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REVIEW

An abbreviated history of liver transplantation

Michael L. Schilsky[1] | **Sukru H. Emre**[2]

[1]Division of Digestive Diseases and Transplantation and Immunology, Department of Medicine and Surgery, Yale University Medical Center, New Haven, Connecticut, USA

[2]Department of Surgery, İzmir University of Economics School of Medicine, Izmir, Turkiye

Correspondence
Michael L. Schilsky, Department of Medicine and Surgery, Yale University Medical Center, 333 Cedar Street, LMP 1080, New Haven, CT 06520, USA.
Email: michael.schilsky@yale.edu

INTRODUCTION

The birth of the field of liver transplantation (LT) had a difficult gestation. Not putting too fine a point on it, the blood-soaked operating room floors and drained blood banks, weary surgeons after marathon operating sessions with overall poor outcomes in the very first cases led to great skepticism about whether to support further efforts for this procedure. The rationale to press onward despite these early challenges was beautifully summarized by Thomas Starzl in the following quotation: "The mortality from the failed early trials and that which occurred later did not mean that LT was causing deaths. These patients were under a death sentence already because of the diseases that had brought them to us."[1] Indeed, Starzl's early cases in Denver, CO, were desperate ones, for whom another favorite Starzl quote rang painfully and poignantly true. For a worried Claudius outed by Hamlet as his father's killer, "Diseases desperate grown By desperate appliance are relieved,
Or not at all." — William Shakespeare Hamlet, Act 4, Scene 3.

Desperate diseases, like Hamlet, end-stage liver failure, and hepatocellular carcinoma (HCC) are best healed by desperate measures, or they won't be cured at all. For Claudius, this meant hatching a plot to get Hamlet out of Denmark and have him killed. And for Starzl, this meant not giving up on LT until it was perfected.

LT was indeed born out of necessity and our ability to treat only a few liver diseases, and even then, only when these diseases were recognized early, and therapy was successful. What seems routine now at many centers across the world, achieving better than

Abbreviations: AASLD, American Association for the Study of Liver Disease; HBV, Hepatitis B Virus; HCC, hepatocellular carcinoma; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; LDLT, living donor liver transplant; LT, liver transplantation; MDT, multidisciplinary team; MELD, Model of End-Stage liver disease; MELD-Na, Model of End-Stage Liver Disease-Sodium; NOTA, National Organ Transplant Act; OPTN, Organ Procurement and Transplantation Network; UW solution, University of Wisconsin solution.

90% early survival with only a few long-term maintenance medications necessary (and rarely over time in some, with no ongoing anti-rejection medications at all) was once thought of as a pipedream and not worthy of further government investment or reimbursement by private insurers. To again quote Starzl, "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." And here, we are surely aware that the patriarch of LT was not referring to the strange hallucinating dreams that opium smokers in the 1870s experienced from the especially long stems that opium pipes had. Although, come to think of it, some adjuvant was needed for the emotions of all concerned with the patients and their loved ones.

What follows is a summary of "how we got there" in short form, as volumes could be and have been written on this subject. LT surgery has transformed care for patients with life-threatening liver diseases and given hope and opportunity to patients transplanted around the world. The creation of a specialty of "Transplant Hepatology" was also one of necessity as there became a need for expertise in managing patients with complications of advanced liver disease, in assisting surgeons in the medical management of complications from the transplant surgery, and afterward in helping manage immunosuppression and recurrent liver disease. The growth of important consultative expertise in anesthesia and critical care medicine for perioperative care drastically improved outcomes, along with the involvement of other specialties of internal medicine including infectious disease, cardiology, hepatopulmonary syndrome specialists, hematologists, and blood banking experts among others. The multidisciplinary nature of best care models for transplantation also grew to include dieticians, social workers, psychiatrists, psychologists, and specialists in addiction medicine. Some of the milestones achieved along the way and their timeline is shown in Table 1. Together we have realized that the miracle that Starzl set out to achieve, transforming the outcomes of this procedure from extraordinary to ordinary in less than half a century, has come to pass. This was not accomplished without figuratively standing on the shoulders of many pioneering giants, including scientists studying immunology and pharmacology, surgeons with expertise in vascular surgery and hepatobiliary surgery, and physicians of many specialties. But most of all, the patients and their loved ones who selflessly put their lives in our hands helped make the outcomes for the next generation of candidates and recipients of liver transplants, better than their own.

TABLE 1 Timeline for milestones in liver transplantation

1963: First human-to-human LT by Starzl
1967: First survival beyond 1 y for LT by Starzl
1968: First human-to-human LT in the United Kingdom by R. Calne
1969: Collins preservation solution
1969: Conceptualization of LDLT by Calne
1969: H. Stahelin's discovery of cyclosporine (1969) with first use in practice (1976)
1974: Bismuth reports on the first adult reduced-size deceased donor liver graft to a pediatric recipient
1984: Goto, Kino, and Hatanaka discover tacrolimus (FK506), introduced into practice.
1984: Shaw performs the first veno-venous bypass for LT
1984: NOTA, established in the United States the framework of a national registry for organ matching and allocation
1987: Belzar and Southard develop a UW preservation solution
1987: Bismuth and concept of split LT
1988: Pichlmayr reports on first split donor graft to 2 recipients
1987: Calne performs first lung, heart, and liver transplant
1989: Raia reports on the first attempt at LDLT
1989: The Human Organ Transplant Act prohibits the buying and selling of organs for transplantation
1989: Broelsch and his team at the University of Chicago perform first US adult to child LDLT
1990: Strong reports on the first adult to child LDLT in Australia
1992: Starzl and Fung attempt the first baboon to human LT
1993: Shinshu group performs first living donor LT
1994: Calne performs first stomach, intestine, pancreas, and liver transplant
1994: Hashikura reports on left lobe LDLT adult to adult
1997: Lo reports on first right lobe LDLT adult to adult
Polyclonal antibodies—Anti-rejection
2000: Sirolimus used for recipients of LT
2000: The Final Rule and structure of OPTN was adopted in the United States
2021: First liver perfusion device given FDA approval
2022: Xenotransplant using genetically modified pig livers

Abbreviations: LDLT, Living Donor Liver Transplantation; LT, liver transplantation; NOTA, National Organ Transplant Act; OPTN, Organ Procurement and Transplantation Network; UW, University of Wisconsin.

A BRIEF HISTORY OF ADVANCES LEADING TO SUCCESSFUL LT

The earliest LTs were technical successes but failures with respect to patient survival. The first immunosuppressive medications utilized were steroids and azathioprine, and overall survival was at best around 30%. In the 1970s, recipients of transplants faced several hurdles to a more successful outcome. These

included the poor medical condition of many recipients at the time they underwent transplant, operative limitations in technique and equipment, and, importantly, the risk of infection and the severe limitations of protocols for immunosuppression. Indeed, the task of achieving the fine balance of preventing organ rejection with adequate immunosuppression while not inviting too high a risk of infection was Herculean. A major step forward toward the achievement of longer-term survival came in the wake of the discovery of cyclosporine. This calcineurin inhibitor was instrumental in changing our ability to prevent rejection of solid organ transplants; however, its first formulations were erratically absorbed, leading to variable success. The discovery of cyclosporine in 1971 by Jean-François Borel (b 1933) — a Belgian microbiologist and immunologist working at Sandoz in Basel, Switzerland — began a new era in immunopharmacology. It was the first immunosuppressive drug that allowed selective immunoregulation of T cells without excessive toxicity. Cyclosporine was isolated from the fungus *Tolypocladium inflatum* that a Sandoz employee brought from vacation in Norway. Cyclosporine was first investigated as an antifungal antibiotic, but its spectrum was too narrow to be of any clinical use. JF Borel discovered its immunosuppressive activity, which he publicized at a meeting in London in 1976. This led to further investigations into its properties involving further immunological tests and investigations into its structure and its synthesis. The new drug was first tested in 1977 by the renowned Cambridge UK transplant surgeon Roy Yorke Calne (later Sir Roy Calne FRS, FRCS [1930–2024]). Cyclosporine has unwanted side effects, notably nephrotoxicity. Even so, animal testing showed cyclosporine to be sufficiently nontoxic to begin clinical trials. These initially failed due to poor absorption of the drug. Once this had been overcome, results were encouraging enough for cyclosporine to be licensed for use in clinical practice. There was some controversy over priority in the discovery of cyclosporine and its preclinical development, but this is not the place to air this argument.

The development of a modified formulation that had better and more predictable absorptive properties was critical for optimizing its use. It was nothing but miraculous that the time from the discovery of cyclosporine to its introduction in the clinic took only 7 years. In addition, having the potential for longer-term posttransplant survival was furthered by the understanding of the need for more careful candidate selection, improving post-liver transplant survival to about 50%.

In 1983, an National Institutes of Health Consensus conference on LT was held, when it was acknowledged that this operation was no longer just experimental, paving the way for government and private payers to reimburse for the operation and posttransplant care. This led to a burst of activity in LT and a rapid growth in the number of LTs performed in the United States and Europe.

The late 1980s and the following decade brought major improvements in transplant outcomes. Critical advances in organ preservation using various preservation solutions, other pharmacologic innovations, and technical innovations in the transplant operation were responsible. In 1987, the University of Wisconsin (UW) solution was introduced and initially hailed as the "solution" for keeping organs in cold storage for a prolonged period, for transport and use. Indeed, we remember the oral presentation at an American Association for the Study of Liver Diseases (AASLD) annual meeting on the discovery and use of the UW solution, where the slogan "don't worry, be happy," taken from a popular song at that time was quoted by the presenter, touting this new storage solution as a means for allowing transplant operations to be performed at elective hours with staff all rested and ready to go at peak performance. That vision was premature as organs stored for a prolonged time in the UW solution did experience higher rates of delayed graft function and primary nonfunction, but it was an advance that allowed an increase in the hours that organs could safely remain in cold storage and permitted the transport of organs further from the retrieval site for transplantation than had been possible previously. On the pharmacologic front, the introduction of tacrolimus as an immunosuppressive in the 1990s was a major step forward. Tacrolimus was discovered in 1984 from the fermentation broth of a Japanese soil sample that contained the bacterium *Streptomyces tsukubaensis.* Tacrolimus is chemically known as a macrolide alctone. It reduces peptidyl-prolyl isomerase activity by binding to the immunophilin FKBP-12 (FK506 binding protein), creating a new complex. The initial formulations of tacrolimus were administered intravenously leading to frequent seizure activity in recipients. The introduction of an oral formulation having less severe swings in blood levels of the drug was crucial for its widespread use. A better understanding of the ranges of levels needed to prevent rejection while lessening toxicity led to better patient outcomes.

Alongside these developments, a major technical hurdle was also overcome by using veno-venous bypass for the LT operation, first performed in 1984, with more widespread adoption over the following years. Veno-venous bypass, as reported by Shaw et al,[2] was devised to address the adverse hemodynamic consequences associated with full cross-clamping of the IVC during LT and has been associated with significantly improved postoperative renal function ($p < 0.001$), reduced intraoperative blood usage ($p < 0.01$), and enhanced 30-day LT survival rates.[2]

Over the years the use of bypass during LT declined. This decrease was linked to an understanding of bypass-related complications and the introduction of the caval-preserving piggyback technique.[3] In addition, advances in anesthesia and perioperative care for recipients of LT have also

contributed to the success of new approaches in current surgical techniques. Thanks to improved techniques, full or partial clamping of the IVC can now be done without requiring veno-venous bypass. Yet bypass is still used and reserved for patients with pre-existing renal impairment before surgery or patients with unstable hemodynamics.

The 1980s also marked the first legislation in the United States, the National Organ Transplant Act (NOTA) adopted in 1984, for the creation of a national transplant registry for matching donor organs with recipients, thereby replacing the many regional and local arrangements. To enhance and streamline the organ procurement and distribution system, NOTA authorized the formation of the Organ Procurement and Transplantation Network (OPTN) to improve the matching process for allocating organs. Managed by a nonprofit organization under federal oversight, NOTA explicitly banned the buying and selling of human organs for transplantation. Nevertheless, it permitted compensation for transplant professionals, hospitals, transporters, and organ procurement organizations for their services. In addition, NOTA allowed reimbursement for living donors to cover expenses related to donation, such as travel costs and lost income. Furthermore, the Act underscored the importance of honoring an individual's documented preferences regarding organ donation.[4]

Also advanced was the "dead donor rule," defining that death must be declared for the donor before organ procurement, which is the underlying principle for organ recovery to this day. In addition, in 1989, as part of the Human Organ Transplant Act, the United States also passed legislation prohibiting the buying or selling of organs for transplantation. It would be just over a decade later in 2000, before more standardization in protocols for the structure and operation of the OPTN were also adopted.

BIRTH OF MULTIDISCIPLINARY TEAMS AND CHANGES IN ORGAN ALLOCATION

In the 1990s and early 2000s, the importance of patient selection for transplant operations and the use of protocolized immunosuppressive regimens were advanced. Previously, the gastroenterologist or hepatologist referred the patient for LT to the transplant center and timely transplant followed when possible. However, with the rapid growth of waiting lists, the need to manage these patients' disease complications and to help optimize the patient for the transplant operation and participate in the aftercare led to the need for and the birth of the "transplant hepatologist" who played a pivotal role in these phases of patient care. Along with the partnership of transplant surgery and hepatology came the recognition of the need for a multidisciplinary team (MDT) model of care and more formal consideration of care pathways for the evaluation, transplant and postoperative management, and long-term care for patients undergoing liver transplants. The MDT care model offers benefits for patients, doctors, and the health care system. It reduces duplicative testing and improves communication among the patient's health care providers. Bringing together team members during visits helps patients receive a well-rounded care plan at one time, avoiding fragmented care across several appointments. By this means, physicians find value in decision-making and less communication burden, compared to traditional arrangements, thereby leading to more efficient care delivery. In addition, the MDT approach results in cost savings by streamlining health care processes.

Introducing an MDT approach can improve care for patients with cirrhosis and complications of portal hypertension, especially in handling conditions like HCC, dealing with venous thrombosis of the portal and mesenteric vessels — reviewed by Dominique Valla elsewhere in this series — and assessing the eligibility for LT. Research results show lower posttransplant relapse rates among patients with alcohol-associated liver disease who receive MDT care.[5] In the field of liver disease, MDT care has proven to be highly effective in HCC management. Current guidelines advocate for liver MDT programs for HCC treatment due to the ability to slow disease progression, aid in detection, and enhance survival rates.[6] These teams typically consist of health care professionals such as nurses, gastroenterologists, transplant and hepatobiliary surgeons, radiologists, interventional radiologists, oncologists, cardiologists, infectious disease specialists, anesthesiologists, pathologists, transplant psychiatrists/psychologists, social workers, and support staff to ensure thorough and coordinated patient care. Many of these MDT programs align with local hospital tumor boards and help fulfill their requirement for MDT membership required by regulatory agencies.

Once LT became successful and patient survival improved significantly, the volume of transplant referrals and number of waitlist candidates far surpassed organ availability. Systems for organ allocation and for decision-making at centers (where there was discretion about who should receive the donor organs) were topics of great discussion. Time on the waitlist was adopted as an early criterion for allocation, but disadvantaged those with less access to advanced medical care and did not distinguish those with more advanced liver disease as being at a higher risk for early mortality, from those with potentially stable disease. These issues were addressed by the adoption of the Model of End-Stage Liver Disease score (MELD, devised and developed at Mayo Clinic) allocation system in the United States in 1993, and subsequent upgrades to MELD-based allocation used for ranking of candidates on the waiting list (MELD-Na, MELD 3.0) helped better allocation of organs and consider the stage of liver disease and gender disparity. Currently, organs remain allocated to

the patient and not a center; however, discretion as to organ acceptance is made by the center with the consent of the potential recipient. Thus, the choice of accepting the donor organ or declining acceptance on behalf of the patient is first made by the center and then patients have the opportunity to consent (or not) to receive the offered donor organ.

ADJUSTMENT OF MODELS OF ALLOCATION AND PRIORITY ON THE WAITING LIST, ACCORDING TO MEDICAL CONDITIONS

Once outcomes improved after the 1980s, it became clear that some patients had conditions that warranted an increase in their priority on the waitlist to help them reach timely LT. Exceptions to the standard allocation rules initially were made by centers when organ allocation was not patient-specific, and later by appeal to regional board members, but are now made through standardized exception criteria or an appeal process to a national review board composed of volunteers from centers throughout the country. The aim of exceptions is to try to adjust for failures of the allocation system to take into account circumstances that might cause mortality and morbidity beyond the priority granted by the standard process. Early on, priority was granted for recurrent ascites and encephalopathy, but it became clear that more stringent and nonsubjective criteria were needed. Encephalopathy was mostly dropped as a criterion, and refractory ascites not responsive to medical therapy or amenable to TIPS were accounted for by applying MELD-Na ie, the MELD score adjusted to the serum sodium (Na) level. For those with HCC, the purpose of the exception was to allow for LT before the individual developed vascular invasion or metastases that would preclude a favorable outcome with transplants. A transition of criteria from arterial-enhancing lesions to more strictly defined imaging criteria with a higher probability that a lesion is HCC is followed. Initial fixed priority was followed by an *escalator* leading to LT that guaranteed transplant but also overtook priority for transplant for patients without exceptions who had very high predicted mortality. Therefore, this was further adjusted to a fixed priority just below the median priority for LTs for that blood type in a donor service area, permitting those without exceptions to receive offers as their estimated mortality rose. Other exceptions that continue to date with a modification of priority for transplant were recognized for genetic disorders based in the liver, most commonly seen in the pediatric age group, and additional liver-related complications relieved with LT, including hepatopulmonary syndrome, portopulmonary syndromes, polycystic liver disease, recurrent cholangitis in patients with primary sclerosing cholangitis and others (see OPTN guidance for further clarification).

INNOVATIONS TO MEET DONOR DEMAND: SPLITTING LIVERS AND LIVING LIVER DONOR TRANSPLANT

The concept of being able to divide a donor liver between recipients was first performed for pediatric patients because of a reduced donor pool associated with the body size of the candidates for LT. The left lateral segment of the donor's liver was often separated from the remaining liver, with the smaller segment going to a pediatric patient and the larger remnant liver going to an adult recipient. The results of this practice were excellent and led to the trial of splitting donor livers to provide organs to 2 adult recipients. While some continue to advocate for expanding this practice, it was not always in the best interest of the recipient to receive a partial graft, especially those with advanced liver disease with severe portal hypertension. Most centers did not continue this practice for their adult recipients, but the use of the split liver for 1 pediatric recipient who can use a left lateral segment and an adult recipient who receives the remainder continues to be favorable, especially with the introduction of *in situ* splitting where vessels and biliary ducts are easier to identify than after the procurement process.

Appropriate recipient selection fit for receiving a partial organ, expertise in both LT and hepatobiliary surgery, logistical planning to minimize total ischemia time, and a skilled transplantation team are crucial for successful outcomes after split LT.[7] The liver can be split either on the so-called *back table* (*ex situ*) in the operating room at the LT hospital or in the donor hospital before cross-clamping using the *in situ* splitting technique, which evolved from living donor LT. The primary advantage of *in situ* splitting is the reduction of total ischemia time compared to the *ex vivo* technique, thereby enhancing graft quality and the potential for inter-center sharing. The use of normothermic machine perfusion, which is a new advance in the field of transplantation, can be used during liver splitting, which presents a novel approach that integrates the strengths of reducing ischemic time and making vascular visualization better. The use of split LT often necessitates interposition grafts which carry a heightened risk of hepatic artery thrombosis. However, technical advances have mitigated this risk and helped in resolving many of the distinctive challenges associated with split LT.[8]

Patient and graft survival rates are comparable between whole-liver transplantations and split-liver transplantations for both pediatric and adult recipients, despite the infrequent use of split grafts. Embracing split-liver donation offers for split LT has the potential to substantially enhance survival outcomes for small children and adults of the appropriate size awaiting LT.[9]

Despite the ability to split livers, and the attempts at creating orderly and fairer allocation protocols, an acute donor shortage has only continued to grow. In addition, in systems outside the United States where so-called

brain death was not accepted for organ donation due to differing religious beliefs and corresponding legislation, there was an even greater need for finding alternative donor organs. This critical impasse led to the first living donor liver transplant (LDLT) for the adult donor to adult recipient performed in Kyoto, Japan in 1994, and later reported in 1997. What followed was an avalanche of interest, but also recognition that pediatric patients in the United States were more disadvantaged due to difficulty with donor organ size matching (fewer children died and donated organs compared to adult deaths and donations). On November 27, 1989, the *New York Times* front page headline[10] read "First US Transplant from Live Donor Is Set." This LT, performed at the University of Chicago, was the culmination of much debate and preparation between the transplant team and those caring for the pediatric patient, among other voices that included an ethical review of live donation before this operation was allowed to proceed. What followed the success of this surgery was an expansion of techniques for LDLT in adults as well, in the United States and Europe. Even further adoption took place in the Far East and other countries with acute deceased donor shortages (where brain death was not accepted for donors). The field of LDLT has been a rich source of ethical debate, but overall it has saved countless lives and as a subset of overall LT, it is still evolving.

Despite being recognized as a life-saving intervention for end-stage liver disease, LDLT remains underutilized in the United States. Studies show that LDLT can greatly improve survival rates for patients with end-stage liver disease at MELD-Na scores as low as 6.[11] Some experts believe that the benefits in terms of life expectancy from LDLT are similar to or even surpass those of life-saving procedures or deceased donor LT.

The evolution of living liver donor incisions has progressed from a *Mercedes* configuration to a reverse L-shaped incision, and then to an upper midline approach. Recently, incisions were further refined with minimally invasive laparoscopic techniques in some centers. However, the adoption of laparoscopy for this procedure has been hindered by technical challenges, including suboptimal instrumentation, challenging ergonomics, and a steep learning curve. The recent introduction of robotic platforms has transformed the field by providing superior optical systems and advanced instruments. This innovation allows for a true replication of open donor surgery in a closed abdomen, enabling all liver donors to benefit from minimally invasive approaches.[12] This advance not only enhances cosmetic outcomes and reduces pain and morbidity but also improves the overall quality of life for donors, while ensuring that safety standards are upheld. In the future, we anticipate a greater adoption of minimally invasive techniques, not only in donor surgery but also for the recipient operation.

Advances in LT resulted in better outcomes which led to the liberalization of the indications for LT. Thus, the shortage of organs has still been a major problem to performing more transplants and saving more lives. To close the gap, a new proposal is to perform *liver swaps* in candidates for liver transplant who otherwise have suitable donors with blood type or a size mismatch. Although this technique is more suitable for countries performing higher rates of LDLT, it could be adopted to centers in the same city or region anywhere. Amazingly, an account of the first 4-way liver paired exchange was published in 2023, the swap being the result of an interdisciplinary collaboration between health care professionals and design economists.[13]

CONQUERING INFECTION, THE ACHILLES HEEL OF LIVER TRANSPLANT

Once the technical aspects of liver transplant evolved and immunosuppression became more effective at staving off rejection, the risks of graft and life-threatening disease due to infection became a major point at issue in transplantation. The liver was only one target of some of the viral and other microbial ailments that lay latent in many, only to explode once the immune system no longer kept them at bay.

Hepatitis B Virus (HBV) infection was a prime example of severe disease that reinfected the graft rapidly and when replication was unchecked once steroids were initiated. Indeed, the surge of unsuccessful transplants for HBV led to a halt of LT for this indication, at a time when the government and insurers would not reimburse due to the dismal outcomes. This was overcome with the utilization of immune globulin to HBV to prevent viral reinfection, and transplant for HBV or for other indications (eg, HCC) in patients who were HBV-infected once again proceeded. Subsequently, effective antiviral therapies for HBV were applied, and when agents with high barriers to mutation and high efficacy, such as tenofovir and entecavir, were introduced, it was possible to utilize these agents as sole therapy. Other patients who received donor organs from patients with exposure to HBV, those with serum antibody positivity to the HBV core antigen (HBcAb) positivity, who were at a risk of reactivation of virus when the recipient received immunosuppression, were prevented from developing active viral infection by the use of these effective antiviral therapies.

Indeed, with effective antiviral therapy, HBV as an indication for transplant has declined rapidly.

Hepatitis C Virus (HCV) was not even identified and tested for pathogen when LT was developing; however, due to HCV prevalence in the blood supply, those who were not infected before transplant and underwent transplant for another disease often became infected after transplant with HCV from transfusions. Once HCV was discovered, testing of the blood supply became possible, and this mode of transmission was markedly

reduced. Notwithstanding, the development of truly effective antiviral therapy for HCV was very challenging, and HCV shot forward to be the most common disease present in pretransplant clinics and the number one reason for LT in the West in the 1990s and early 2000s. The development of orally administered direct-acting antiviral agents that were highly effective and had minimal side effects in recipients changed this forever, even to the point of making it possible for organs infected with HCV, to be considered as donor organs, something unthinkable years before.

Herpes simplex virus and cytomegalovirus are two other agents that plague many patients after LT, affecting not only the graft but also having the potential to cause systemic disease. The development of assays for better detection in serum and testing for tissue specimens along with effective antiviral treatment for Herpes simplex virus and cytomegalovirus were game changers that saved many lives. The introduction of testing followed by posttransplant prophylaxis based on the risk of reactivation of Herpes simplex virus and cytomegalovirus are common to most immunosuppression protocols, improving outcomes overall.

Human Immunodeficiency Virus (HIV) infection was once a fatal disorder but even when early therapy changed outcomes, HIV remained a barrier for LT. There were early concerns about performing transplantation in patients with an already suppressed immune system and a high risk of infection. Another early barrier was the concern for infection of transplant surgeons through needlestick or other exposure to infected blood. This was eventually mitigated by a better understanding of the true risk of transmission and by the adoption of criteria for recipients who were HIV-infected that minimized viral loads in those patients, reducing the risk for transmission. The results of initial studies showed that transplant in this population was possible without undue risk of infection, and that immunosuppression was needed despite the underlying HIV infection. Newer agents for HIV therapy with less drug-drug interaction with anti-calcineurin agents led to even fewer complications of management. Indeed, more recently the use of HIV-infected donor organs for transplantation of recipients who were HIV-infected was championed in the “HOPE Act” legislation, and a formal National Institutes of Health study is being conducted for solid organ transplantation.

NEW AND FUTURE OPPORTUNITIES FOR EXPANSION OF THE POOL OF AVAILABLE DONOR ORGANS

The acute donor shortage, noted above, has led to the use of split donor organs, deceased donor organs, and LDLT to help alleviate the shortage. Further expansion of the donor pool is still pressing, and so other options are being exploited and further developed. One very promising technique to improve donor organ quality includes the use of organ perfusion devices to help preserve and recondition donor organs to achieve a more successful LT outcome and, as noted above, can also be used to perform *in situ* splitting of donor organs. The favorable results of recent research led to trials of various methods for perfusion, including the use of hypothermic and normothermic devices, and combinations of these. There appears to be an early success in the use of perfusion devices in deceased cadaveric donor organs to help reduce the risk of cholangiopathy, and there is an ongoing discussion about the *true reconditioning* of organs that might otherwise have been deemed unusable. The full range of opportunities for using perfusion devices is evolving and may include options for fixing steatosis in organs, performing *ex vivo* treatments of the donor organ including genetic therapies, and assessment of donor organ quality. In addition, the dream of having the organ preserved until optimal timing for the transplant team or optimization of the condition of the recipient is one that may be fulfilled in the immediate future, realizing the dream that was first conceived when the UW solution was developed. The developing field of perfusion devices also brings different material and logistical challenges, including the cost and use of the needed disposables, the transport of the devices and personnel needed for their operation, and space within operating room suites. Despite extensive clinical research into maintaining end-stage liver disease patients alive with artificial support systems, while awaiting LT, there is still no consensus on the benefit of such expensive therapy.[14]

Xenotransplant was thought possibly to be a means of providing organs for acute needs and potentially to alleviate the organ shortage. There were concerns about the compatibility of the organs immunologically but also the zoonotic transmission of infectious agents from non-human donors to patients. Porcine cells were tried in some in vitro devices designed to augment liver function in patients with liver failure and are still being explored today. In an initial foray into xenotransplant in 1992, Starzl and Fung[15] attempted to use a baboon liver to help replace the liver of an HIV-coinfected patient with liver failure from HBV, based on the concept that the virus may not infect the baboon liver. Unfortunately, the graft and patient survived only 70 days and had a complicated postoperative course. More recently, experiments were performed on the ongoing use of porcine livers that have been genetically engineered to reduce the risk of rejection. These have been tried in deceased individuals, the first performed in China; however, there was recently the use of a genetically modified porcine kidney for transplantation into a living recipient with renal failure in Boston. Headlines in the news followed him through his successful discharge from the hospital (*NY Times*, April 2024). The same concerns about infectious zoonotic transmission remain, but, additionally, some have raised

TABLE 2 Challenges in the field of liver transplantation

Expanding indications for LT
Alleviation of the donor organ shortage
Optimizing utilization and quality of recovered organs
Acceptance and utilization of living liver donation
The possibility of xenotransplantation
Minimizing side effects of immunosuppression
Achieving immune tolerance for all recipients
Noninvasive testing for graft rejection
Preventing recurrent liver disease in liver grafts
Assuring fair and equal access to organ transplantation

Abbreviations: LT, liver transplantation.

ethical concerns about the use of animals for this purpose. Most certainly the debate will continue as this technology is developed further.[16]

Donor recovery centers where patients are brought from other hospitals for the purpose of donor organ recovery are now being developed in many regions across the United States. These sites have the expertise to manage and monitor organs recovered from deceased patients, and thereby relieve the burden in the donor hospital where the future donor is occupying a bed. In addition, having facilities able to provide support for multiorgan recovery and facilitate organ rehabilitation through the use of perfusion devices is very useful. Other testing on the donor as well as evaluation of tissue pathology from biopsy is enhanced by assuring that all services are available timely and enhance the utilization of organs.

THE FUTURE

Even now mundane but necessary approaches to improving the LT experience are being fostered.[17] The future, however, will bring expanded indications for liver transplants through innovative protocols that push the boundaries of our current practices (Table 2).[18] A good example of taking on a once clear contraindication to transplant is the case of a cholangiocarcionoma. For carefully selected patients with cholangiocarcinoma, combined preoperative treatment with a liver transplant can yield a clear survival benefit and has led to the adoption of standard exceptions and center protocols for this tumor. More recently, metastatic colon cancer is being explored as an indication for liver transplant. Even this dreaded disease can, with proper patient selection and protocols utilizing newer oncologic therapies, yield successful outcomes with LT that are more favorable than current care. This may apply to more cancers with liver involvement or with liver injury from treatments of cancer leading to liver failure despite cancer remission.

We can also anticipate the use of *ex vivo* gene therapy performed in donor livers in perfusion devices before the transplantation of the graft. We anticipate that, in the not-too-distant future, such innovative approaches will become commonplace for the purposes of enhancing graft quality and even treatment of some genetic disorders, as well as expanded efforts at organ reconditioning to enable the utilization of organs that would otherwise be discarded.

The transplant operation will evolve continuously over time and the adoption of new techniques as they evolve is a given.[17] As noted above, the use of robotic devices for transplant surgery may help with the microsurgical aspects of the operation, and minimally invasive surgery will make healing and recovery easier. We can envision the *in vitro cultivation* of blood vessels and bile ducts that will be grown and used for transplantation and other nontransplant surgical operations. The use of multiorgan transplants will likely be more routine. Immunosuppression will be minimized, and tolerance protocols expanded. As in the beginning of LT, faith in the operation and the MDT by the recipient and their families will remain the driving force for the partnership needed for successful LT.

We can apply to LT what was eloquently described by Mark Twain in the following, “continuous improvement is better than delayed perfection.” With so many waiting for suitable organs, the need for this life-saving procedure continues, and delay to achieve perfection is not a viable option. We therefore must continue to improve and revamp the ship — and not as Gerald Ford’s campaign manager Rogers Morton famously said in 1976, simply “rearrange the furniture on the deck” — while we too, meanwhile, are passengers in this heroic journey.

SERIES EDITOR’S POSTSCRIPT

Michael Schilsky and his former surgical colleague of longstanding, Sukru Emre — now enjoying relocation and retirement *of sorts* in Istanbul in his native Turkey — have performed an inestimable service to the hepatology community at every level and discipline, with this succinct lucid history of every aspect of LT — scientific, clinical, sociological, and ethical. Beneficiaries of the personal experience of these two giants in the field range from trainees in hepatology and surgery to seasoned practitioners in liver disease management and LT (especially the current Series Editor) and other surgical persuasions, and for all affiliated clinicians, other service providers, scientists, and relevant administrators. I have had the personal pleasure, not forgetting an education in the topic of Wilson disease (WD), from friendship with Mike, including spending time with him and his wife on their all-too-brief visit to London a few years ago.

I cannot emphasize enough how much this essay embodies the discipline that is LT, ranging from basic

science aspects, considerations of the care of end-stage liver disease and patients with HCC, evolving surgical techniques, the vexed question of liver allocation and the often agonizing challenge of prioritizing patients on the waitlist, the ethics of choosing, and the rarely mentioned sociological concerns.

Michael Schilsky is a native of New York City; in particular, he hails from the Borough of Bronx, but you'd be hard-pressed to detect it in his soft-spoken accent. He attended the famous Bronx High School of Science. This aspect of his education seems somewhat ironic given his Professorial appointment at Yale University, because the esteemed former 17th President of Yale (1963–1977) and one-time US Ambassador to the United Kingdom (1977–1981) Kingman Brewster Jr (1919–1988) sought to restrict entrants to Yale from Michael's high school, which remains a regrettable bigoted decision. Michael's medical perambulations started at the University of Chicago's Pritzker School of Medicine (MD, 1982), followed by internship, residency, and GI Fellowship at the Albert Einstein College of Medicine, back in the Bronx, and postdoctoral research there at the Liver Research Center. He transitioned to Mt Sinai Hospital, where he met his close collaborator in LT, Sukru Emre, then to Cornell and Columbia in 2004, and Yale in 2007 when Emre moved there. Michael achieved Professorial status at Yale (2017) and an Honorary Professorship (2023) at Aarhus University in Denmark. Aside from his role in the care of liver disease and patients with LT, he is best known universally as an acclaimed WD guru, a worthy successor to Irmin Sternlieb (1925–2008), his distinguished mentor at Albert Einstein.

Sukru Emre was born and educated in Konya, Turkey, and he graduated in Medicine at the University of Istanbul, followed by subspecialty training in hepatopancreaticobiliary surgery, and an ultimate appointment there as an Associate Professor of Surgery. Since no LT was being conducted in Turkey then, Sukru completed a transplant research fellowship at SUNY Downstate, and clinical surgical LT training at Mt Sinai Hospital, where his skills were rewarded with a faculty position and finally promotion to full professorship. Among his many awards and honors, is his recognition — no surprise — as one of the most influential Turks in America. But for me, as I recall painfully the scenario set by the opening sentences of this essay during my time with Yale LT, the turnaround in outcomes, recipient numbers, and satisfaction of all achieved by team Emre-Schilsky at Yale are nothing short of elegant and praiseworthy.

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The authors owe a debt of gratitude to the scientists and clinicians who persevered at the beginnings of transplantation, to our colleagues who toil long hours with a goal of saving and preserving life, and to our patients for their trust in us and from whom we learn to make a better future.

CONFLICTS OF INTEREST

Michael L. Schilsky received grants from Vivet Therapeutics, Orphalan, and the Wilson Disease Association. He advises DepYmed and Arbormed. The remaining author has no conflicts to report.

ORCID

Michael L. Schilsky https://orcid.org/0000–0001–9043–0554
Sukru H. Emre https://orcid.org/0000–0001–7562–8570

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