History of pediatric liver transplantation in Europe

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The european history of pediatric liver transplantation (LT) began ... in 1965, when Jean-Bernard Otte went to Denver (Colorado) to meet the pioneer Thomas Starzl (1) who performed many years ago the first tentatives of LT in animal. A long period followed these initial assays, concerning essentially the operative process, the numerous changes it was necessary to modify, even in animal and, later on, in human patients at the ultimate stages of chronic liver disease. The exceptionnal work of Starzl was his certitude to be able to define, finally, the ways necessary to obtain progressively a better selection and preoperative care, before this type of heavy surgery, and that permanent certitude that, more or less rapidly, success will be obtained at the end of this long way in experimental surgery. Financial, ethical, and, over all surgical techniques of Starzl were dominated by that LT was the obsessional way to avoid the death, and the price to pay appeared light comparatively with the great number of patients potentially concerned. Thomas Starzl remained the only surgeon in the world never discouraged by the poor resuls initially obtained. The surgical process has been frequently modified like the preoperative care concerning essentially the poor nutrional status of the patients that was necessary to be corrected, the choice of the immunosuppressive drugs to avoid the rejection of the liver graft, and many other difficulties never able to reduce the efforts of Starzl. That is an admirable exemple showing the greatest problems in new therapies are able to be resolved by a so gifted, obstinate, and genious man as Thomas Starzl. Unfortunately, in 1984 (2) the National Institute of Health organised at Bethesda, in the USA, an international meeting for evaluating the possibilities to continue the federal financial support in this field, or to stop it, that has been finally decided. Then, in different places in the United States and in Europe, after poor long term results of the surgery in children with biliary atresia formerly proposed to treat by hepatoportoenterostomy, numerous medico-surgical teams (3,4,8) decided the opportunity to progress by LT in children, that has been performed by Starzl in a child (*) in 1968 for the first time in the world. A second pediatric LT was performed by Otte in Europe in 1971 (1). Ten years later, in this team, pediatric LT was programmed in 1984 (5). This new surgical approach was stimulated by new immunological drugs avoiding the rejection of the liver grafts in the recipient. Thomas Starzl evaluated the necessity to know the permanent modifications in pharmocological immunosuppressive drugs. This knowledge was acquired by Starzl during a sabbatical year in Roy Calne surgical unit in Cambridge where he went with his wife and their three children in 1975 (7).

This stay gave to this surgeon a medical point of view about physiology and pathologic data in liver diseases. More precisely, working in the laboratory of the pathologist POSTER, he studied the role of pancreas in permitting the liver to grow back after its partial removal. It was **the first stage** of medical LT problems studied in Europe.

The second stage of this long story is the visit organised in 1965-66 by Jean Bernard Otto (5), in Denver (Colorado) where he met Starzl, with the objective of discovering problems in experimental LT, showing his fascination for this surgery, and the dream it would be an original and efficient way to treat severe and chronic liver diseases in children. Since this first meeting, Jean Bernard Otte remained well motivated to follow the efforts made by Starzl. After the first european LT in adults in 1968 by Calne in Cambridge (7,9) Jean-Bernard Otte in 1969 (5) and Calne (7) programmed the possibilities to perform the identical surgery in children. This motivation showed how Otte was concerned by the needs in pediatrics and the large number of children as potential LT candidates. For example, only 13% of children initially operated for biliary atresia along hepatoenterostomy had a long term of survival (10). That explains how Otte and Lerut (5,6,17) were able to perform in 1971 the first european pediatric LT after unsuccessful Kasai (12) surgery. Finally, this program was performed before the success of the assays of Broelsch (18), working in Hambourg after his former successful performances in Chicago.

The third stage was experienced in our team since 1965, in Bicêtre Hospital, in Medical University of South-Paris (10). The small pediatric liver unit created at the same time by Alex Mowat (8) in the unit for liver diseases in adults leaded in London by Roger Williams in Kings College Hospital had the same problems as we did in Bicêtre (15), but in worse conditions for clinical and research activities. We had a close friendship between London and Paris, frequently discussing both

* The child, 3 years of age, formerly operated for biliary atresia, survived only 5 days after the LT.

together in numerous meetings organized in different pediatric places in Europe and in USA. At that time, it was the birth of a new sub-speciality, "pediatric liver diseases", and we established with London a friendly and vigourous competition. Unfortunately, the precocious and imprevisible death of Alex has been experienced by us as the most severe privation in european pediatric hepatology. Howeever, the program of LT in children initiated by Alex Mowat, before his death, has been prolonged under leadership of his co-worker Georgina Mieli-Vergagni (4).

Therefore, the pediatric LT found its wide dimension in Europe in the surgical unit for children leaded by Jean Bernard Otte and Jan Lerut (17). After our unsuccessful tentative asking Didier Houssin and Henri Bismuth well experienced in LT in adults in our University (16), to develop LT in children, we decided to establish a specific pediatric program of LT in our Bicêtre hospital. That is why I visited Otte in 1985, asking him largest informations as possible, about his pediatric experience. After the numerous details he gave me, he proposed I meet directly the parents of 4 children operated in his group for a LT, because, for us, the ethical aspects were as heavy as the surgical difficulties. After an extraordinary proposal to help us so widely we needed in our waiting list, Otte proposed to perform in his group the 10 children needing urgently a LT and to help us in the specific formation of all our co-workers (pediatricians, surgeons, nurses, anesthesists, urgentists, psychiatrics, social workers), implicated in our own project. On my return to Bicêtre, we decided to develop quickly all the superb possibilities given to us. One year later, in March 1986, the first orthoptic LT in a small child has been performed in our team by Jacques Valayer (11). Short time later, the number of children needing this surgery in our waiting list leaded us to ask Didier Houssin, a surgeon well experienced in LT in adults and working at Cochin Hospital near of Bicêtre, his complementary aid for LT in the oldest children in our waiting list. It was a few months before his nomination as the leader of the "Etablissement Français des Greffes" (EFG) in France (60). Today, over than 650 children have been operated on with 80% of long term success and good quality of life.

First technical progress in children concerned the possibilities to reduce the size of liver grafts from cadaveric adults donors (16,18,19). Many points of view in different surgical procedures were proposed, as split liver (20,21) wich was the beginning of a new technical way. However, the most important progress is the extraordinary development of the *"living-related liver transplantation"* (LRLT). This procedure was extensively developed in Japan for adults recipients, because the procurement of cadaveric grafts from adults was not permitted in this country for cultural and legal reasons. The success of this type of liver-graft explains the later large extension in children recipients after other technical surgery procedures (21,22). In the last ten years, LRLT was successfully proposed in Chicago and later on, in Hamburg by Broelsch (22-24). A persistent organ shortage and the numerous deaths of infants and children on the waiting list have forced to introduce pediatric LRLT in Europe. Nowadays, most large pediatric liver transplant programs are routinely performed LRLT together with cadaveric transplantation (25,26). Hepatic artery postoperative thrombosis is also sometimes observed. A same percentage of post-operative complications in recipients are observed in both origin of liver graft (26, 27). In donors of liver graft, LRLT is a very low risk of partial hepatectomy in adults with normal liver, and the demonstration of similar results with transplantation of a full-size liver or of liver reduced was obvious (24). That is why ethical discussion (25), must consider the therapeutic possibilities for the recipient, the risk for the donor (lower than 1%), and the total liberty of choice for the parents. These ethical rules must always be discussed with the parents of a potential recipient, and the final decision depends exclusively on them. The postoperative complications and long term results are identical with transplantation from cadaveric donor (about 80% of ten years survival).

The extensive experience with LRLT increased the pediatric indications for LT. Numerous chronic severe cholestatic diseases (28,29,30) and metabolic conditions (28-34), obtained after LRLT a perfect solution. In the near future, the list of them will be extended. However, we can't forget the post-operative complications. Also, the nutritionnal status of the potential recipient have to be carefully evaluated and corrected before the prelevement of the graft (43). Sometimes, this possibility is very difficult, because the transplantation is decided in very acute liver deficiency (44,45). The medial surveillance in intensive care units (44,46,47), is always necessary to prevent and to treat these postoperative complications.

The possibilities to perform a LT in very young babies, less than 1 year of age, has been hardly discussed. Today, a concensus considers that it is widely accessible in well experienced teams (48,49,50,51,52) when the viral or metabolic liver disease cannot be controlled outside this surgical solution. Its generally established the lower limits in babies are five months of age and five kilos of weight.

In the different main teams well experienced in pediatric liver transplantation (Genova ; London and Birmingham ; Bergama ; Barcelona, Madrid, and Valencia ; Coimbra ; Brussels ; Hamburg, Heidelberg and Hanover ; Groningen ; Paris and Lyon) the results are almost identical independently of the indications, age (under 16), surgical technique, immunosuppressive protocol. For example, in our group Bicêtre-Cochin, between March 1986 and March 2002, the actuarial curve for 648 LT in 568 children is 79% of long term survival, more than 10 postoperative years), 75 retransplantations (12%) were performed, median of age is 3 years at the date of LT, the graft was whole liver in

38%, reduced in 46%, bipartide in 13%, and from living donor only 3%.

This extraordinary history initiated more than forty years with the obstination of the pioneers, their competence, and every one working in the most experienced teams, I would like to mention that all this progress has been possible only by the discovery of an immuno-suppressive drug avoiding the rejection of an external graft by the specific immunological answer in the recipients. After a long time of many difficulties, the solution has been discovered by an agronomical engineer working in a research laboratory in Basel (Switzerland) at Sandoz Society with the initial goal to find new anti-malignant drugs from Norvegian wild mushrooms. Jean François Borel (54-56), between 1973 and 1976, established the specific and reversible role of the "ciclosporin" against the T-lymphocytes cells. This fact, comparatively with the others drugs formerly used with a very low efficiency (azathioprin prednisone), gave an extraordinary advance in LT, and persuaded Roy Calne (7,57,58) to test clinically this new drug in LT children. After difficult dosages in animal and human patients, Thomas Starzl (1) established the ciclosporine, given oraly in association with azathioprine and prednisone under lower dosages, was absolutely efficient, and able to inhibit the rejection of external grafts in recipients. The way of the immuno-suppressive strategy was widely open for a long term : the other immunosuppressive drugs later on experienced as OKT3 or FK 506 obtained nothing more, with the same side effects. However, today, "Tacromilus" (Prograf R) is widely or exclusively given in different teams, with more efficiency and less side effects observed with ciclosporine. The association of prednisone needs smaller dosages than with ciclosporin. We hope the near future will confirm this new and latest progress.

The indications for liver transplantation are extensively progressing in pediatrics, explaining, nowadays, how we are asking more cadaveric or living donors we need to give a large number to children with severe liver disease, the realistic way to have a normal life. In France, after the historic role of *"France Transplant"* (Jean Dausset* and Christian Cabrol**) the allocation of grafts to patients on the waiting list, the creation of the *"Etablissement Français des Greffes" (EFG)* in 1992, under the dynamic leadership of Didier Houssin (60), is crossing and extending the role of *"Eurotransplant"* created formerly in 1969 (61) the new rules governing kidney and liver allocation to children less than 16 years of age is an essential progress. However, the waiting time for liver transplantation in children is not yet adapted to the duration on the list, and many children even today still die while their waiting for a liver graft (62). Alternative therapies, such as gene therapy and hepatocytes transplantation may alleviate the needs of grafts, specially in children with metabolic disease.

I would like to say my gratitude and my admiration for every one who has given their exceptional willing to go more further, and who have given to liver sick children the possibility to live, to grow, and to be happy in life. Its not an hazard if we find at the beginning of this superb story the same leaders, and the same names than today (1,5,9,58,59). They demonstrated, in front of each new difficulty, that with their competence, obstination, and love for sick children, the fundamental reasons permitting to give them the best of life.

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* Nobel Prize 1980 for his work in the "histocompability"
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