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# History and Evolution of Liver Transplantation

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## 1. Introduction

Historically, in ancient civilization, man had already imagined changes in the morphology, structure and function of the human body. Egyptian and Greco-Roman mythology provided examples of the metamorphoses sung by Homer and Ovid, symbolic incarnations of the “comédie humaine” with its strength, weakness, vices and virtues. The liver has been the noble organ, the organ of life from time immemorial—liver in English, Leber in German, derived from the verb to live. An Indian legend from the 12<sup>th</sup> century B.C recounts the power of Shiva, who xenotransplanted an elephant head onto a child induce the Indian god Gaesha.[1] In ancient China, Yue-Jen (407-310 B.B.) induced anesthesia lasting 3 days by “the absorption of extremely strong wine, opened up the chest of two soldiers and after examining them, exchanged their hearts and transplanted them”. The first reference to the concept of organ transplantation and replacement for therapeutic purposes appears to be Hua-To (136 to 208 A.D.) who replaced diseased organs with healthy ones in patients under anesthesia induced with a mixture of Indian hemp.

Although attempts at transplantation date back to ancient times, the impetus for modern transplantation was World War II and Battle of Britain. Royal Air Force pilots often were severely burned when their planes crashed. The mortality rate associated with burns corresponds to the size of the area of the skin that has been injured and the survival rate can be improved if the burned skin is replaced. For this reason, British doctors, attempted skin transplantation from other human donors as a mode of therapy. However, these attempts were uniformly unsuccessful. The transplanted skin became necrotic and fell off over several days.[2] This problem led investigators in 1940s to study skin transplantation in animal models. It remained for Sir Peter Medawar in 1944 to establish that the failure of a skin graft to “take” was the result of a process later termed immunological rejection.[3] Later studies by Gowens in 1948 revealed that lymphocytes play a major role in transplant rejection.[4] In 1951, it was shown that cortisone therapy significantly prolonged survival of skin allograft.[5] In 1959, Schwartz and Dameshek reported drug-induced immune-tolerance using 6-mercaptopurine.[6] Later in 1961, Calne and Murray showed that azathioprine therapy suppressed the rejection reaction and prolonged allograft survival.[7]

Once clinicians were confident that adequate immunosuppression was available, solid organ transplantation for end stage organ disease entered its early investigative phase. This was not possible without the application of the principles of vascular anastomosis pioneered by Alexis Carrel in 1902, for which he was awarded the Nobel Prize for Medicine in 1912.[8]

Further refinements in surgical techniques and suture materials have enabled Murray and his colleagues to perform the first successful kidney transplant in 1955.[9] This was a living donor transplant performed between identical twins. However, later attempts to perform renal transplantation when the donor and recipient were not genetically identical failed because no effective immunosuppressive therapy was available. From the early 1960s, a combination of azathioprine and corticosteroids was used with success to prevent graft rejection after kidney transplantation. In 1963, Woodruff described the immunosuppressive effect of antilymphocytic serum which destroyed the recipient active lymphocytes.[10] The success of kidney transplantation paved the way to think and perform liver transplantation for end-stage liver disease.

In 1955, Welch reported on his efforts to transplant an auxiliary liver into the right paravertebral gutter of non-immunosuppressed mongrel dogs.[11] In 1958, Francis Moore described the standard technique of canine liver orthotopic liver transplantation.[12] In 1963, Starzl attempted the first human orthotopic liver transplantation in a 3-years-old boy who suffered from biliary atresia, however, the patient died before the operation was completed.[13] Following this first unsuccessful attempt, the procedure evolved slowly and although his series remained largely unsuccessful, many of the technical principles that still guide liver transplantation were established. In 1967, Starzl and colleagues at the University of Colorado reported the first successful clinical liver transplantation.[14]

Between 1966 and 1973, Starzl and colleagues performed three chimpanzee-to-human xenotransplantation of liver as well.[15] There have been 12 cases of clinical xenotransplantation including four cases of chimpanzee-to-human, seven cases of baboon-to-human and one case of pig-to-human.[16]

In 1978, Roy Calne opened liver transplantation unit in Cambridge, UK, and performed the first liver transplantation in Europe and the second largest transplantation series in the world.[17] Until 1977, Starzl and Calne contributed the majority of performed liver transplantation worldwide.[18]

The first hetero-topic liver transplants in man were reported by Apsolon in 1965; however, the first long-term survivor with this technique was reported by Fortner in 1973.[19]

In 1984, Shaw et al introduced the venovenous bypass system at Pittsburg University, leading to better hemodynamic stability during the standard liver transplantation.[20]

At the same time, Broelsch et al.[21] in the USA and Bismuth et al.[22] in France performed independently the first reduced-size liver transplantation. Thereafter, Pichlmayr et al.[23] reported the first split liver transplantation 1988. Meanwhile, Tzakis et al. introduced the piggyback technique with preservation of the recipient's vena cava.[24] With the increasing number of the patients on the waiting list, transplantation of partial liver grafts from living donors evolved to increase the donor pool. For this purpose, Broelsch et al. established the technique of segmental living donor liver transplantation (LDLT), and Strong et al. performed the first successful LDLT in 1989, implanting a left lateral segment into a pediatric patient.[25] In 1990, Broelsch et al. reported the first series of LDLT in the USA.[21] In 1991, the first domino liver transplantation using liver from donors affected by familial amyloidotic polyneuropathy type I was introduced by Holmgren et al.[26] In 1992, Belghiti and coworkers introduced a modified piggyback technique with a cavo-caval side-to-side

anastomosis.[27] One year later, Hashikura and colleagues transplanted a left hepatic lobe into an adult recipient in 1993,[28] and Yamaoka et al. implanted a right lobe into a pediatric recipient.[29] In 1996, Lo et al. performed the first successful liver transplantation using an extended right lobe from a living donor for an adult recipient.[30] In 1998, Tzakis et al. introduced liver transplantation with cavo-portal hemitransposition in the presence of diffuse portal vein thrombosis.[31] In 2002, Cherqui et al. reported first donor hepatectomy by a full laparoscopic procedure in which a left lateral lobectomy was successfully performed for liver transplantation in a child.[32]

## 2. Evolution of immunosuppression

Rejection of the transplant remained a major problem until cyclosporine-A was discovered by Jean Borel.[33] The 1-year survival rate following liver transplantation was 30% to 50% prior to the discovery of cyclosporine-A,[34,35] however, after the introduction of cyclosporine-A, the 1-year and 3-year survival rates were 74% and 67% in the first 1000 recipients treated with cyclosporine-A at the University of Pittsburgh in the early 1980s.[36] After these good results, growth of liver transplantation was facilitated by the conclusion of the National Institute of Health Consensus Development Conference in 1983 that liver transplantation is not an experimental procedure but an effective therapy that deserves broader application.[34] Shortly thereafter, the first monoclonal antibody OKT3 was discovered by Cosimi in 1981 and proved effective in treating acute transplant rejection and was sometimes used along with cyclosporine-A based regimen as immunoprophylaxis especially in North American Centers or to treat steroid resistant graft rejection.[37] Since then, many new immunosuppressive agents were introduced. In 1990, Mycophenolate mofetil (MMF, CellCept) was introduced by University of Wisconsin and proved, in combination with cyclosporine-A, to further reduce the incidence of graft rejection episodes better than azathioprine with less toxic effects.[38] In the same year, Rapamycin (Sirolimus) was introduced.[39] It is like cyclosporine-A but it has a different mechanism of action. It inhibits lymphocyte proliferation through prevention of ligation of IL-2 to the IL-2 receptors.[40] In 1994, Ochiai in Japan introduced tacrolimus (FK506, Prograf) and proved to reduce the incidence of transplant rejection more than cyclosporine A. It is like cyclosporine-A but hundred times more potent and is indicated in severe acute rejection resistant to standard immunosuppressive protocols and in chronic rejection.[41]

Greater understanding of the underlying liver disease, improved surgical and anaesthetic techniques, reliable immunosuppression and dependable postoperative care over the last few years have contributed towards improved results of liver transplantation. This success has resulted in a disproportionate increase in demand of liver transplantation and the appearance of a major problem of shortage of available donor organs, leading to a prolonged waiting times and high mortality on the waiting list.[42]

## 3. The progress in liver transplantation with donor shortage

The donor shortage together with the development of surgical skills of liver resections based on the knowledge of segmental anatomy of the liver described by Couinaud,[43] opened the door for innovative methods of transplantation including auxiliary liver transplantation, reduced-liver transplantation (RLT), split liver transplantation (SLT) and living donor liver

transplantation (LDLT).[44,45] Also, The donor shortage had led to the evolution of hepatocyte and stem cells transplantation which will be the future in the liver transplantation.

### 3.1 Auxiliary liver transplantation

Auxiliary liver transplantation (ALTx) consists of either implanting a healthy liver graft placed heterotopically or orthotopically while leaving all or part of the native liver. This concept was originated from an experimental work of Welch in 1955.[46, 47]

The first auxiliary liver transplantation in human was performed by Absolon in 1964,[48] and it was till 1972 when an auxiliary transplantation truly prolonged a human life.[49] During the following two decades, ALTx was done solely in a heterotopic manner - heterotopic auxiliary liver transplantation (HALTx), where a graft (usually partial) is placed below the un-resected native liver. The initial clinical results of HALTx were rather disappointing with a high rate of technical failure, probably due to inadequate portal perfusion of the graft and insufficient drainage of hepatic blood flow in an area of low pressure which had led to temporary abandonment of HALTx in the early 70s.[50-52]

Many efforts have been made ever since to improve post-transplant survival. Most notably, based upon the experiences in animal studies,[52-58] the contributions of Terpstra's group have improved the surgical techniques of HALTx with markedly increased post-HALTx survival rate.[58-63] Since 1980s', the concept of ALTx has further been extended by the introduction of a new approach -auxiliary partial orthotopic liver transplantation (APOLTx), where the left or the right lobe of the native liver is resected and replaced by an auxiliary graft.[64-71] The physiological position of the hepatic graft by this approach results in an optimal outflow pressure. Accumulating clinical results have shown a reduced incidence of post-transplant portal thrombosis.[65, 72, 73]

For certain types of non-cirrhotic metabolic disorders, such as type 1 Crigler-Najjar syndrome, urea cycle enzyme deficiencies, disorders of fatty acid metabolism, familial hypercholesterolemia, hemophilia and ornithine transcarbamylase deficiency, an auxiliary liver may correct the partial enzymatic deficiency responsible for the disease without the need to remove the otherwise normal native liver.[65, 66] A significant minority of patients with acute liver failure who fulfill the transplant criteria would have had complete morphological and functional recovery of their liver if they had not undergone orthotopic liver transplantation.[74] These considerations have led to the concept of auxiliary liver transplantation, which doesn't exclude the potential for spontaneous regeneration of the native liver and eventual withdrawal of immunosuppression drugs.[75-78]

In selected patient aged <40 years without hemodynamic instability, the use of ABO compatible, non-steatotic grafts harvested from young donors with normal liver function, can restore normal liver function and prevent the occurrence of irreversible brain damage. After standard immunosuppression, the recovery of the native liver is assessed by biopsies, hepatobiliary scintigraphy and computed tomography. When there is evidence of sufficient regeneration of the native liver, immunosuppression can be discontinued progressively. Complete regeneration of the native liver can be observed in >50% of patients, who can be withdrawn from immunosuppression. Therefore, the advantages of the auxiliary liver transplantation seem to balance with the potential inconvenience of this technique in

selected patients.[79-81] ALTx also preserves the patient's native liver, which remains accessible for future gene transfer therapy.[82]

### **3.2 Reduced-sized liver transplantation (RLT)**

It was first reported in 1984 by Bismuth, and involves ex-vivo resection of an adult cadaveric liver in order to create an appropriate sized liver graft for an infant or small child. It was introduced as a surgical solution for decreasing the pediatric liver transplant waiting list mortality using organs from donors much larger than the recipient, but does not increase the total number of livers available for transplantation. This is because the reduced-sized portion is not used and discarded.[22]

Initially, RLT was criticized because it disadvantaged adult patients awaiting liver transplantation and was to be associated with inferior results. The allegations regarding inferior graft and patient survival were proven wrong,[83-85] and several proponents of this technique actually reported a lower incidence of vascular complications since the caliber of the hepatic artery was larger than that seen in a pediatric donor.[86] Since this technique resulted in discarding the remaining portion of liver, it clearly had a negative impact on adult population awaiting liver transplantation, and for that reason, is rarely used today.

### **3.3 Split liver transplantation (SLT)**

In 1988, Pichlmayer in Germany and Bismuth in France simultaneously performed split liver transplantation (SLT), an ex-vivo splitting of a cadaveric liver allowing transplantation to a pediatric recipient and one adult.[23, 87] Unlike RLT, SLT resulted in an increased number of organs in donor pool with each cadaveric liver giving rise to two functioning allografts. The initial results of SLT, reported by Broelsch,[21] had a high rate of graft failure with a survival rate of only 67% in children and 20% in adults receiving a split liver transplants. In addition, 35% of patients required retransplantation and more than a quarter had biliary complications.[22] More recently, in-situ SLT has provided patient and graft survival similar to that seen in whole cadaveric transplantation.[88-90] The practical feasibility of split-liver transplantation as well as the increased safety of conventional liver surgery suddenly opened up the idea of removing part of the liver from a living donor.

### **3.4 Living donor liver transplantation (LDLT)**

This has been made possible by recent advances in hepatic surgery; first, improved understanding of the anatomy and the techniques of hepatic resections,[91] second, growing evidence that the operative risk of partial hepatectomy in a non-cirrhotic liver is extremely low,[92, 93] third, widespread success with RLT,[25, 83-85, 94] and fourth, the successful application of SLT.[95]

#### **3.4.1 LDLT in pediatrics**

LDLT was first introduced in pediatric population. In 1988, Raia in Brazil reported the first LDLT, establishing the technical feasibility of this procedure, yet both pediatric recipients died of complications.[96] Strong and colleagues subsequently reported the first successful pediatric LDLT using a left lobe graft from the child's mother.[25] Broelsch reported the first

successful series of LDLT with an overall graft survival of 75% and patient survival of 85%. [97] Furthermore, he was the first to report a prospective ethical analysis of this radical surgical innovation prior to performing their first LDLT. [98]

LDLT in children involves the removal of an adult donor left lateral segment (segment 2 and 3). Monosegment transplantation (segment 3) was introduced in Japan to solve the problem of “Large for size” grafts in small children. [99] The donor operation has been associated with a low and acceptable risk for complications. The donors being related to the recipients (parents), the risk for the donor is balanced by the great benefit to be received by the transplant recipient, as well as the donor’s psychological benefit.

LDLT was initially restricted to children with chronic disease, in relatively stable condition, in order to avoid a major psychological pressure on the potential donor. [98] With larger experience, it was extended to emergency cases such as fulminant hepatic failure. Auxiliary transplantation, initially developed in this indication, [78] and in metabolic disorders, [100] could also be performed with a living donor liver. [101-104]

The continued shortage of cadaver livers in the face of growing list of recipients plus the advantages of LDLT have led to the introduction of LDLT in adults.

### 3.4.2 Adult-to-adult LDLT

The expansion of LDLT to the adult population began in the countries where the availability of deceased donors was scarce, and in some cases, totally unavailable. [105-107] The law for deceased organ retrieval was instituted in Japan in 1998, however, the lack of societal acceptance of organ retrieval from brain dead donors resulted in live donation being the main source of grafts for patients awaiting transplantation in Japan and other countries in Asia. [108]

On November 2, 1993, the Shinshu group performed the first successful adult-to-adult LDLT. [28] By June 2002, there were 433 adult LDLT cases recorded in European Liver Transplantation Registry, [109] with 3 years graft and patient survival rate of 65% and 68% respectively. According to the United Network for Organ Sharing (UNOS), 731 adult LDLT cases have been performed in the United States by October 2001. The 3 years graft survival was 47% between 1998 and 1999 (n=156) but it improved significantly to 61% between July 1999 and June 2001 (n=285). [110] According to the Japanese Liver Transplantation Society, 1063 adult LDLT procedures were performed in Japan by the end of 2002. The 5 years survival rates were 83% in children and 69% in adults. [111] The lesser outcome in adults compared to that in children indicates that problems remain in adult LDLT.

In LDLT, donor safety must be assured. This may be achieved by optimizing graft size to ensure safety of both donor and recipient, technical expertise in liver procurement from the donor as well as ethical problems of using non-related live donors. As regarding the optimum size of the graft, it was found that, a graft volume of >40% of the recipient standard liver volume is necessary, [112] while for the living donor the remnant liver mass must be more than 30% of the whole liver. [113] The term “standard liver volume” has become a key concept in LDLT and it has been estimated using the following formula: [114]

$$\text{Standard liver volume (SV) in ml} = 706.2 \times (\text{body surface area [m}^2\text{]}) + 2.4.$$

In order to obtain the optimum graft size in adult-to-adult living donor transplantation, many graft types have been introduced. The strategy of selection of left or right liver graft is influenced by the patient's preoperative condition as patient with advanced liver disease require a larger liver mass.[115] The model for end-stage liver disease (MELD) score could become a satisfactory criterion for differentiating between high and low-risk patients and therefore determine the type of graft to use.[116] In the initial adult LDLT procedures only a left liver graft was used. In 1998, the Shinshu group reported satisfactory results using a left liver graft in 13 patients.[107] To cover wide range of recipient body weight, the right lobe graft was introduced in 1998 in Kyoto university.[117] In the same year, the University of Colorado group also introduced the right liver graft in adult LDLT,[118] the group performed 80 adult LDLT. In the first 10 cases, the right lobe graft was procured without the middle hepatic vein (MHV), 3 grafts were lost. As a result, the group included the MHV in the right lobe graft in the subsequent 70 cases. No graft loss was experienced.[119] The reason may be due to the prevention of congestion of the anterior segment of the right lobe which is drained by the MHV. However, the right lobe graft including the MHV was first introduced by the Hong Kong group in 1996.[106] In this situation, the volume of the remnant liver should be at least greater than 30% and the anatomy of vein 4 must be precisely evaluated before this procedure is accepted. However, the outcome of initial 8 donors and recipients were not without complications, one recipient died and the recipients as well as the donors experienced high morbidity.[106] The next 92 patients subsequently received extended right liver grafts (right lobe graft including the MHV) with the following innovations: elimination of venovenous bypass from the routine protocol, preservation of segment 4 venous drainage for donors, venoplasty of MHV and right hepatic vein (RHV) into a single orifice for better venous return and easy vein reconstruction in recipients and preservation of the blood supply to the right hepatic ducts. Over time the mortality rate of recipient decrease from 16% in the initial 50 cases to 0% in more recent patients.[120]

Lee, aggressively reconstructed the MHV tributaries in right liver grafts without the MHV trunk and named this type of graft a modified right lobe graft.[121] Ghobrial, also recommended reconstruction of the MHV tributary veins when the RHV in the graft was <1.5 cm in diameter.[90] All MHV tributaries with a size >5 mm should be preserved during donor hepatectomy and reconstructed with autogenous interposition vein grafts.[122]

Right hepatectomy imposes an increased surgical risk on the donor due to the reduced residual liver volume. A recent report indicated that in 25% of potential donors, the right liver had an estimated volume of >70% of the whole.[123] Since safe donation was possible only when estimated residual liver volume was >30%, right hepatectomy is not possible for some potential donors. The University of Tokyo group was the first to design the right lateral sector graft consisting of segment 6 and 7 in those donors with right livers over 70% of liver volume and the estimated volume of the right lateral segments is greater than that of the left liver and at the same time >40% of the recipient's standard liver volume.[124] Between January 2000 and April 2001, 6 of 32 adult-to-adult LDLT with a right lateral sector graft were performed. The postoperative course was uneventful in all donors and all recipients survived the operation.[125]

Lee et al, were the first to devise dual grafts from 2 living donors.[126] Most commonly, both donors donate the left liver or left lateral segment. The first left liver graft is orthotopically implanted in the original left position, the second left liver graft is rotated 180



degrees and positioned heterotopically in the right upper quadrant fossa. Because the bile duct is now located behind the portal vein and hepatic artery, bile duct reconstruction is necessary before reconstruction of vessels. An interposition vein graft might be necessary for the reconstruction of the hepatic or portal vein. By the end of 2003, this technique was used in 93 patients with satisfactory results. However the procedure has limited appeal due to the high requirements of economic and medical resources including 3 operating rooms and 3 surgical teams working simultaneously.[127]

#### 4. Hepatocyte and stem cells transplantation

Additional approaches, as therapeutic alternative in attempt to reduce the significant mortality in the waiting list for liver transplantation is hepatocyte transplantation. A number of experiments have shown the feasibility of total liver parenchymal cell replacement by transplanted hepatocytes.[128-132] Hepatocyte transplantation might be able to bridge a period needed for regeneration of the acute liver failure patient's own liver or stretch the waiting time for a suitable liver donation. Although the first animal experiments with this technique began in 1967 [133], it was first applied in humans only in 1992.[134] Isolated Hepatocyte transplantation has long been recognized as a potential treatment for life-threatening liver disease. The basis for proceeding with clinical trials has been provided by extensive laboratory work in animal models.[135-140] The most important advantage of this treatment compared to liver transplantation, is its simplicity, since no surgery is required for cell implantation. The cell transplantation has been used for, temporary metabolic support of patients in end-stage liver failure awaiting whole-organ transplantation, as method to support liver function and facilitate the regeneration of the native liver in cases of fulminant hepatic failure, and in a manner similar to gene therapy as a form of "cellular therapy" for patients with genetic defects in vital liver functions. The patients can be treated by the infusion of  $10^7$ - $10^{10}$  allogenic hepatocytes, obtained from adult cadaveric livers, into the splenic artery or portal vein.[141] The main obstacle to wider usage of hepatocyte transplantation is the rapid elimination of the transplanted hepatocytes by recipient macrophages.[142]

Alternatives to the transplantation of allogenic human hepatocytes include the transplantation of hepatocytes derived from fetal, adult, or embryonic stem cells, engineered immortalized cells, or hepatocytes derived from other animal species.[143] Stem cells are one of the best approaches to obtaining cell stores. This approach can be used for clinical treatment by selecting small cell population that could effectively repopulate the host liver.[144]

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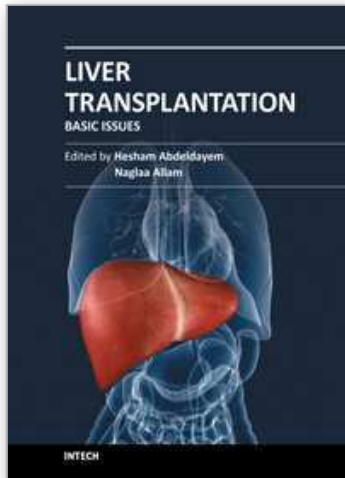
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## **Liver Transplantation - Basic Issues**

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This book covers a wide spectrum of topics including history of liver transplantation, ischemia-reperfusion injury, immunology of liver transplantation, viral hepatitis and liver transplantation, other indications for liver transplantation, prognostic factors and perioperative period. The authors of the chapters are experts in their respective fields. They are proponents covering different aspects of liver transplantation and come from many centers across the world. The interdisciplinary approach and the authority of the contributors resulted in a valuable reference to anyone interested in developing a global view in liver transplantation including medical students, residents, fellows, nurses, and practicing physicians and surgeons as well as researchers in the field of liver transplantation.

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