

The history of renal transplantation in France



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ABSTRACT

The history of renal transplantation in France began with 2 surgeons from Lyon, M. Jaboulay and A. Carrel. The latter initiated the proper techniques of vascular suture, performed the first experiments in animals, initially in Lyon, then in Chicago with C. Guthrie and demonstrated that failure in obtaining a prolonged success was due to an immunological rejection of the graft. Trials in humans began in France in the 1950s with transplants from healthy donors. All ended in failure, although in 1953 the conjunction of a donor mother and a previous irradiation of the recipient allowed a survival of 3 weeks in the patient. J. Hamburger in France and J. Murray in the USA tried transplantations in monozygotic twins, then dizygotic ones, which represented the first successes. A decisive jump occurred with the arrival of immunosuppressors (combination of azathioprine and prednisone) which allowed R. Küss to win the first success in recipients that were unrelated to their donors. At the same time, J. Dausset described the Human Leucocyte Antigen (HLA) groups, markers of tissular immunogenicity, thus allowing the most appropriate donors to be selected. To the living donors were added soon the patients in irreversible coma, which made it possible to increase the number of grafts. Despite obstacles and doubts, kidney transplantation developed rapidly and was accepted as the most efficient treatment of chronic renal failure. The role of French and American physicians was decisive in this success.

KEYWORDS: transplantation, kidney, history

The early beginnings

Organ transplantation is an old idea. It is not easy to say with precision where and by whom the first trials were realized. It is reported that Saint Cosmo and Saint Damian grafted a Moorish leg to replace the necrotic leg of a patient, an event that was considered to be a miracle. In the sixteenth century, Gaspare Tagliacozzi successfully performed autografts of the nose but failed in the allografts (1). The eighteenth century saw the development of unsuccessful animal graft experiments. The pioneers of renal transplantation in France were two surgeons in Lyon: Mathieu Jaboulay (1860-1913) and Alexis Carrel (1873-1944). Mathieu Jaboulay implemented on the dog an original process of non-stenosing arterial suture with separate U-shaped points after interposition or not of an arterial fragment (2). He tried in 1906 the xenograft of a pig kidney and then of a goat kidney to the bend of the elbow of two women with renal insufficiency (3). It was a failure, but it showed the feasibility of the technique. Alexis Carrel developed the end-to-end vascular suture techniques that are still widely used in transplantation. This was published in the "Journal de médecine de Lyon" (4, 5). In 1906, he moved to the USA where he worked with Charles Guthrie in Chicago. Both of them realized organ transplantations in animals and published a number of scientific articles where they described the successive improvements of their techniques of vascular anastomoses. They demonstrated for the first time that a vein could be substituted to an artery and reported their experiments of organ transplantations (6, 7). Their main conclusion was that using appropriate techniques of vascular suture, autografts were most of the time successful in animals whereas homografts never were. Alexis Carrel wrote at this time: "From a clinical standpoint, the transplantation of organs may become important and may open new fields in

biology and therapy" (8). He was awarded the Nobel prize in 1912 "in recognition of his work on the vascular suture and the transplantation of blood cells and organs", He accepted in 1908 a position at the Rockefeller Institute in New York where he stayed until 1939. He realized the first fully functional renal self-transplantation on a bitch and was the first to study the chemical composition of the urine from the transplant, to describe the histology of the rejected kidney showing "an important infiltration of small round cells around the vessels and the collecting ducts", to hypothesize the responsibility of the spleen and the bone marrow in the production of antibodies and to suggest utilization of irradiation to diminish the immune capacity of the leukocytes (6, 9). He concluded that: "an animal which has undergone a double nephrectomy and the grafting of both kidneys from another animal can secrete almost normal urine with his new organs, and live in good health, at least for a few weeks. This demonstrates that it is possible to reestablish efficiently the functions of transplanted kidneys" (9). Alexis Carrel can be considered as the main pioneer of renal transplantation. He was also at the origin of tissue culture. He returned to France in 1939. Unfortunately, the end of his life was clouded by the defense of eugenism in his book "L'Homme, cet inconnu (Man, this unknown)".

Unsuccessful attempts of renal transplantation in man in France (1950-1952)

The first homograft of a human kidney in man was performed by Yuri Voronoy (1895-1961) in 1936 in Kiev (10). He transplanted in the thigh of a uremic patient a kidney from a healthy man who had died in an accident. The transplant did not function and the recipient died 2 days later. Human kidney transplantations started in France in the fifties. From 1950 to 1952 almost ten renal transplantations were

performed after removal of a kidney from guillotined criminals immediately after their execution or from patients in whom a kidney had to be removed for therapeutic reasons. Several teams were active: René Küss (Paris), Charles Dubost (Paris), Marcel Servelle (Strasbourg). Early failures occurred in each case, but these trials allowed progress in the surgical technique to be realized. In particular, René Küss described the ideal heterotopic position of the grafted kidney in the iliac fossa with anastomosis of the renal vein to the iliac vein, of the renal artery to the hypogastric artery and of the ureter to the bladder. These unsuccessful trials were published in the "Mémoires de l'Académie de Chirurgie" in 1951 (11-13). These failures did not discourage French surgeons and nephrologists, and in 1952, Jean Hamburger and Louis Michon performed the graft of one kidney of his mother in a young man whose the only kidney had been removed after a fall from a ladder. For the first time a survival of 3 weeks was observed (14). This intervention was widely reported by the media and had a worldwide impact. It showed that the main problem to be solved remained the immunological rejection of the graft as written by the authors: "After the 17th day of the transplant, no complication disturbed evolution; but the satisfaction that was derived from this observation was followed by the most intense anxiety six days later due to the sudden arrest of the transplanted kidney". The challenge did not seem achievable at that time as evidenced by this 1955 citation of David Hume: "In the present state of our knowledge, renal homotransplantation does not seem to be justified in the treatment of human diseases" (15). There were two approaches to address this difficult issue: to find a donor the most genetically related to the recipient, to treat the recipient so as to attenuate and, if possible, control the reject of the graft.

The first successes

The three main pioneers of successful renal transplantation in France were a nephrologist, Jean Hamburger, an urologist, René Küss and an immunologist, Jean Dausset. They addressed the main problem still unresolved that was the immunological rejection of the graft.

Jean Hamburger (1909-1992), after having been the assistant of Louis Pasteur Vallery-Radot at Broussais Hospital, created the first department of nephrology in France at Necker Hospital in Paris (Figure 1).



Figure 1 - Jean Hamburger.
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His main collaborators were Gabriel Richet, Jean Crosnier and Jean-Louis Funck-Brentano. He was the first president of the International Society of Nephrology and chaired the first International Congress of Nephrology (Evian and Geneva, 1960). In addition to his scientific achievements, he was a writer and published several books on the human fate, in particular "La Puissance et la fragilité: Essai sur les métamorphoses de la médecine et de l'homme (Power and fragility: An essay on the metamorphoses of medicine and man)". His achievements in the progress of renal transplantation are numerous and were inspired by his conviction that "The great

destiny of man is to refuse his destiny". He succeeded in diminishing the immune rejection with total body irradiation of the recipient and matching the HLA characteristics of the donor and of the recipient. As mentioned above, he was the first to realize a transplant from a mother to her son with a survival of 3 weeks and was the second (5 months after Joseph Murray) to obtain a successful transplant between dizygotic twins genetically different (rejection of a skin graft from the donor by the recipient, dissimilar blood groups) after sub-lethal irradiation and isolation in a sterile room (16). The recipient died 26 years later from a bladder carcinoma. This was followed by a successful transplant from a cousin that was rejected 18 years later, which necessitated a second transplant. The recipient was still living 32 years after the first transplant. In 1964, he transplanted a cadaver kidney in a patient who lived more than 25 years. He also demonstrated the successful treatment of acute rejection (15 days after surgery) with prednisone. In 1965, Jean Hamburger drew conclusions from the review of his first 45 transplantations (17). He found that 29 of them were in a satisfactory condition after 6 months with a normal blood pressure and a mean glomerular filtration rate of 73 ml/min. Cellular infiltration was visible in all renal biopsy specimens, but tended to diminish later. Glomerular lesions and progressive interstitial fibrosis were observed more rarely. In late crises, even if biopsy specimens showed gross oedema and cellular infiltration, a satisfactory reversal could be obtained. As a whole, one could be optimistic on the future of renal transplantation.

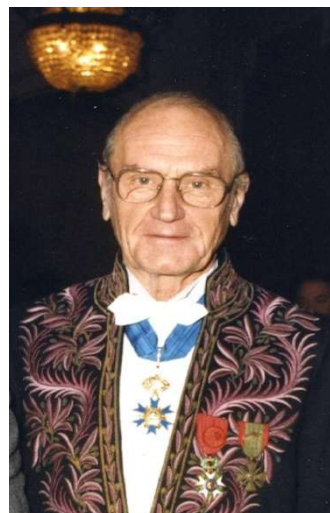


Figure 2 - René Küss with an academician cloth.
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René Küss (1913-2006) was head of the department of urology in "La Pitié" Hospital in Paris (Figure 2).

His main collaborator was Marcel Legrain, head of the department of nephrology in the same hospital. Their purpose was to realize successful transplantation between unrelated persons. The results obtained by Joseph Murray and Jean Hamburger in dizygotic twins left a persistent doubt about the possible role of an induction of this tolerance by an exchange of cells during the intra-uterine life. The answer to

this question was given by René Küss and Marcel Legrain who realized in 1960 at Foch Hospital, for the first time, three successful renal grafts outside of gemellarity, once between brother and sister and twice without any kinship. These successes were due to the efficacy of the conditioning with an immunosuppressive treatment including 6-mercaptopurine and prednisone (18). The grafts functioned for 5, 17 and 18 months, respectively, and were followed by other successful grafts between unrelated donors and recipients (19). Therefore, total body irradiation was no longer needed. René Küss was awarded the Medawar Prize in 2002 for his contribution to kidney transplantation. This prize was simultaneously attributed to Georges Mathé who was the first to realize bone marrow transplantations and participated in the first successful attempts by René Küss.



Figure 3 - Jean Dausset. ©Bibliothèque de l'Académie Nationale de Médecine.

Jean Dausset (1916-2009) was head of the department of hemato-immunology at St Louis Hospital in Paris (Figure 3). He was appointed later professor at the "Collège de France", which represents the highest distinction for researchers working in all fields of knowledge. He

was the first to describe the HLA system of leucocyte and tissue groups which enables the selection of donors, in a series of publications between 1952 and 1963 (20, 21). His main collaborator was Jean Colombani. He was awarded the Nobel prize in 1980 for the discovery of the HLA groups. He created «France transplant» in 1970 allowing the rapid transfer of a kidney from a donor with a compatible HLA group. Before him, Peter Medawar in UK had performed a series of skin homografts in rabbits in 1944. If he recognized the immunological nature of the rejections, he limited his observations to histological morphology (22). However, some years later, he inoculated intrauterine fetuses with spleen cells of a donor mouse to induce chimerism, which resulted in the acceptance of grafts of the donor by the chimeric mice. Therefore, he could conclude that homograft rejection was not obligatory. This discovery earned Peter Medawar the Nobel prize in 1966 (22).

Progresses in renal transplantation have also to be attributed in France to other researchers than Jean Hamburger, René Küss and Jean Dausset and the teams working with them. In 1959, Pierre Mollaret and Maurice Goulon defined a new entity, the irreversible coma, ("le coma dépassé") in patients without any cerebral activity who were maintained in artificial survival by artificial breathing and whose hearts were still beating. Kidneys were removed from these patients after agreement of their family and successfully transplanted with results similar to those obtained with transplantations from related donors. Their studies were at the origin of a new stage in renal transplantation allowing their number to be greatly increased (23). To diminish the immune reaction was also the preoccupation of French teams. Jules Traeger and Jean Perrin proposed lymphocyte depletion by cannulation of the thoracic duct. The collected lymphocytes were utilized to prepare an anti-lymphocyte serum which found a place next to the couple azathioprine – prednisone (24). This treatment was quickly abandoned because of its side effects. It is the precursor of the use of monoclonal antibodies.

What did occur simultaneously in USA?

In parallel with the studies carried out in France, the United States were actively participating in this race towards the development of effective and well-tolerated renal transplants. In 1950, Richard Lawler (1896-1982) working in Chicago performed an intra-abdominal cadaveric renal transplant in a patient with polycystic renal disease after removal of one of his kidneys that functioned for 53 days (25). David Hume (1917-1973) working in Boston realized nine kidney transplantations between 1951 and 1953. The donors were patients who had died after surgery. Except in one case, the grafted kidneys were placed in the thigh and the ureter brought to the skin. Four kidneys only functioned, briefly for three of them, but for almost 6 months for the latter (26). The first real success was obtained in 1954 by Joseph Murray (1917-2012) with a graft between monozygotic twins. The recipient died 25 years later (27). This was followed in 1959 by 2 successful grafts between dizygotic twins after radiotherapy that were performed in collaboration with John Merrill (1917-1984) (28), but grafts between unrelated persons were rejected (29). Success was soon obtained by conditioning the recipient with azathioprine. Using this drug alone allowed Joseph Murray to win a first long-term success in 1962 (30). Chemical immunosuppression, then used by the different teams, too happy to abandon irradiation, contributed greatly to the development of renal transplantation. One year later, Thoma Starzl exhibited previously unmatched results relating the efficacy of azathioprine and cortisone (31).

Conclusion

In spite of all these progresses, everybody was not convinced of the future of renal transplantation at that time, even the most famous immunologists. Frank Macfarlane Burnett (Australia) was awarded the Nobel prize in 1960 for his works on immune tolerance and clonal selection. In a review entitled "The new approach to immunology" he wrote: "Much thought has been given to ways by which tissues or organs not genetically and antigenically identical with the patient might be made to survive and function in the alien environment. On the whole, the present outlook is highly unfavorable to success..." (32). For this reason, we must be particularly grateful to the French and American medical doctors who persisted despite their failures in pursuing their quest for a successful renal transplant. The best conclusion is given by Thomas Starzl, who wrote in 1990: "These events and subsequent ones could not have transpired in the way they did without French pioneers, Hamburger the physician and Küss the surgeon, and their friends in Boston whose vision was greater than that given to most men and women. Workers in the two cities founded a clinical discipline where none existed before and then persisted despite allegations of folly or worse. The French successes with kidney transplantation over the three-year period from 1959 through early 1962 kept the flames alive when all other efforts were failing" (33).

REFERENCES

1. Corradi A. Dell'antica autoplastica Italiana in Memorie del Regio Istituto lombardo di scienze e lettere. Classe di scienze matematiche e naturali, volume 13, Milano, 1875.
2. Jaboulay M, Briau E. Recherches expérimentales sur la suture et la greffe artérielle. Lyon Méd. 1896;81:97-99.
3. Jaboulay M. Greffe du rein au pli du coude par suture artérielle et veineuse. Lyon Méd. 1906;107:575-577.
4. Carrel A. Anastomose bout à bout de la jugulaire et de la carotide primitive. Lyon Méd. 1902; 99: 114.

5. Carrel A. La technique opératoire des anastomoses vasculaires et la transplantation des viscères. *Lyon Med.*, 1902; 98 :859-864.
6. Carrel A, Guthrie CC. Successful transplantation of both kidneys from a dog into a bitch with removal of both normal kidneys from the latter. *Science* 1906; 23: 394–395.
7. Carrel A, Guthrie CC. Functions of a transplanted kidney. *Science* 1905; 22:473.
8. Carrel A. The transplantation of organs: a preliminary communication. *JAMA* 1905; 45:1645–1646.
9. Carrel A. Transplantation in mass of the kidney. *J. Exp. Med.* 1908; 10:98.
10. Voronoy U. Sobre del bloqueo del aparato reticuloendotelial del hombre en algunas formas de intoxicación por el sublimado y sobre la transplantación del riñón cadavérico como método de tratamiento de la anuria consecutiva a aquella intoxicación. *Siglo Med.* 1937; 97:296.
11. Küss R, Teinturier J, et Milliez P. Quelques essais de greffe de rein chez l'homme. *Mem Acad Chir* 1951; 77:755-764.
12. Dubost C, Oeconomos N, Nema A, Milliez P. Résultats d'une tentative de greffe rénale. *Bull Soc Med Hop Paris* 1951; 67: 1372-82.
13. Servelle M, Soulie P, Rougeulle J, Delahaye G. Greffe d'un rein de supplé à une malade avec rein unique congénital, atteinte de néphrite chronique hypertensive azotémique. *Bull Soc Med Hop Paris* 1951; 67: 99-104.
14. Michon L, Hamburger J, Oeconomos N, Delinotte P, Richet G, Vaysse J, Antoine B. Une tentative de transplantation rénale chez l'homme. Aspects médicaux et biologiques. *Presse Med.* 1953; 61: 1419- 1423.
15. Hume D, Merrill JP, Miller BF, Thorn GWE. Experiences with renal homotransplantations in the humans: report of nine cases. *J Clin Invest.* 1955; 34: 327-382.
16. Hamburger J, Vaysse J, Crosnier J, Tubiana M, Lalanne CM, Antoine B, Auvert J, Soulier JP, Dormont J, Salmon CH, Maissonnet M, Amiel JL. Transplantation de rein entre jumeaux non homozygotes après irradiation du receveur. Bonne fonction au 4e mois. *Presse Med* 1959; 67:1771-1775.
17. Hamburger J, Crosnier J, Dormont J. Experience with 45 renal homotransplantations in man. *Lancet* 1965; 285: 985-992.
18. Küss R., Legrain M., Camey M., Désarménien J., Mathé G., Nedey R. , Vour'ch C. Homotransplantation rénale chez l'homme (à propos de 3 cas). *Mem. Acad. Chir.* 1961; 87: 183-196.
19. Grapin C, Michel F, Charpentier B, Frantz P, Fries D, Kuss R, Legrain M, Luciani H, Mohamedi D, Poisson J. Long-term prognosis of renal transplantation: a retrospective study of 90 patients living more than 10 years with a functioning allograft. *Transplant Proc.* 1987; 19:3765-3766.
20. Colombani J, Dausset J, Préaux J. Homogreffes de peau chez l'homme en relation avec les iso-antigènes leucocytaires. *Nouv. Rev. Fr.Hematol.* 1963; 3: 499-505.
21. Dausset J, Colombani J, Feingold N, Rapaport F. Un système de groupes leucocytaires et ses rapports avec l'histocompatibilité. *Nouv. Rev. Fr. Hematol.* 1965; 5: 17-22.
22. Medawar PB. The behavior and fate of skin autografts and skin homografts in rabbits. *J. Anat.* 1944; 78: 176-199.
23. Mollaret P, Goulon M. : Le coma dépassé, *Rev. Neurol.* 1959 ; 101: 3-11.
24. Traeger J, Perrin J, Fries D, Saubier E, Carraz M, Bonnet P, Archimbaud JP, Bernhardt JP, Brochier J, Betuel H, Veysseyre C, Bryon PA, Prevot J, Jouvenceau A, Banssillon V, Zech P, Rollet A. Utilisation chez l'homme d'une globuline anti-lymphocytaire: résultats cliniques en transplantation rénale *Lyon Med.* 1968; 219: 307-369.
25. Lawler RH, West JW, McNulty PH, Clancy EJ, Murphy RP. Homotransplantation of the kidney in the human. *JAMA* 1950;144: 844–845.
26. Hume DM, Merrill JP, Miller BF, Thorn GW. Experiences with renal homotransplantation in the human: Report of nine cases. *J Clin Invest.* 1955;34: 327–382.
27. Merrill JP, Murray JE, Harrison JH, and Guild WR. Successful homotransplantations of the human kidney between identical twins. *J Am Med Assoc.* 1956; 160: 277-282.
28. Merrill JP, Murray JE, Harrison JH, Friedman EA, Dealy JB, Damin GJ. Successful homotransplantation of the human kidney between non-identical twins. *New Engl J Med* 1960; 262: 1251-1260.
29. Murray JE, Merrill JP, Damin GJ, Alexandre GV, Harrison JH. Kidney transplantation in modified recipients. *Ann Surg* 1962; 156:337-355.
30. Murray JE, Merrill JP, Harrison JH, Wilson RE, Dammin GJ. Prolonged survival of human kidneys homografts by immunosuppressive drug therapy. *N Engl J Med.* 1963; 268: 1315-1323.
31. Starzl T.E, Marchiorio T.L, Peters G.N, et al. Renal heterotransplantation from baboon to man; Experience with 6 cases. *Transplantation*, 1964; 2: 752-776.
32. Burnett FM. The new approach to immunology. 1961; 264: 24-34.
33. Starzl T. The French heritage in renal transplantation. *Transplant Rev.* 1993; 7: 65-71.