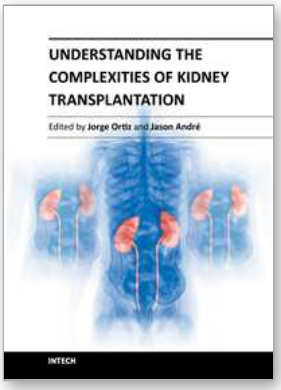

Understanding the Complexities of Kidney Transplantation
Edited by Prof. Jorge Ortiz

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Kidney transplantation is a complex field that incorporates several different specialties to manage the transplant patient. This book was created because of the importance of kidney transplantation. This volume focuses on the complexities of the transplant patient. In particular, there is a focus on the comorbidities and special considerations for a transplant patient and how they affect kidney transplant outcomes. Contributors to this book are from all over the world and are experts in their individual fields. They were all individually approached to add a chapter to this book and with their efforts this book was formed. Understanding the Complexities of Kidney Transplantation gives the reader an excellent foundation to build upon to truly understand kidney transplantation.

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