History of Liver Transplantation

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"It was all nothing but a kind of a wild science fiction at the beginning, but as realistic as the dream of putting a man on the surface of the moon was at that time. They both did not sound like anything very rational, but they both turned out to work at around the same time."

Thomas Starzl, MD

Introduction

In the above quote from an interview at the 2014 International Small Bowel Transplant Symposium [1], Dr. Thomas Starzl compares the pioneering of liver transplantation to the Space Race. Starzl performed the first successful human liver transplantation in 1967. Two years later, the United States ended the Space Race by landing on the moon in 1969.

Beyond the contemporary nature of these two enormous achievements, however, are many deeper similarities. Both endeavors pushed what was once science fiction—the *Frankenstein* of Mary Shelley and *From the Earth to the Moon* of Jules Verne—into the forefront of reality. Both opened up entire frontiers of what was possible: replacing failing organs and traveling to another celestial body. Both were races against time, with human lives and national pride on the line. Most importantly, both stories are culminations of decades of perseverance through failures, setbacks, and surprises.

If there was ever a story that captured the elaborate dance between clinical medicine and scientific research, and how each propels the other to new heights, it would be the story of organ transplantation. The failure of the liver, an organ recognized since prehistoric times to be essential to life, had been universally fatal throughout mankind's history. We now have the ability to cure it. As you shall see, the journey was long and riddled with one obstacle after another, but they were overcome by scientists, physicians, surgeons, policymakers, and patients working toward a common goal. However, recording history is an imperfect art, and the story of liver transplantation continues to be revised and debated even today.

A lot has been accomplished in a relatively short timeframe, and today, liver transplantation is an established therapy that is safer than ever. In contrast, just 50 years ago, we simply could not treat patients with end-stage liver disease (ESLD). Thus, while caring for patients with ESLD today can be challenging and exhausting, we now have more surgical and medical options than ever before.

How Our Ancient Ancestors Viewed the Liver

Surgically replacing the liver is a very modern invention, but our ancestors knew a surprising amount about the liver, even if they could not manipulate it. Many scholars believe that the ancient Greek myth of Prometheus—a Titan who stole fire from Zeus and gifted it to man—was evidence that the Greeks knew about the incredible regenerative ability of the liver. As eternal punishment for his act, Prometheus was chained to a mountain in the Caucasus, and an eagle would peck out his liver every day, only for the liver to grow back, and the punishment repeated the next day.

Several prominent Greek physicians made particular observations of the liver. Herophilus and later Galen, for example, wrote about the lobar nature of liver anatomy [2], an observation that unlocked the secret of safe liver surgery two millennia later. Hippocrates and then Celsus also made mention of draining liver abscesses in their works [3].

Not surprisingly, liver medicine did not advance much during the Middle Ages. In the nineteenth century, there was anecdotal evidence depicting salvage liver resections in the setting of trauma [2]. These accounts made it very clear that the liver bleeds easily and heavily—a feature which would mount a formidable obstacle for the pioneers of liver transplantation. And thus the liver continued, until the end of the nineteenth century, to be viewed as inoperable.

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At the time, patients with ESLD universally had poor prognoses. The course of clinical decline—the ascites, peritonitis, variceal bleeding, and encephalopathy—seemed irreversible, and physicians were powerless to provide more than supportive care.

Overcoming the Early Surgical and Immunological Barriers of Transplantation

In the early twentieth century, there was a great interest in the scientific and medical communities for organ grafting. Isolated reports of attempts at animal solid-organ transplants emerged around this time, but they were largely unsuccessful.

The first attempt at *human* solid-organ transplantation came in 1906, when French surgeon Dr. Mathieu Jaboulay reported two cases of kidney xenotransplantation. The first was the left kidney of a pig that was transplanted into the antecubital space of a woman with nephrotic syndrome; the second was a goat kidney transplanted into a woman who had lost a kidney due to infection [4, 5]. Neither graft worked, which Jaboulay attributed to vascular thrombosis.

Around the same time, one of Jaboulay's students, Dr. Alexis Carrel, was making important contributions to organ transplantation by pioneering end-to-end suture techniques that could reconnect vessels. This included anastomosing fragile veins—a feat considered impossible at the time. Using these techniques, he then experimented on a variety of transplant operations in animals. In a landmark paper published in the Journal of the American Medical Association in 1908, Carrel described the transplantation of kidneys, spleens, and even faces in various animal models [6]. He also reported the use of cold fluids to preserve the tissue for transplantation, a practice which continues even today. In many cases, the cats and dogs who underwent these invasive surgeries had good outcomes months after the procedure. But consistent with previous findings, Carrel observed that organs transplanted between zoologically distant organisms underwent deterioration, which he termed "cytolysis." Altogether, Carrel's vascular surgery innovations and systematic transplantation experiments in animals cleared an important technical hurdle to transplantation in humans. Carrel was awarded the Nobel Prize in Physiology or Medicine in 1912.

Sophisticated experimental work in animal models continued for the next three decades. The technical hurdle of transplantation (i.e., the vascular anastomosis) appeared to have been mastered, but in many cases, the organs were still not surviving. No one understood why this was happening, short of the "biological incompatibility" described by Carrel and his predecessors. Many leaders in the field thus saw organ transplantation as ultimately nonviable, and interest began to wane. In addition, much of the focus in research and clinical care was now being shifted toward the World Wars.

It was Professor Peter Medawar, a British biologist, who eventually solved the mystery of biological incompatibility. He was recruited by the British Medical Research Council to work on skin allotransplantation, as necessitated by the trauma and burns from World War II. His work unveiled the immune system as the main vehicle of biological incompatibility and established many of the tenants of immunological tolerance and rejection. He and his student Dr. Frank Burnet even demonstrated that tolerance to foreign tissue could be "acquired" early during embryogenesis, which would then prevent the recipient from rejecting this foreign tissue in the future. Medawar and Burnet published extensively on this subject in the 1950s and eventually won a Nobel Prize in Physiology or Medicine in 1960. Medawar was knighted by the British government in 1965, and in 1968, he was elected as the first President of the Transplantation Society (TTS), which is one of the world's largest transplantation organizations today.

With Medawar's work showing that the immune system was at the core of organ rejection, interest in transplantation revived. Thus came a string of successes in the field of kidney transplantation, starting with the first successful kidney transplant in 1954.

The Preclinical Successes with Liver Transplantation

The liver was long considered an organ too complex to manipulate, with its dual blood supply and its venous drainage into the inferior vena cava (IVC), a vein most surgically unforgiving. Thus, successful liver transplants in humans lagged more than a decade behind kidney transplants.

The 1950s brought several breakthroughs in preclinical liver transplantation. Dr. Vittorio Staudacher from the University of Milan was (recently) credited with the first liver transplant procedure in canines, reported in 1952 [7, 8]. Previously, the achievement was credited to Dr. Cristopher Welch from Albany Medical College, who in 1955 published a one-page manuscript describing his work on transplanting auxiliary liver segments into the abdominal cavity of dogs [9]. Although using auxiliary segments bypassed the need for a hepatectomy, the transplanted segments nonetheless deteriorated, which was likely due to a combination of rejection and ischemia. One year later, Dr. Jack Cannon from the University of California, Los Angeles, described orthotopic liver transplantation, in which the animal's own liver (presumably a canine) was removed and replaced by a full-size donor liver into the correct anatomic position [10].

Work in the dog model was further expounded by three surgeons who all went on to become the fathers of human liver transplantation. In 1958, Dr. Francis Moore, the Chief

of Surgery at the Brigham Hospital, was looking to extend their success with kidney transplantation into the field of liver transplantation. He established a formal canine liver transplantation program, which performed over 30 canine liver transplants and published extensively on various surgical aspects of the demanding procedure [11, 12].

Dr. Thomas Starzl, meanwhile, was working out of Northwestern University in Chicago. As a surgical resident, Starzl had a strong interest in the physiology of portal venous circulation and developed several surgical models to remove and replace the liver, including abdominal multi-visceral organ transplantation [13, 14]. He was then awarded a Markle Scholars in Medicine Fellowship, which funded him to formally study liver transplantation and engineer it into a viable clinical service [15]. Starzl and his team eventually performed over 80 liver transplants in dogs [16].

Both groups made progress in tackling what was then a substantial surgical roadblock. Clamping the portal vein and the IVC in their dog model, an essential step during the removal of the native liver, usually resulted in the death of the animal [17]. Moore and colleagues developed a veno-venous bypass system that shunted the blood from the IVC and the portal vein to the superior vena cava (SVC). Starzl's team, on the other hand, pioneered the strategy of using a portocaval shunt to first divert blood from the portal vein to the IVC and then draining the IVC to the SVC via an iliac vein cannula and avoiding the clamped liver [18].

The third individual who helped usher in the era of successful liver transplantation was an English surgeon Dr. Roy Calne. As a medical student in 1950, Calne was taking care of a patient with kidney failure and saddened by the reality that their entire team could not provide anything more than supportive care [19]. He was interested in unraveling the immune system to allow humans to benefit from transplants—something that even Medawar did not believe could happen [13]. Calne's early work as a faculty focused on developing strategies to suppress the immune system. The only tool available at that time was whole-body irradiation, which Calne found ineffective in the setting of solid-organ transplantation. He worked on a relatively novel drug—6-mercaptopurine (6-MP)—and demonstrated that it prolonged kidney graft survival in dogs [19].

Encouraged by Medawar, Calne applied for and received a Harkness Fellowship in 1960, which allowed him to travel to Harvard Medical School. He observed Moore and his canine liver transplant experiments, which were dubbed the "sputnik" procedures (again drawing a parallel between liver transplantation and the Space Race) [18]. He started a series of experiments with Murray in dogs to test the efficacy of several new immunosuppressive compounds. One of them—azathioprine—was found to be more effective than 6-MP and actually allowed for long-term graft survival [12]. Starzl also tested azathioprine in dogs and found the *combination* of azathioprine and steroids to be even more efficacious. Calne returned to England in 1961 and subsequently initiated the clinical use of azathioprine and steroids for his kidney transplant program. In 1965, Calne was promoted as the Chair of Surgery at the University of Cambridge.

The First Human Attempt and the Moratorium

In 1962, Starzl joined the University of Colorado in Denver as an Associate Professor of Surgery. Denver was one of the only centers outside of Boston that had a commitment to transplantation and also had one of the few dialysis units in the country at the time [1]. There, Starzl started a successful kidney transplant program [1, 20]. Given the increasingly successful worldwide experience with kidney transplantation, the opportunity was ripe for an attempt at liver transplantation [14].

On March 1, 1963, Starzl attempted a liver transplant for a 3-year-old boy with biliary atresia, a congenital defect in the bile ducts. To reduce the risk of organ rejection, the patient underwent a pre-transplant thymectomy, as well as 13 days of azathioprine treatment [21]. But as Starzl recalls, upon starting the operation: "Nothing we had done in advance could have prepared us for the enormity of the task. Several hours were required just to make the incision and enter the abdomen. Every piece of tissue that was cut contained the small veins under high pressure that had resulted from obstruction of the portal vein by the diseased liver. Inside the abdomen, Bennie's liver was encased in scar tissue left over from operations performed shortly after his birth. His intestine and stomach were stuck to the liver in this mass of bloody scar. To make things worse, Bennie's blood would not clot…he bled to death as we worked desperately to stop the hemorrhage. The operation could not be completed." [22]

Despite this adverse outcome, the effort continued, and several more liver transplants were attempted thereafter. Two were performed by Starzl for primary liver cancer. Both adult patients tolerated the initial surgery, but only survived for 7 and 22 days, succumbing to pulmonary embolism, likely from the veno-venous bypass tubing [23]. Among the next four attempts, including two by Starzl, and one by Moore, none survived beyond 23 days. In addition, several attempts at auxiliary liver transplantation in the United States (three by Starzl), Australia, and the United Kingdom were also unsuccessful [20]. Thus, liver transplantation continued to be viewed as an insurmountable challenge and an impractical risk, and a voluntary worldwide moratorium was placed on this procedure.

While kidney transplant programs continued to thrive, liver transplantation ceased. However, Starzl did not give up. He and others reexamined the early outcomes, returned to

the laboratory, and worked to find solutions during this moratorium. Starzl continued experimentation on various aspects of transplantation, including xenotransplantation and tissue-type matching [13]. In 1966, a preservation chamber was developed in Denver which improved organ survival ex vivo [24]. Most importantly, Starzl and his team began preparing and testing antihuman antilymphocyte globulin (ALG), obtained from inoculated horses. It was the first time that antibodies targeted against the cells of the adaptive immune system were used as immunosuppression. Trials using ALG in combination with azathioprine and steroids, first in dogs and then in kidney transplant patients, demonstrated its clinical efficacy [15, 20].

In addition, several individuals, including Calne, Starzl, and, French surgeon, Dr. Henri Garnier, began observing an interesting immunological property of the liver. In some species, such as pigs, an orthotopic liver transplant could survive indefinitely without any immunosuppression. Furthermore, if *another* organ was transplanted at the same time as the liver, that organ would also have prolonged survival [18]. Unfortunately, the same observation could not be made in humans and dogs, which still rejected their grafts. However, a certain subset of the dogs in the transplant cohort continued to accept their graft long after immunosuppression was stopped. These observations suggested that the liver was an immune "privileged" organ and might eventually be immune-tolerated by the recipient, a discovery which renewed hope in successful liver transplantation.

The First Human Successes on Both Sides of the Atlantic

After 3 years of renewed focus, Starzl reopened the liver transplantation program in Denver. On July of 1967, Starzl performed what would be the first successful liver transplantation. The patient was a 19-month-old girl with hepatocellular carcinoma and ESLD. She underwent a successful liver transplant as well as a splenectomy, with the donor liver maintained in a preservation chamber for 3 hours [20]. She was treated postoperatively with azathioprine, prednisolone, and ALG. She had good liver function for a year but unfortunately succumbed to cancer recurrence [25].

Starzl went on to perform seven more liver transplants, all in the pediatric population (ages 13 months to 16 years). The most common indication was for biliary atresia. Of these first eight patients, four died within the first 6 months due to liver infarction and sepsis, two died of liver cancer recurrence after 1 year post-transplantation, and one died of chronic rejection [25]. The last patient, as of 2002, was still alive and off immunosuppression [23].

In Europe, a liver transplant had been attempted in 1964 by Dr. Jean Demirleau, but the patient only survived for 3 hours [26]. Calne, who had continued to perform experimental liver transplants in pigs in England, observed Starzl's program gaining momentum in Denver and was ready to attempt a liver transplant at his home institution of Addenbrooke's Hospital at the University of Cambridge.

A well-told story of Calne's first liver transplantation unfolded as such. In 1968, a lady with a primary liver malignancy was referred to Calne. She was anxious to proceed despite the dangers disclosed to her, because "she said she had nothing to lose" [18]. A few weeks later, a young child became irreversibly comatose due to a viral infection of the brain stem, and the parents gave permission for the child's kidneys and liver to be used to help other patients.

When Calne presented the potential donor and recipient to a council of his medical colleagues, they all swiftly opposed the operation, citing a spectrum of medical and ethical risks. But Calne had an ace card: he introduced the world-famous Moore, who happened to be in Cambridge visiting his son, to the council [17]. Moore affirmed his support by simply saying, "Roy, you have to do it." Suddenly, the tide of the room changed [18]. Calne, with Moore as the first assistant, proceeded immediately to the operating room.

Per Calne's accounts, that first operation went smoothly. He utilized a "piggyback" technique, in which the donor IVC was anastomosed directly to the side of the recipient's IVC (which is otherwise left intact), instead of the conventional method of replacing the recipient's retrohepatic IVC with the IVC of the graft. This technique was necessary because of the size mismatch between the pediatric donor and the adult recipient, but as Calne smugly notes, "this operation was re-invented years later by other teams, who had not read our 1968 report in the British Medical Journal." [18] Unfortunately, Calne's patient passed away 3 months later due to pneumonia, secondary to immunosuppression.

The First Decade: From Few to Many

In the first few years, the mortality associated with this experimental procedure remained dismal. A survey published by the American College of Surgeons and the National Institutes of Health Organ Transplant Registry in 1972 showed that, by 1969, 81 orthotopic and 32 heterotopic liver transplants had been performed, the majority of which were from either Denver (Starzl's group) or Cambridge (Calne's group) [27]. Only 9% of patients (13 patients, all with orthotropic liver grafts) survived beyond 1 year. For the next decade, outcomes had only marginally improved—1-year survival was 23.7% for the Cambridge group and 38% for the Denver group [28]. There was pressure to arrest liver transplantation programs—the procedure was dangerous as well as a huge drain of resources (e.g., a single liver transplant could consume the supply of an entire blood bank).

Several important evolutions in liver transplantation occurred in the next decade as the learning curve continued:

First, the pioneering centers developed pipelines to overcome the logistical demands of liver transplantation, which involved coordinating two operations (a donor operation and a recipient operation) that were often separated by time and space, and a vast multitude of nonsurgical providers who must act in perfect unison to keep patients stable and organs viable. In England, Calne partnered with former colleague Dr. Roger Williams, a liver failure expert from King's College Hospital in London. Williams was the rare internal medicine physician who shared Calne's enthusiasm for liver transplantation because Williams knew firsthand the poor prognosis of these patients without an operation. Whenever a prospective donor at any neighboring hospital became available, teams from both Addenbrooke and King's would be mobilized. An intensive care team from King's would bring the liver patient to the donor hospital, where a surgical team from Addenbrooke would converge at the same time. The surgical team would wait in sterile operating room attire, while the ventilator for the donor patient was turned off. After the anesthesiologist declared cessation of cardiac activity, the donor liver and kidneys were perfused surgically with cooling solution, removed, and further preserved with sterile ice. At this point, the recipient would be taken to the operating room. After recovering for 2 weeks, the patient would be transferred back to either King's or Addenbrooke [18].

Second, the concept of brain death ("coma depasse") became accepted. Previously, a patient with irreversible brain injury had to be disconnected from life support—usually artificial ventilation—and the heart allowed to fully stop on its own, before the patient was considered "deceased" and suitable to donate organs. In 1968, for the first time, donation after brain death but with a beating heart was allowed in France. Brain death was accepted in the United States that same year, and later in England in 1976 [29]. This change refined the organ donation procedures, allowed grafts to be more easily transported, and resulted in better graft and patient survival.

Third, the final breakthrough was the discovery of cyclosporine in 1972 by Swiss physician Dr. Jean Borel, which Calne called a "watershed moment" in transplantation [19]. Calne first used it in liver transplantation in 1978 [28]. Cyclosporine could specifically target lymphocytes, the main vehicles of immune rejection. The concomitant use of cyclosporine with steroids starting in the 1980s dramatically improved outcomes, leading to 1-year survival close to 70% [28, 30]. Cyclosporine was approved by the Food and Drug Administration (FDA) in 1983, and its use has led to lower toxicity and overall improved outcomes across both kidney and liver transplants.

In 1980, Starzl moved to the University of Pittsburgh. Immediately, their liver transplant program blossomed, which Starzl attributed to the large supply of cyclosporine available [1]. Pittsburgh became the worldwide leader in liver transplantation, with many surgeons and physicians traveling there in the 1980s to receive training in this newly emerging field. Dr. Russell Strong, for example, trained there in 1984 and went on to not only start the first transplantation unit in Australia but also perform the first living donor liver transplant in 1989 [31]. Dr. Carlos Esquivel, one of our co-authors, also trained under Starzl during this period and subsequently founded a transplant program at the California Pacific Medical Center in San Francisco in 1988. By that time, Pittsburgh had already reached 1000 human liver transplants [30].

From an Experimental Procedure to a Mainstream Clinical Service

Despite this progress in the late 1970s, liver transplantation was still not widely accepted as a reliable treatment. Experience was limited to only a handful of centers in the United States and Europe. One particular area of challenge was transplanting livers in infants and young patients, for whom suitable donors were rare and technical aspects more daunting. The rate of mortality from vascular complications in these patients was unacceptably high, resulting in another self-imposed moratorium for young children. In 1984, after working with Starzl for a few years, Esquivel moved to the Children's Hospital of Pittsburgh and began focusing exclusively on young children. His group published the first series of liver transplants in patients younger than 1 year of age in 1987 [32]. While outcomes improved, the scarcity of donors remained a problem [33].

For the next few years, the surgical techniques continued to be refined, anesthesia support improved, and a second generation of surgeons slowly took on the mantle of liver transplantation, primarily by joining donor teams. In addition, newer preservation solutions became available which staved off ischemic injury and allowed more control over the logistics of transplantation. This culminated in the University of Wisconsin solution, developed by James Southard and Folkert Belzer in 1987 [34]. The UW solution mimics intracellular osmolarities using inert substances while scavenging free radicals and remains the gold standard for cold preservation solution even today.

On June 20, 1983, the US Surgeon General Everett Koop, encouraged by Starzl and President Ronald Reagan, called for a National Institutes of Health (NIH) Consensus Development Conference on liver transplantation in Bethesda, Maryland. Liver transplant teams from four countries—the United States, Germany, England, and the Netherlands—gathered to present their data. After reviewing the outcome of 531 liver transplant cases, including comparisons to ESLD

patients who did not receive a liver transplant, the expert panel approved liver transplantation as a valid "clinical service" to aid patients with cirrhosis and liver failure [35]. Liver transplantation was no longer an experimental procedure reserved as a last-ditch effort, but a standard treatment that could be utilized electively. This shift was further bolstered by a large study in 1989, by Starzl and colleagues, which examined 1179 liver transplant patients, whom had 1- and 5-year survival rates of 73% and 64% on cyclosporine, exceeding that of ESLD [36].

Partially because of these findings and the NIH consensus, more and more transplant centers emerged across the world in the 1980s. This was followed by a liver transplant by Dr. Carl-Gustav Groth, a protégé of Starzl, in Sweden in 1984 [20]; in Brazil [37] and Australia [31] in 1985; and in France, by Dr. Henri Bismuth in 1993 [38].

In Asia, the first described attempt at liver transplantation was by Dr. Nakayama in Japan in 1964 [39]. The second case (1978) was in China for a patient with advanced hepatocellular carcinoma [40]. While liver transplantation took off rather slowly in Asia, several Asian countries were instrumental in pushing the frontiers of living donor liver transplantation (LDLT). This was driven by several region-unique factors such as cultural and religious views against organ harvesting, the late adoption of brain death criteria in 1987 [39], and the high incidence of hepatitis B and C infections and resultant liver cancer.

Governing Fair Organ Allocation

As the indications for liver transplantation and the centers that could safely perform them expanded, the demand quickly exceeded the availability of livers. In 1988, there were 616 patients on the waiting list in the United States. By 1998, the number had risen to 12,000. Along with increased transplant demands, the average wait times increased and mortality while waiting for a liver grew exponentially.

In the first two decades of liver transplantation in the United States, allocations were managed by the individual transplant centers themselves [35]. In 1984, Congress passed the National Organ Transplant Act (NOTA) giving the federal government broad oversight over organ allocation, including prohibiting the sale of organs (see Chap. 2).

Suddenly, the organ allocation policies in the United States underwent several major changes in the 1990s. Initially, organ allocation was based on the length of time on the wait list. However, this prompted clinicians to aggressively enlist their patients earlier and earlier, thus inflating the wait list. In 1998, UNOS introduced a system of stratifying patients into four levels of acuity. Status 1 was emergent need, status 2 was intensive care unit (ICU), status 3 was inpatient, and status 4 was outpatient. Available organs were given to status 1 patients first, and so forth. Several problems with this allocation strategy emerged, including the fact that within a specific UNOS geographic region, there were multiple patients with the same status. This led to the development of the Child–Turcotte–Pugh score, which attempted to further stratify patients based on disease severity using several metrics, some of which were subjective.

In 1998, the US Department of Health and Human Services, under pressure from both the public and Congress, issued a regulation known as "the Organ Procurement and Transplantation Network (OPTN) Final Rule." This provision called for more objective and uniform organ allocation policies that would eliminate some of the geographic variability in terms of wait times. After much work, the Model for End-Stage Liver Disease (MELD) and Pediatric End-Stage Liver Disease (PELD) systems were implemented in 2002 as the central component of organ allocation priority. The MELD and PELD scores are well-studied metrics which can be calculated based on objective laboratory data and have been shown to predict mortality while on wait list. Therefore, a patient with a higher MELD or PELD score would get higher priority than a patient with a lower score.

In Europe, allocation systems vary by country and even by institution. In the late 2000s, many European transplant centers shifted to incorporating MELD/PELD as part of the criteria, based on the experience from the United States [41].

Organ Shortage Drives Surgical Innovation

Increasing the organ supply is an important ongoing effort in the field of liver transplantation. Promoting the use of expanded criteria donors (ECD) (e.g., donors who are older, have comorbidities, or have blood-borne infection history) is one strategy. ECD also includes donation after cardiac death (DCD). DCDs grew from 0.5% of liver transplants in 1999 to over 4.5% in 2008 [42]. These factors make the graft suboptimal, and when obtaining consent from liver transplant recipients today, disclosure about the quality and nature of the graft constitutes a key component. By using ECDs, more patients are able to come off the wait list and receive a life-preserving organ.

In addition, newer surgical techniques have allowed for LDLT. Living donation for kidneys has been around since its inception, but the liver is a non-paired organ, and surgically splitting the liver safely into two functional units (and relying on the remaining liver to regenerate) is a much newer breakthrough. The first required step was to be able to reduce a cadaveric donor liver down to appropriate size for the recipient. Recently, it was reported that Dr. Henry Gans and colleagues from the New York Hospital-Cornell Medical Center performed the first reduced-size liver transplant in 1969 [43]. Gans had resected the left lobe of the donor liver

for a 24-year-old patient with ESLD whose abdomen was not large enough to accommodate the entire graft. It was Dr. Bismuth who had been classically credited with the first successful downsizing of an adult deceased donor liver into just the left lobe and successfully transplanting this reduced liver into a pediatric recipient in 1984 [44]. These pioneering cases, although utilizing cadaveric livers, established the tenet that livers can be split along its lobar planes and still function well as grafts.

A few years later, the first reported attempt at LDLT was performed in 1988 by Dr. Silvana Raia and colleagues in Sao Paulo, Brazil [37]. The patient was a young 4-year-old girl whose mother donated her left lateral segment; unfortunately, the child died 6 days postoperatively from hemolytic anemia, secondary to blood type mismatch. The mother recovered well after her donor procedure and eventually became pregnant again.

In 1989, Dr. Strong, who had trained with Starzl, reported on using the left lateral segment in a LDLT in Brisbane for a pediatric recipient [45]. This was considered the first successful LDLT in the world. Later that year, Raia performed a second LDLT for a 19-month-old girl with Caroli's disease. In this case, a healthy 40-year-old altruistic man volunteered for organ donation [37]. Natural expansions of LDLT techniques came shortly thereafter. In 1993, the first successful left lobe living donor transplant between adults [46] and the first successful right liver graft from adult to child [47] were performed. This was followed in 1996 by the first successful extended right lobe for adult-to-adult liver transplantation, performed in Hong Kong [48].

The first LDLT in the United States was performed by Dr. Christoph Broelsch at the University of Chicago in 1989. However, the utilization of LDLT in the United States appears to have peaked in 2002, when around 10% of liver transplantations involved a living donor [49]. One primary reason was the medical and ethical concerns of subjecting a healthy individual to a surgical procedure and possible liver failure, without any direct benefit to that individual. Partial hepatectomies for living donors carry a reported mortality of 0.5–1% and a morbidity of 20%—one living donor even required a liver transplant himself [50, 51]!

Split cadaveric livers were another method developed to address the organ shortage. An adult-sized graft from a deceased donor would be split along anatomic planes—initially on a back table—and prepared for transplantation into two separate recipients, usually one adult (receiving the larger right lobe) and one child (left lobe). Dr. Rudolf Pichlmayr from Germany first performed and described this technique in 1988 [52]. Broelsch and Strong subsequently championed this technique at their respective institutions in Chicago and Brisbane. Broelsch published a series in 1989, detailing 9 whole livers that were split to treat 18 patients [53]. Patient and graft survival were similar to whole organ transplantation, although biliary complications were higher in the split liver group. In 1996, a group from Germany published on splitting the liver in situ in a deceased donor [54]. This newer technique has the benefit of better hemostasis and reduced ischemia times. However, currently, the surgical complexity of splitting a liver and the prospect of sacrificing one good liver for two riskier grafts have prevented widespread adoption of this technique.

Despite these advanced techniques, however, the organ shortage crisis has persisted and appears to be worsening. In 2010, for example, 11,352 new patients were added to the liver wait list, but only 6291 patients underwent liver transplantation [55]. The outcomes of both LDLT and split livers will continue to improve until they are equivalent to that of cadaveric whole liver transplant, but it remains to be seen whether they can be adopted widely enough to put a dent on the organ shortage.

The Next Generation of Strategies to Protect the Liver Graft

Several important next-generation immunosuppressants have been introduced in the past two decades. In the late 1980s, many liver grafts continued to show signs of rejection even while on cyclosporine. After much preclinical work by Starzl and colleagues at Pittsburgh, tacrolimus (FK-506) was first used in liver transplantation in 1989 and was then fast-tracked by the FDA in 1993 [56]. Similar to cyclosporine, tacrolimus suppressed the calcineurin axis and modulated the ability of T cells to respond to and attack the allograft. By using tacrolimus, almost three quarters of grafts which were rejecting while on cyclosporine were rescued [57]. Another antimetabolite, mycophenolic acid mofetil, was approved for use in 1995 and has replaced azathioprine at many centers. Four years later, rapamycin, an mTOR inhibitor studied extensively by Calne since 1989, was approved for clinical use as an immunosuppressant.

As our understanding of immunology improved, the therapeutic potential of recombinant antibodies became apparent. Starzl's ALG was the first drug in this category. Since then, a multitude of others have appeared. Some of the "biologic" immunosuppressants in this category include basiliximab (targets IL-2 receptors on T cells), alemtuzumab (targets CD52 on mature lymphocytes), and the fusion proteins abatacept and belatacept (blocks CD80 and CD86, which are costimulation signals for T cells). These and other newer antibodies increase the arsenal for transplant physicians today in helping patients stave off rejection.

Next, strategies are being developed to help select patients taper off immunosuppression completely. This approach is based on earlier observations that the liver is more tolerogenic than other organs. Starzl and the Pittsburgh group

showed that with careful selection and monitoring, complete withdrawal of immunosuppression appeared safe in some liver transplant patients. The same has been observed on some kidney cases [58]. Many of these instances of tolerance were discovered serendipitously after the patient had stopped taking their medications, with no apparent adverse effects.

A recent strategy to *induce* tolerance in liver recipients is also based on early observations by Starzl and Calne, specifically regarding the natural history of the recipient's immune system post-transplant. They found that some recipients had circulating immune cells which originated from the donor and termed it "microchimerism." In addition, these patients' own immune cells seemed less reactive toward the graft. Today, many academic centers around the world are piloting protocols to introduce donor bone marrow cells to the recipient *prior* to receiving the solid-organ transplant, as a means to induce chimerism. This strategy is used initially in conjunction with more traditional immunosuppressants, which are then tapered off over time.

Future

> When a life-saving operation, despite an extremely high early mortality, is shown to be possible, it eventually becomes established, the errors are recognized and eliminated, and a new generation of surgeons wonders why the pioneers had such a hard time. (Sir Roy Calne, MD [18])

As of 2010, there are 142 liver transplant centers in Europe, 129 in the United States, and many more in over 80 countries around the world [35, 59]. Within the United States, there are more than 50,000 patients living with transplanted livers as of 2009. It is amazing what has been accomplished in just five decades since the first successful liver transplantation. In 2012, Starzl and Calne won the Lasker-DeBakey Clinical Medical Research Award, one of the most prestigious awards given in medicine, for their work in pioneering liver transplantation.

Organ shortage will continue to be a problem for the foreseeable future. Many leaders in the field have advocated for more LDLT, especially for the pediatric population [60]. Xenotransplantation, engineered tissues suitable for transplant, and liver replacement devices are other avenues which are being actively investigated.

As liver transplant outcomes continue to improve, patients are living longer, and we are now seeing many of the long-term complications associated with immunosuppression. This includes the metabolic diseases secondary to the drugs themselves, as well as de novo cancers. As a result, the aforementioned strategies to reduce or eliminate immunosuppression will continue to be studied exhaustively. There will also be more tolerance induction programs, utilizing more robust induction protocols.

Liver transplantation and transplantation as a whole have been one of the most remarkable therapeutic advances in the past century. Many giants of the field were acknowledged above, but we must also remember the countless patients and their families whom we will never be able to name and how their willingness to sacrifice at a time of desperation contributed just as much to the endeavor.

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