TRANSPLANTATION OF THE LIVER

EDITION 3

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TRANSPLANTATION OF THE LIVER

Third Edition

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FOREWORD

Over the past 50 years, liver transplantation has advanced dramatically and is considered the definitive treatment for most types of liver failure, both acute and chronic, as well as for hepatocellular carcinoma in both children and adults. Although most other solid organs were attempted to be experimentally transplanted close to 100 years ago, liver transplantation was not reported until 1952 by Vittorio Staudacher from Milan, Italy. With the first human liver transplant performed in 1963, the stage was set for advances in organ preservation, immunosuppression, and surgical technical refinements that led to the first successful human liver transplant performed on July 27, 1967. With the advent of cyclosporine in 1980 and tacrolimus 10 years later, the future was primed for substantial change.

With this better immunosuppression, a rapid proliferation on new centers began in the mid-1980s. Two of the largest and most successful programs were founded by Dr. Ronald Busuttil in 1983 and Dr. Göran Klintmalm in 1985. In 1995, these surgeons published a state-of-the-art book on liver transplantation. The various chapters were contributed by surgeons, internists, and pediatricians with extensive experience and expertise in various aspects of patient selection, the operation itself, and preoperative and postoperative care. Immunologists and others who provided essential components of the substructure also were represented. The book was a great success at every level of the healthcare hierarchy, from students to professors.

By the time of the book's launch in 1995, the combination of acceptable results and the number of centers with well-trained surgeons had made liver replacement the universally accepted "last court of appeal" for virtually all patients dying of nonneoplastic liver disease and for a selected subgroup of those with malignant hepatic tumors that could not be removed with conventional subtotal hepatic resection. It was also apparent, even from a casual reading of the first edition of *Transplantation of the Liver*, that organ supply had already become the principal deterrent to further expansion of these services. Liver xenotransplantation was discussed as a potential way to deal with the impending crisis; however, with the opposition by the public, as well as within the profession, to using closely related species (e.g., the baboon) as donors, this possibility was and still remains remote.

In 2005, the second edition of *Transplantation of the Liver* was published. In that text, Busuttil and Klintmalm and their contributing authors emphasized practical ways of expanding or more efficiently utilizing the human organ pool. These included the acceptance of cadaveric livers that were once discarded, the division of one organ for transplantation into two recipients, and the scrupulously careful use of live volunteer donors. Another way of stretching the supply is to reduce the need for retransplantation. In the past, such hopes depended almost exclusively on the development of more potent immunosuppressive drugs. Almost all were designed to attack specific targets in the immunologic cascade of rejection. However, some of the most promising possibilities are instead based on strategies that exploit leukocyte chimerism-dependent mechanisms of alloengraftment and acquired tolerance.

Now in 2015, Drs. Busuttil and Klintmalm have successfully created the third edition of *Transplantation of the Liver*. The latest edition adds to the first two by increasing the number of chapters from 89 in the second edition to 107 in the current one. Topics that have been expanded upon include many of the new problems that face the liver transplant community today, such as the use of death after cardiac donation (DCD) grafts; liver transplantation for the treatment of cholangiocarcinoma; management of portopulmonary hypertension; an expanded analysis of the use of extended criteria donors; extracorporeal resuscitation of grafts; combined liver-kidney and multiorgan transplantation; management of the HCV epidemic; and discussion of the current treatment of antibody-mediated rejection of liver grafts, which was not considered a major problem before.

As in the previous edition, each chapter is followed by a Pearls and Pitfalls section that alerts the reader to specific points that might otherwise be missed. Some of these sections are so helpful that it may be beneficial to peruse the Pearls and Pitfalls before tackling the main text.

In both the inaugural and second editions of *Transplantation of the Liver*, I concluded my Foreword as follows:

> *The creation of a genuine classic is a cause for wonder, which inevitably increases with time. Years from now, Drs. Busuttil and Klintmalm are apt to look back at their work product and ask themselves how they had been able in their earlier life to construct something this good.*

They have, in fact, succeeded in raising the bar yet again and making their work product even better in the third edition of *Transplantation of the Liver*.

Thomas E. Starzl, MD, PhD

PREFACE: A NEW CHAPTER

The first edition of *Transplantation of the Liver* was published in 1996. At that time, the practice of liver transplantation had developed internationally and was acknowledged as the definitive treatment for virtually all types of end-stage liver disease. The first edition was designed to serve as a platform to codify what had evolved in the development of liver transplantation since 1963, when Dr. Thomas E. Starzl performed the first clinical liver transplant. Additionally, it focused on the many advances in the field that had developed since that sentinel event.

In 2005 the second edition was published, and by that time a revolutionary change in organ allocation had been enacted by the Organ Procurement and Transplantation Network (OPTN), which had a significant impact on the practice of liver transplantation. Based on the Model for End-Stage Liver Disease (MELD) and the Pediatric Model for End-Stage Liver Disease (PELD), the new allocation system completely altered the algorithm for patient evaluation, maintenance, wait listing, and priority for transplantation. Since the implementation of these changes, there has been a dramatic shift toward organs being allocated to the sickest of recipients and to patients with hepatocellular carcinoma and other primary hepatic malignancies who were allowed to be listed because they fulfilled the approved exception criteria. As a result, this current edition thoroughly discusses these changes in indications, the benefits, and the potential risks.

As editors, our ambition has always been that this textbook would be considered state of the art while concurrently keeping the format for general reference. To that end, we have completely updated all of the chapters and added new ones to reflect new knowledge and expertise.

The third edition of *Transplantation of the Liver* essentially follows the same format as its predecessors. The Pearls and Pitfalls sections have been expanded significantly as these summaries are intended to serve as salient words of wisdom from experienced mentors to share with their less-experienced counterparts in the field.

As in the previous editions, when recruiting new authors, we turned to individuals recognized for their expertise in a particular specialty. When possible, we strived to have different views that might apply to a specific issue or problem because, in many cases, successful approaches are often varied. Furthermore, all chapters have been updated to be relevant to our current practice. Chapter 1, on the history of liver transplantation, has been entirely reworked to illustrate the tremendous contributions of transplant pioneers for the benefit of current clinicians in the field who may not have had the opportunity to interact with them personally. We highly recommend this chapter for every reader.

Several new chapters reflect recent developments in the specialty. In "Part I: General Considerations," we have incorporated a chapter that discusses regulatory and ethical issues in organ donation, including donation after cardiac death versus brain death. We have expanded "Part II: Patient Evaluation: Adult" with two new chapters. One chapter focuses on liver transplantation for cholangiocarcinoma, and the other examines nonalcoholic steatotic hepatitis (NASH), a diagnosis that may very well overtake hepatitis C as the most common indication for liver transplantation in many countries during the next few years. A new chapter on pulmonary hypertension and hepatopulmonary syndrome has also been included in "Part IV: Special Considerations in Patient Evaluation."

A chapter on extended criteria donors was added to "Part V: Operation," reflecting the ever-increasing need for donors that necessarily compels us to accept donors whom we rarely used when the first edition of this textbook was published. "Part VI: Split and Living Donor Transplantation" has been greatly expanded as a direct result of the substantial increased experience and knowledge in this field. Chapters on biliary and vascular reconstructions, small-for-size syndrome, minimally invasive living donor hepatectomy, and dual grafts for transplantation have been added. "In Part VII: Unusual Operative Problems," a new chapter on the varied techniques of arterial reconstruction is featured.

Two new chapters can be found in "Part VIII: Postoperative Care." The first broaches an increasingly common yet delicate challenge: the transition of pediatric patients to adulthood. This topic was not adequately addressed in prior editions and is a growing issue that puts a very special and novel demand on the transplant care team. The second new chapter concerns recurrent hepatitis C after liver transplantation, which is a significant problem today. Hopefully, with the new drugs that have recently become available, this will be primarily of historical interest by the time the fourth edition is contemplated. The complex and difficult complication of graft-versus-host disease was given a separate chapter in "Part X: Immunology of Liver Transplantation." Along with the maturation of liver transplantation, large numbers of patients are living several decades after transplantation. Thus, we thought it prudent to address the effect of long-term toxicity of immunosuppressive therapy with a new chapter in

"Part XI: Immunosuppression." Finally, in "Part XIII: Future Developments in Liver Transplantation," there are two new chapters that look to the future. The first chapter discusses stem cell and liver regeneration, and the second focuses on extracorporeal perfusion to resuscitate marginal grafts.

It has been extremely gratifying personally and professionally to watch our field develop and flourish before our eyes. We both feel very fortunate and humbled to have the opportunity to safeguard the mantle created by the father of liver transplantation, Dr. Starzl, as leaders of our own programs. We appreciate being able to pass this mantle along through our textbook and our respective fellowship programs. We dedicate this work to Dr. Starzl and his contemporary pioneers Drs. Roy Calne, Rudolph Pichlmayr, and Henri Bismuth. May this text serve as an ode to their vision and the legacy that they have created worldwide.

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We wish to express our appreciation to Colleen Devaney and Therese Dangremond for their tireless efforts and dedication to the third edition of *Transplantation of the Liver*. Without their commitment to excellence, as well as the invaluable mentorship of Dr. Thomas E. Starzl, this work would not have been possible.

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CHAPTER 1

The History of Liver Transplantation

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CHAPTER OUTLINE

The history of liver transplantation is a complicated story to tell—it is a story of great successes and tragic failures. It is a story of both individual heroics and the power of collaboration. It is a story that has many overlapping themes that all evolved simultaneously—there were developments in immunosuppression, creation of animal models, advances in organ preservation, and the results from human trials. Each of these themes unfolded at the same time. And at that same time, the story was affected by issues of organ supply that inspired advances and regulatory developments that helped bring the field into maturation.

The modern framework and procedures for organ transplantation were born from the bold efforts of a small number of centers in North America and Europe between 1954 and 1967. It was a time when it would have been easy to have been marginalized from the mainstream, when the conventional wisdom was that transplanting tissue from one human to another was at

TABLE 1-1 **Milestones of Liver Transplantation**

Year	Description	Reference
1952	First report on liver transplantation (Vittorio Staudacher, University of Milan)	1
1955	First report on auxiliary liver transplantation (C. Stuart Welch, Albany Medical College)	5
1958-1960	Formal research programs of total hepatectomy and liver replacement in dogs	14,128
1960	Azathioprine introduced for organ transplantation	39,40
1963	Azathioprine-prednisone cocktail introduced for organ transplantation	50
1963	In situ preservation-procurement method described	129
1963	First human liver transplantation (Thomas Starzl, University of Colorado)	53
1966	First liver xenotransplantation (chimpanzee donor)	23
1966	Antilymphocyte globulin introduced for organ transplantation	65
1967	First successful liver transplantation (Thomas Starzl, University of Colorado)	16
1967-1968	Acceptance of brain death concept	130
1968	First successful liver transplantation in Europe (Roy Calne, University of Cambridge)	78
1976	Improved slush liver preservation permits long-distance procurement	25,26
1979	Systematic use of arterial and venous grafts for cadaver organ revascularization	24
1979	Cyclosporine introduced for organ transplantation	89
1980	Cyclosporine-prednisone introduced for organ transplantation	90
1981	80% 1-year liver recipient survival reported using cyclosporine-prednisone	91
1983	Introduction of pump-driven venovenous bypass without anticoagulation	57,58
1983-1984	U.S. Consensus Development Conference concludes liver transplantation is a "clinical service"	92
1984	Standardization of in situ preservation-procurement techniques for multiple cadaver organs	54,55
1984	First reduced-size graft liver transplantation (Henri Bismuth, Paul Brousse Hospital, Paris)	84
1984	First ex situ reduced-size graft liver transplantation (Rudolf Pichlmayr, University of Hannover)	103
1984	National Organ Transplant Act introduced in the United States	119,131
1987	UW solution introduced for organ preservation (F. Belzer, J.H. Southard, University of Wisconsin)	28
1987	First report on extensive marginal donor use (Leonard Makowka, University of Pittsburgh)	100
1987	Scientific Registry of Transplant Recipients created in the United States	121
1989	Tacrolimus introduced for organ transplantation	97
1989	First living donor liver transplantation (Russell Strong, Stephen Lynch, University of Queensland)	108
1994-1998	First right lobe living donor liver transplantation (Yoshio Yamaoka, Kyoto University)	109,110
1995	First in situ split-liver transplantation (Xavier Rogiers, University of Hamburg)	106
2000	First successful ex vivo porcine xenoperfusion (Marlon Levy, Baylor University Medical Center)	118
2002	MELD score introduced in the United States for organ allocation	132
2006	Donor Risk Index score to quantify marginal donor risk (Sandy Feng, University of Michigan)	102
2010	First report of liver hypothermic machine perfusion (James Guarrera, Columbia University)	121

MELD, Model for End-Stage Liver Disease; *UW*, University of Wisconsin.

best, not possible, and at worst, an unethical undertaking. Although kidney transplantation opened the door to the possibility of "transplantation," it was liver transplantation that truly became the driving force behind the innovations and discoveries that ultimately advanced the entire field of transplantation. Liver transplantation drove the progress in developing immunosuppression, the improvements in organ preservation, and the advances in anesthesia and intensive care unit care. The research and models created for liver transplantation gave insight into the metabolic interrelations of the intra-abdominal organs, provided an understanding of liver-based inborn errors of metabolism, and fostered an understanding of liver growth and regeneration.

The story of liver transplantation unfolds through six related themes that weave back and forth at different points throughout the timeline. It is helpful to view this complicated history through the lens of the following six topics: animal models, immunosuppression, organ preservation, human trials, regulatory developments, and organ supply (Table 1-1).

INTRODUCTION: THE GENESIS OF LIVER TRANSPLANTATION

The transplantation of all of the other major organs can be traced back to the early 1900s,[1,2] but for liver transplantation the first reported liver transplant was in 1952 at the fifty-fourth Congress of the Italian Society of Surgery. In 1952 Vittorio Staudacher from the University of Milan (Fig. 1-1) published a series of experiments in which the first description of the technique of liver transplantation in four dogs was outlined.[3,4] This first liver transplant was an orthotopic liver transplant, where the host liver was removed and fully replaced by the donor allograft, and in his report Staudacher clearly describes the procedure in five steps that resemble the modern transplant operation. In the

Dr. Vittorio Staudacher
University of Milan
Milan, Italy

FIGURE 1-1 ■ The first liver transplantation was performed in 1952 on a dog by Vittorio Staudacher at the University of Milan. The results were presented to the fifty-fourth Congress of the Italian Society of Surgery in 1952. This landmark surgery remained unknown for many decades before it came to the attention of researchers. (From Busuttil RW, De Carlis LG, Mihaylov PV, et al. The first report of orthotopic liver transplantation in the western world. *Am J Transpl.* 2012;12:13851387.)

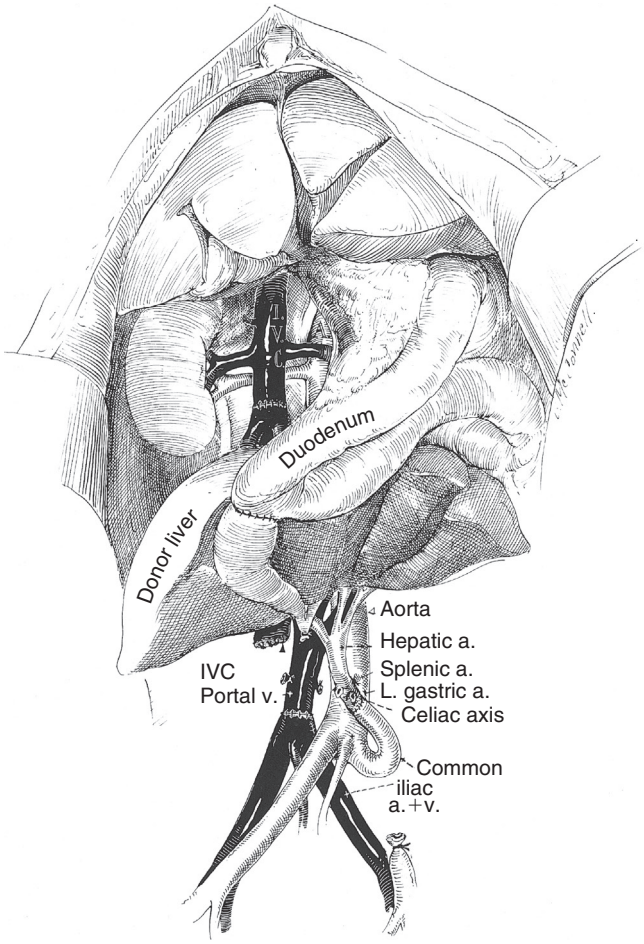


FIGURE 1-2 ■ **Auxiliary liver homotransplantation in dogs (the Welch procedure).** Note that the reconstituted portal venous inflow is from the inferior vena caval bed rather than from the splanchnic organs. Biliary drainage was with cholecystoduodenostomy. *a.*, Artery; *IVC,* inferior vena cava; *L,* left; *v.*, vein. (From Starzl TE, Marchioro TL, Rowlands DT Jr, et al. Immunosuppression after experimental and clinical homotransplantation of the liver. *Ann Surg.* 1964;160:411-439.)

discussion Staudacher commented that no one had reported a liver transplant previously. Although Staudacher's achievements were known by some colleagues in Italy, his work went essentially unnoticed for almost 6 decades.

In 1955 C. Stuart Welch of Albany Medical College reported the first heterotopic liver transplant in a one-page article published in *Transplantation Bulletin*, the forerunner of the present day journal *Transplantation*.[5] For more than 50 years, Welch's report was considered the first reported liver transplant until the recent discovery of Staudacher's published work. In Welch's "auxiliary liver transplant," a hepatic allograft was implanted into the right paravertebral gutter of dogs without disturbing the native liver.[5] Welch followed up this publication with a more complete description published in *Surgery* in 1956.[6] These auxiliary livers were revascularized by anastomosing the allograft hepatic artery to the recipient aortoiliac system, and by an end-to-end anastomosis of the allograft portal vein to the host inferior vena cava (Fig. 1-2). By including a short length of donor retrohepatic vena cava, Welch avoided anastomosing multiple hepatic veins and instead required just one anastomosis; the upper end of the caval segment of the graft was anastomosed to the recipient vena cava, and the lower end was ligated.

In contrast to other types of transplanted organs, an auxiliary liver transplant allograft underwent a marked shrinkage beginning within 3 to 4 days of the surgery. Initially the atrophy was attributed to liver rejection. The central dogma at the time was that liver size and regeneration were governed by the amount of portal venous inflow (known as the "flow hypothesis" of hepatic homeostasis). Because the portal vein of the auxiliary liver allograft received ample systemic blood from the host vena cava, it was felt that the atrophy was not related to blood flow but was instead ascribed to immunological factors. It would be more than 10 years before the cause of the auxiliary allograft atrophy was fully appreciated and the idea of rejection being the culprit was refuted. It ultimately became apparent that the atrophy was due to the absence of hepatotrophic factors such as insulin, which are present in high concentrations in the splanchnic circulation but were missing from the systemic blood from the vena cava that perfused the auxiliary liver.[7-10]

In 1960 Michael Francis Addison Woodruff of the University of Otago Dunedin School of Medicine in New Zealand published a compendium of work in transplantation[11] up to 1959, and at that time the only references to liver transplantation were Welch's two articles on heterotopic liver transplantation[5,6] and a

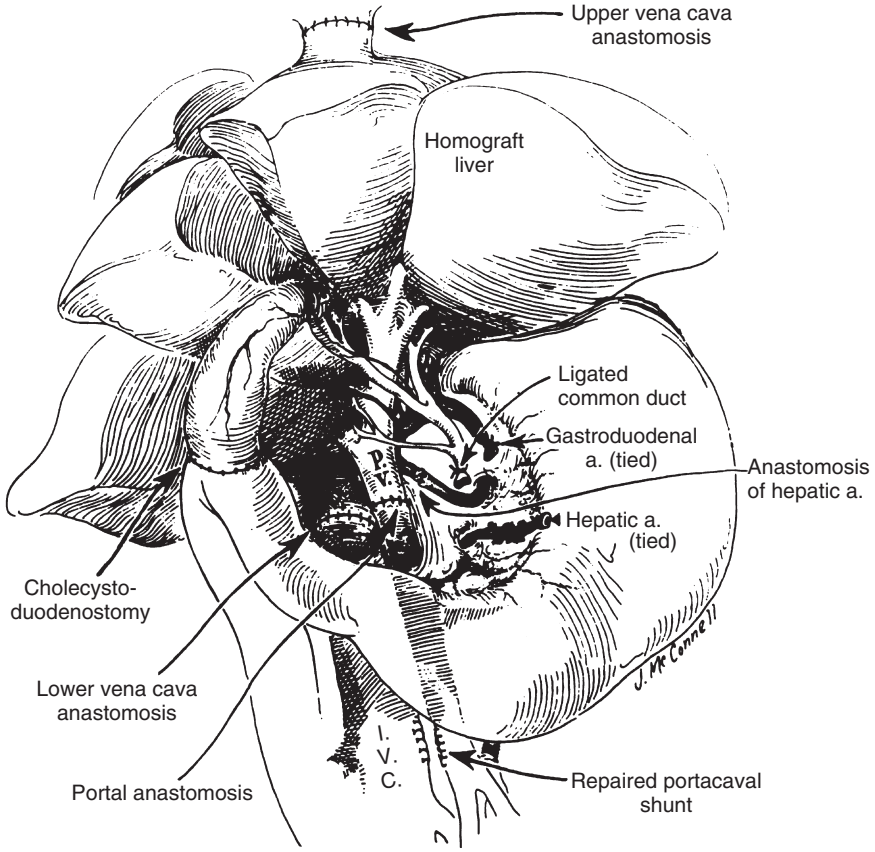


FIGURE 1-3 ■ Completed liver replacement in the dog. The fact that the recipient was a dog rather than a human is identifiable only by the multilobar appearance of the liver. *a.,* Artery; *I.V.C.,* inferior vena cava; *P.V.,* portal vein. (From Brettschneider L, Daloze PM, Huguet C, et al. The use of combined preservation techniques for extended storage of orthotopic liver homografts. *Surg Gynecol Obstet.* 1968;126:263-274.)

brief report by Jack Cannon of University of California, Los Angeles (UCLA) published in 1956 that described the liver transplant activities in animals performed at the recently founded UCLA School of Medicine.[12] This article by Cannon was considered for many years to be the first experimental description of an orthotopic liver transplant, until the recently discovered work of Staudacher.[3]

However, by the time Woodruff's book was published in 1960, there were already two centers—the Peter Bent Brigham Hospital in Boston[13] and Northwestern University in Chicago[14]—that both independently began studying liver transplantation in 1958, each center looking at the field from different vantage points. The investigations from the Brigham Hospital were done under the direction of Francis D. Moore,[13,15,16] and because the focus came from a center with an established history with kidney transplantation, this group approached liver transplantation from an immunological perspective with a therapeutic objective. In contrast, the work from the Northwestern University group led by Thomas E. Starzl[14,17] stemmed from work regarding the metabolic interrelationships of the liver with the pancreas and intestine, which evolved from earlier investigations done at the University of Miami in the field of hepatotrophic physiology. In this circumstance, liver replacement was being performed for the purpose of studying these metabolic relationships.[18,19] In these investigations the Northwestern University group pioneered a new method of total hepatectomy in which the host's retrohepatic inferior vena cava was preserved,[20] (heralding the approach that would come to be known as the piggyback variation of liver transplantation in humans[21-23]). For liver replacement in the dog, it was simpler to excise the host retrohepatic vena cava along with the native liver and to replace it with the comparable caval segment of the donor. The vena caval anastomosis above and below the liver and the hepatic arterial and biliary tract anastomoses were performed with conventional methods[13,14] (Fig. 1-3). When different means of portal revascularization were systematically tested in the laboratory at the Northwestern University program (Fig. 1-4), it was discovered that any deviation from the normal portal supply resulted in reduced survival.

The research teams at Northwestern University in Chicago and the Brigham Hospital in Boston were unaware of each other's activities until late 1959, and direct contact between the programs was not established until the 1960 meeting of the American Surgical Association. By then the cumulative total of liver replacement procedures in nonimmunosuppressed dogs was 111 (80 at the Northwestern University program,[14] 31 at the Brigham Hospital program[13]). The

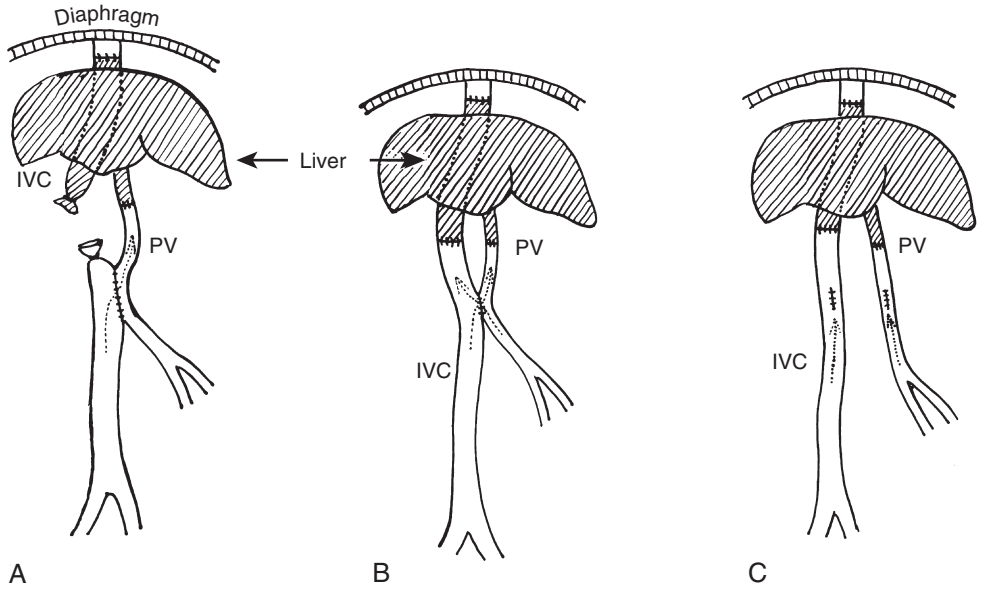


FIGURE 1-4 ■ Alternative methods of portal vein revascularization. A, Reverse Eck fistula. **B,** With small side-to-side portacaval shunt. **C,** Anatomically normal. Survival was best with **C**. *IVC,* Inferior vena cava; *PV,* portal vein. (From Starzl TE, Kaupp HA Jr, Brock DR, et al. Reconstructive problems in canine liver homotransplantation with special reference to the postoperative role of hepatic venous flow. *Surg Gynecol Obstet.* 1960;111:733-743.) *IVC*, Inferior vena cava; *PV*, portal vein.

outcomes from these canine liver transplants were published in 1960 in separate papers and in different journals.

ANIMAL MODELS: PREREQUISITES FOR CANINE REPLACEMENT

The two prerequisites for perioperative survival of canine liver transplant were independently established in each laboratory, both at the Brigham Hospital in Boston and at Northwestern University in Chicago. The first requirement for a successful canine liver replacement was prevention of ischemic injury to the allograft. At the Brigham Hospital program this was accomplished by immersing the liver in iced saline. At the Northwestern University program the method of hypothermia was influenced by F. John Lewis, who along with Norman Shumway pioneered total body hypothermia for open heart surgery while at the University of Minnesota.[24] The livers were cooled by the intravascular infusion of chilled lactated Ringer solution (Fig. 1-5) and monitoring core temperature with thermal probes. This now-universal step in preservation of organs had never been used before, apparently because of the fear of damaging the microcirculation. In time, better liver preservation was obtained by altering the osmotic, oncotic, and electrolyte composition (i.e., Collins,[25] Schalm,[26] and University of Wisconsin solutions[27-29]).

The second prerequisite for successful canine liver replacement was avoiding damage to the recipient splanchnic and systemic venous beds when venous drainage was obstructed during the host hepatectomy and graft implantation. In both laboratories this was accomplished by using external venovenous bypasses to decompress the venous drainage, although the particular details of the bypasses differed at each center.

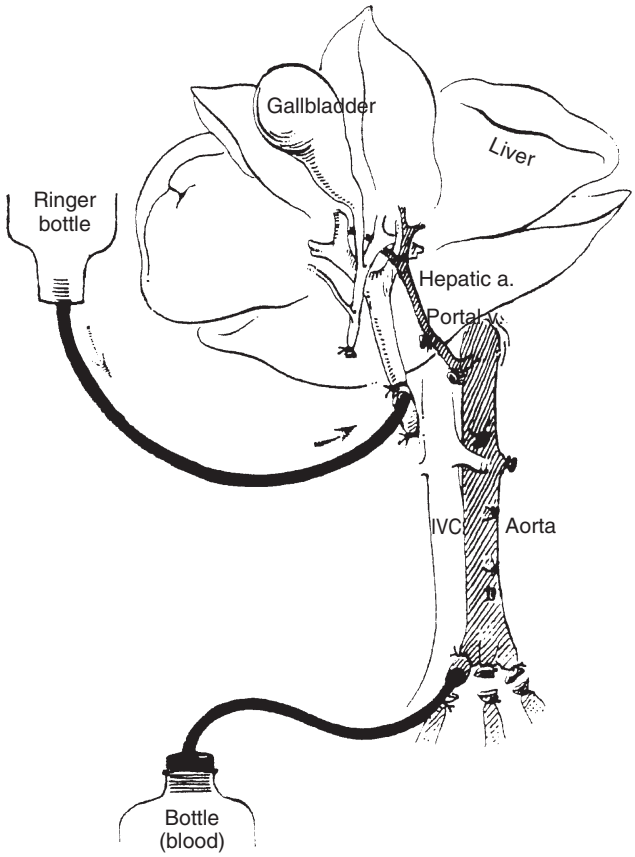


FIGURE 1-5 ■ Cooling of the canine hepatic allograft by infusion of chilled lactated Ringer solution into the donor portal vein. The animals were simultaneously exsanguinated. *a.,* Artery; *IVC,* inferior vena cava; *v.,* vein. (From Starzl TE, Kaupp HA Jr, Brock DR, et al. Reconstructive problems in canine liver homotransplantation with special reference to the postoperative role of hepatic venous flow. *Surg Gynecol Obstet.* 1960;111:733-743.)

ANIMAL MODELS: PATHOLOGY OF LIVER REJECTION

Until 1960 the kidney had been the only organ allograft whose unmodified rejection had been systematically studied. With development of the canine liver replacement models at each of the two programs, the pathology of rejection in a transplanted liver could now be studied. These initial histopathological assessments were done by David Brock at the Northwestern University program and Gustav Dammin at the Brigham Hospital program. Most of the transplanted canine livers were destroyed in about 5 to 10 days. The pathological examination of the transplanted livers typically showed a heavy concentration of mononuclear cells, both in the portal triads and in and around the central veins, all with extensive hepatocyte necrosis.[16,17]

A curious exception was noticed in the sixty-third liver replacement experiment. The serum bilirubin level reached a peak at 11 days but then progressively declined.[17] The predominant histopathological findings in the allograft by day 21 were more those of repair and regeneration rather than rejection. This was the first recorded exception to the existing dogma that once rejection was initiated, it was an inescapable process. Five years later, similar observations were made by Ken A. Porter of St Mary's Medical School in London, assessing the allografts of long-surviving canine liver recipients from experiments done at the University of Colorado program, where rejection had developed and then spontaneously reversed under stable daily doses of azathioprine.[30]

IMMUNOSUPPRESSION: HOST IRRADIATION AND CYTOABLATION

Just when the surgical research in nonimmunosuppressed dogs began to lose momentum, it was dramatically revitalized. From January 1959 to February 1962, there were seven successful human kidney transplantations performed, the first by Joseph Murray[31] at the Brigham Hospital in Boston (work for which he received the 1990 Nobel Prize in medicine) then six more times by the independent teams led by Jean Hamburger[32] and Rene Kuss,[33] both of whom were in Paris (Table 1-2). For these seven transplants the immunosuppression came from preconditioning the patients with sublethal doses of 4.5 Gy total body irradiation. The first two recipients (they received fraternal twin kidneys) had continuous graft function for more than 2 decades without any further posttransplant immunosuppression. They were the first examples of acquired immunological tolerance in humans.

Exploring a substitute for irradiation, Willard Goodwin, a urologist from UCLA, pretreated recipients with myelotoxic doses of cyclophosphamide and methotrexate.[34] One recipient had a prolonged survival of 143 days and had rejection that was successfully reversed several times with prednisone. Despite these initial moderate successes with cytoablation, it quickly became apparent that cytoablation by medication was not going to be a feasible means through which liver transplantation might occur.

IMMUNOSUPPRESSION: 6-MERCAPTOPURINE AND AZATHIOPRINE

The real advances needed for liver transplantation required the arrival of the era of drug immunosuppression, and 6-mercaptopurine (6-MP) is generally considered the drug that heralded in this era. Much of the initial research that would be crucial for immunosuppression for liver transplantation was studied in kidney transplant models. In 1950, working at Wellcome Research Laboratories, Gertrude Elion and George Hitchings[35] used innovative drug development methods to create 6-MP (work for which they received the Nobel Prize in medicine in 1988). The researchers Robert Schwartz and William Dameshek at Tufts Medical School in Boston first established that 6-MP was immunosuppressive[36,37] and not require overt bone marrow depression to be successful. Using a skin allograft model in rabbits, William Meeker Jr. and Robert Good at the University of Minnesota showed 6-MP provided a modest prolongation of skin allograft survival.[38] Upon learning of the immunosuppressive potential of 6-MP, both Roy Calne (then a surgical trainee) in London[39] and Charles Zukoski at the Medical College of Virginia in Richmond[40] independently performed experiments using transplant models with canine kidney allograft, reporting survival of up to 40 days.

After developing 6-MP, Elion and Hitchings used their drug development techniques to synthesize an imidazole derivative of 6-MP called azathioprine, a prodrug of 6-MP that required processing in the liver to become active and thereby prolonged the effects of the drug. By the end of 1960, both Zukoski, working with David

TABLE 1-2 **Kidney Transplantation: 6 Months or Greater Survival as of March 1963**

Date	Program	Surgeon	Donor	Survival (mo)	Alive/Dead
1/24/1959	Peter Bent Brigham Hospital, Boston	J.E. Murray	Fraternal twin	>50	Alive
6/29/1959	Necker Hospital—University of Paris	J. Hamburger	Fraternal twin	>45	Alive
6/22/1960	Centre Medico-Chirugical Foch, Seine	R. Kuss	Unrelated	18	Dead
12/19/1960	Necker Hospital—University of Paris	J. Hamburger	Mother	12	Dead
3/12/1961	Centre Medico-Chirugical Foch, Seine	R. Kuss	Unrelated	18	Dead
2/12/1962	Necker Hospital—University of Paris	J. Hamburger	Cousin	>13	Alive
4/5/1962	Peter Bent Brigham Hospital, Boston	J.E. Murray	Unrelated	11	Alive

Hume in Richmond,[41] and Calne, who had moved to Boston for a fellowship with Murray,[42,43] were using azathioprine in kidney transplants[42] with survival results that would sometimes reach 100 days.

ANIMAL MODELS: TOWARD LIVER TRANSPLANTATION BY KIDNEY TRANSPLANT EXPERIENCE

Calne's experiments showing transplant rejection could sometimes be substantially delayed with azathioprine encouraged the Brigham Hospital program in Boston to pursue human kidney transplant trials. When the trials of kidney transplant with azathioprine began in Boston in 1960-61, there were initially high expectations,[44] and the idea of actually transplanting livers seemed less remote. In 1961 William R. Waddell left Massachusetts General Hospital to become chair of surgery at the University of Colorado, where he was joined by Starzl, coming from Northwestern University in Chicago. Their goal at that point was to pursue development of liver transplantation, especially considering the 3 years of experience Starzl had gained at Northwestern University working with the canine hepatic replacement models (Fig. 1-6). Unfortunately, the plans for liver transplantation were shelved when reports of the Boston clinical trial of kidney transplantation described disappointing results. The report by Murray et al,[44] published in the *Annals of Surgery*, did have one positive element, because it described a kidney allograft transplanted from an unrelated donor in April 1962[45] that was still functioning 120 days later using azathioprine immunosuppression. That kidney ultimately functioned for another 13 months after this report for a total of 17 months, and it was the first example of 1-year survival of a human organ allograft without host conditioning with total body irradiation. This positive element in the report was tempered by the fact it was the only recipient of the first 13 treated solely with drug immunosuppression that survived for more than 6 months.[44-46]

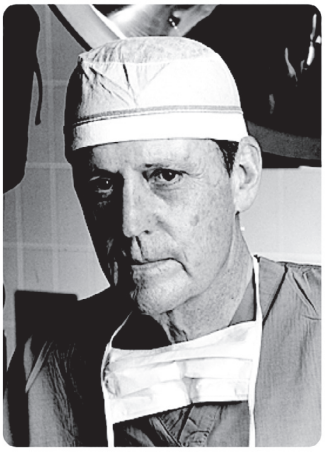


FIGURE 1-6 ■ Thomas Starzl started his career at Northwestern University, where he performed canine hepatic replacements for studying metabolic interrelationships of the liver with the pancreas and intestine. When he moved to the University of Colorado in 1962, those canine models laid the groundwork for developing human liver transplantation. He performed the first human liver transplant in 1963. In 1981 he moved to the University of Pittsburgh, making it the largest liver transplant program in the world.

In the spring of 1962 the University of Colorado group of Waddell and Starzl, working at the Denver Veterans Administration hospital, obtained a supply of azathioprine and began developing experience with the drug. Initially the plan had been to study azathioprine in a liver transplant model, but it became clear quickly that the operation of liver replacement in dogs was too difficult and fraught with technical challenges to use it to evaluate an immunosuppressive drug. So the group decided to use the simpler canine kidney model first as a precursor to liver transplantation. The results from this transplant model yielded similar results to other laboratories with survival that sometimes approached 100 days. However, two key observations came from these canine transplant models that would affect future immunosuppressive management strategies. The first observation was that the allograft rejection that occurred after azathioprine monotherapy could be reversed by delayed addition of large doses of prednisone.[47] The second observation was that pretreatment of the animals with azathioprine for 7 to 30 days before transplant doubled their mean survival, which to that point had been 36 days.[48]

HUMAN TRIALS: THE HUMAN KIDNEY TRANSPLANT TRIALS

Beginning in late 1962, the long-standing kidney transplant program at Brigham Hospital in Boston was joined by two other centers in performing human kidney transplantation: the group at the University of Colorado in Denver comprising Starzl and Waddell and the group at the Medical College of Virginia in Richmond led by Hume (Fig. 1-7). The groups at Colorado and Virginia were in close contact with each other, collaborating on ideas,[49] and both realized early that a combination of "azathioprine and steroids" was key to a successful outcome; however, they approached the strategy from different directions. The University of Colorado group reserved steroids for when rejection occurred, which invariably happened with azathioprine monotherapy. The Medical College of Virginia group used reduced-dose steroids from the time of the transplant as part of a dual drug combination.

The University of Colorado group began human kidney transplants in 1962 using a protocol that gave daily doses of azathioprine 1 to 2 weeks before transplant, as well as continuing it after, and added high doses of prednisone to treat any rejection. The successful results of the first 10 kidney cases using this protocol were described in the report "The Reversal of Rejection in Human Renal Homografts With Subsequent Development of Homograft Tolerance."[50] The term *tolerance* referred to the time-related decline of need for maintenance immunosuppression. Based on their results using this protocol, Starzl and the University of Colorado group concluded that renal transplantation had reached the level of a bona fide (albeit still flawed) clinical service.

In 1963 a small conference organized by the National Research Council ultimately became a landmark event in transplantation. Twenty-five of the leading transplant clinicians and scientists from around the world assembled to review the current status of human kidney transplantation.[51] The results were very discouraging because less than 10% of the several hundred human allograft recipients had survived more than 3 months.[52] Of those treated with total body irradiation for immunosuppression, only 6 patients had survival close to 1 year. The results of those with drug-based immunosuppression were equally poor, as Murray reported that of his first 10 patients treated with 6-MP or azathioprine, only the one survived a year, whereas the others died within 6 months. Some participants at the conference began to question whether human transplantation could still be justified. Ultimately the Colorado group described their success with their immunosuppressive protocol of using azathioprine and adding large doses of prednisone with any rejection, which allowed a 1-year survival rate that exceeded 70%.[51] Because the Colorado group, which had been a late invite to the meeting, reported more surviving recipients than the rest of the world's other centers combined, the audience was incredulous, and it provoked intense discussions. However, the fact that Starzl brought with him the wall charts (on the advice of Goodwin, who was aware of the results) that detailed the daily progress, urine output, and laboratory work of each patient, quelled the debate (Fig. 1-8). As Clyde Barker of the University of Pennsylvania described the events: "The gloom was dispelled by only one presentation given by Tom Starzl, a virtually unknown newcomer to the field, who was invited to the conference as an afterthought.... The outlook for renal transplantation was completely changed by Starzl's report."[51]

Before the 1963 National Research Council conference there were only the three active kidney transplant centers in the United States (Brigham Hospital, University of Colorado, and Medical College of Virginia). Within a year of the conference, and as word of the effectiveness of this new immunosuppression protocol spread, 50 new transplant programs began in hospitals throughout the United States, with a similar proliferation of transplant centers across Europe.[49] Some of the benefits of kidney transplantation proved to be truly long lasting in some cases, because eight of the recipients from the University of Colorado program from 1962 to 1963 still had their kidney transplants 40 years later (making them the longest-surviving organ allograft recipients in the world) and some of them have lasted 50 years.[24]

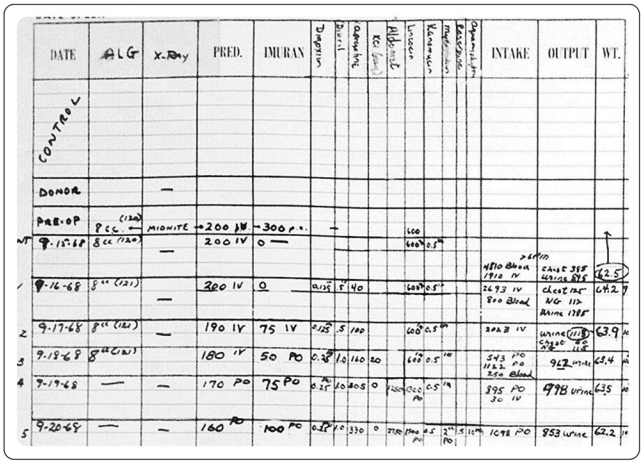


FIGURE 1-8 ■ A segment of a typical kidney transplant wall chart from the University of Colorado program, 1968. The wall chart was designed by T.E. Starzl, and the original version was hand drawn. Note the antilymphocyte globulin (ALG), Imuran, prednisone (Pred.), and x-ray dosing.

FIGURE 1-7 ■ Francis D. Moore, Joseph E. Murray, and David Hume were an integral part of the Peter Bent Brigham Hospital kidney team in Boston that performed the first human kidney transplant in 1954. Hume moved to the Medical College of Virginia in Richmond in 1956 to become the chairman of the Department of Surgery, where he initiated kidney transplant. In late 1962 the Brigham Hospital, Medical College of Virginia, and the University of Colorado were the three programs performing kidney transplants in the United States.

HUMAN TRIALS: THE HUMAN LIVER TRANSPLANT TRIALS OF 1963

Although the follow-up evaluations of the kidney transplant trials were still short, the successful human kidney transplant experience at the Colorado program encouraged the decision to go forward with the exponentially more difficult initiative of liver transplantation (Fig. 1-9). The first attempted human liver transplant was on March 1, 1963, in a 3-year-old boy with biliary atresia named Bennie Solis. Bennie had been operated on numerous times previously and had deteriorated to the point of being unconscious and ventilated.[53] Unfortunately, Bennie bled to death during the actual transplant operation, because of the many high-pressure venous collaterals that had formed and an uncontrollable coagulopathy. This result occurred despite the fact that the operative team had performed more than 200 similar transplant operations in animal models. The complexity and difficulty was so extreme, it took the team several hours just to make the incision and enter the abdomen, because of the significant collateralized adhesions.

Two more liver transplantations were performed over the next 4 months in two adults, one transplanted May 5, 1963, for a hepatoma, and the second transplanted June 3, 1963, for a cholangiocarcinoma. The donor procurement for these transplants had successful allograft preservation accomplished by transfemoral infusion of a chilled perfusate into the aorta of the non–heart-beating donors after cross-clamping the aorta at the diaphragm (Fig. 1-10)—in much the same way as the first stage of the multiple organ procurement operation still performed today.[54,55] The cold ischemia time for the two procurements was 2.5 hours and 8 hours, respectively, and neither recipient had any significant ischemic damage as evidenced by modest increases in the liver enzyme levels after transplant. For the operative procedure the various anastomoses were performed in the same way as in the dog experiments except for the biliary tract reconstruction. (The complete operation was drawn in 1963 [Fig. 1-11], and that picture could still be used today to depict a human liver transplantation.) The immunosuppression protocol for the recipients in the University of Colorado group's liver transplantation trials derived from that center's experience in the human kidney transplant trials, with azathioprine administered both before and after transplantation, adding a high-dose course of prednisone with the onset of rejection.

Although both procedures seemed satisfactory, these recipients—the second and third recipients of the trial, died after 22 and 7.5 days, respectively. Both patients died in part because of pulmonary emboli, although interestingly, both were also found to have extrahepatic micrometastasis[56] of their cancers at autopsy, although with no rejection of the allograft. The strategy of controlling the coagulation using transfusion of blood products and ε-aminocaproic acid for fibrinolysis, which was adopted following the uncontrolled coagulopathy of the first transplant, had unintentionally backfired. During the implantation of the livers, passive venovenous bypass with plastic

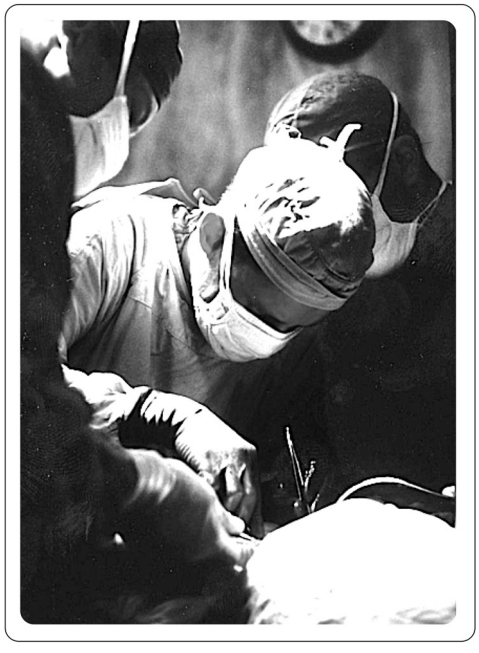


FIGURE 1-9 ■ Thomas E. Starzl at the University of Colorado in 1963 performing one of the first liver transplants from the initial human liver trials at the Denver Veterans Administration hospital.

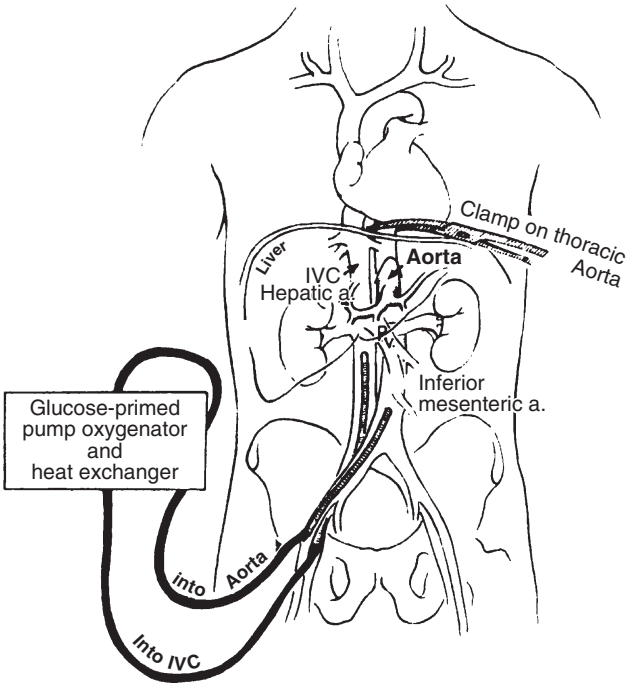


FIGURE 1-10 ■ **Extracorporeal perfusion of the deceased donors reported in 1963.** "The venous drainage was from the inferior vena cava and the arterial inflow was through the aorta after insertion of the catheters through the femoral vessels. Note clamp on thoracic aorta to perfuse the lower half of the corpse selectively. A glucose-primed pump oxygenator was used with a heat exchanger." *a.,* Artery; *IVC,* inferior vena cava. (From Starzl TE, Marchioro TL, Von Kaulla KN, et al. Homotransplantation of the liver in humans. *Surg Gynecol Obstet.* 1963;117:659-676.)

tubing was used, similar to the technique used in the canine model. However, in the humans who had been given coagulation-promoting therapy, clots formed in the bypass tubing and passed to the lungs, causing abscesses and lung damage that contributed to their deaths (and to the next two recipients to follow). Ironically, the use of the venovenous bypass to decompress the venous system—something that was so crucial to survival in the canine experiments—was not necessary for most human recipients. (A motor-driven venovenous bypass system introduced in Pittsburgh in the 1980s[57-59] and later use of percutaneous catheters have made the procedure easier, but in many centers bypass is only used selectively, if at all, and never in infants or small children). Ultimately, venous decompression was shown to be expendable in dogs submitted to common bile duct ligation several weeks in advance of transplantation—an animal model of cirrhosis and portal hypertension—and the venous collaterals that developed enabled transplantation without venovenous bypass.[60]

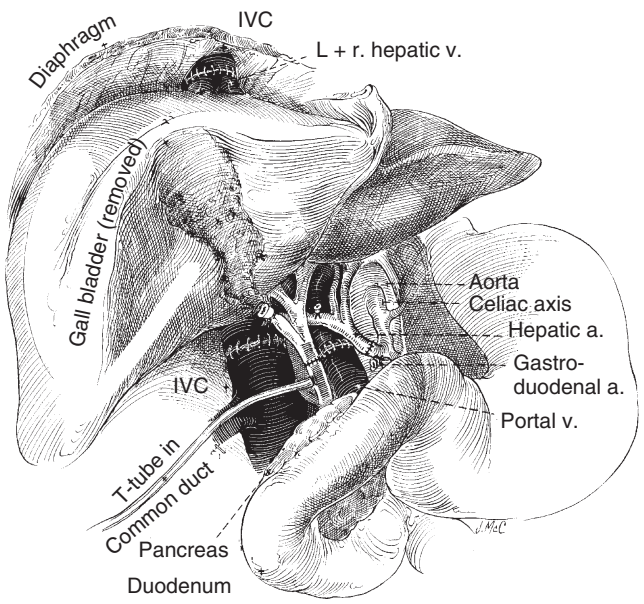


FIGURE 1-11 ■ The operation carried out in the first two patients who survived liver replacement on May 5 and June 3, 1963. The patients lived for 22 and 7.5 days. *a.*, Artery; *IVC*, inferior vena cava; *L*, left; *r.*, right; *v.*, vein. (From Starzl TE. *Experience in hepatic transplantation.* Philadelphia, PA: Saunders; 1969:138.)

HUMAN TRIALS: THE LIVER TRANSPLANT MORATORIUM

During the last half of 1963, two more liver transplantations were performed by Starzl's group at the University of Colorado,[7] and one each at the Brigham Hospital in Boston by Moore[61] and at the Hospital St Antoine in Paris by Jean Demirleau[62,63] (Table 1-3). The transplant in Paris was the first liver transplant in Europe, and used a 71-year-old donor into a 75-year-old recipient, making this also the first transplant using what would be today called a "marginal donor."[63] The operation lasted 4 hours, but the patient died 3 hours after transplant from uncontrollable fibrinolysis.

After the deaths of these seven patients in three different centers, there was great pessimism worldwide that the operation was too difficult to be practical, that the methods of organ preservation were inadequate for an organ so sensitive to ischemic damage, and that the available immunosuppression options were too primitive to allow success. This sentiment was reinforced by the fact that long-term survival following liver transplantation had not yet even been achieved in the experimental animal models. Clinical activity in liver transplantation ceased for 3.5 years between January 1964 and the summer of 1967. The worldwide moratorium was voluntary, but the decision to stop was reinforced by widespread criticism that transplantation was too formidable to be practical. During the moratorium on liver transplantation, the field did not stay still; problems that contributed to the failures of the transplants of 1963 were addressed, and advances were made across the field, in immunosuppression, organ preservation, and operative techniques.

TABLE 1-3 **The First Seven Human Liver Recipients**

Date	Age	Program	Surgeon	Liver Disease	Survival (Days)	Cause of Death
3/1/1963	3	University of Colorado, Denver	T.E. Starzl	Biliary atresia	0	Intraoperative bleeding
5/5/1963	48	University of Colorado, Denver	T.E. Starzl	HCC	22	Pulmonary emboli, sepsis
6/3/1963	68	University of Colorado, Denver	T.E. Starzl	Cholangiocarcinoma	7	Pulmonary emboli
7/10/1963	52	University of Colorado, Denver	T.E. Starzl	HCC	6	Pulononary emboli, liver failure
9/16/1963	58	Brigham Hospital, Boston	F.D. Moore	Colon metastasis	11	Pneumonitis, liver abscess/failure
10/4/1963	29	University of Colorado, Denver	T.E. Starzl	HCC	23	Pulmonary emboli, sepsis
1/?/1964	75	Hospital St Antoine, Paris	J. Demirleau	Colon metastasis	0	Intraoperative bleeding

HCC, Hepatocellular carcinoma.

IMMUNOSUPPRESSION: ANTILYMPHOCYTE GLOBULIN

A constant objective during the liver transplant moratorium was to improve immunosuppression regimens. With regard to human kidney transplant trials, despite achieving consistent success with 1-year survival of 70%, there was disappointment that the 30% mortality could not be improved upon,[64] in spite of the increased experience with kidney transplant techniques as well as refinements in the azathioprine-prednisone protocol and the application of histocompatibility matching. The events leading to the typical patient death or graft loss were predictable—the continuing function of the transplant kidney was dependent on toxic doses of prednisone.[65,66] For some patients, if the clinicians reduced the prednisone, the graft failed and had to be removed, but if the prednisone dose was not removed, the graft could be saved, but often at the cost of a lethal infection.

Between 1963 and 1966, antilymphocyte globulin (ALG) was prepared from antilymphocyte serum obtained from horses immunized against dog for preclinical canine studies, or against human lymphoid cells for later human trials.[67] In the preclinical canine studies, the efficacy of dog-specific ALG was demonstrated in kidney transplant models when it was given either 5 to 30 days before transplant, at the time of transplant, or from 20 to 30 days after transplant.[65]

After extensive and successful preclinical canine studies, human-specific ALG was introduced clinically in human kidney recipients in a trial at the University of Colorado in June 1966.[64-68] With a 1- to 4-month course of ALG added as an adjuvant to the basic azathioprine and prednisone protocol to create a "triple-drug cocktail," the quantities of both azathioprine and especially the prednisone were reduced and the function of the graft was better maintained Ultimately, the mortality in these kidney recipients was further decreased, approaching 10% using the triple-drug cocktail.[64]

ORGAN PRESERVATION: EXTRACORPOREAL HYPOTHERMIC PERFUSION AND EX VIVO PERFUSION

The techniques of graft procurement and preservation first developed for the liver grafts led to advances that could be applied to other whole organs. The first advancement was core cooling by infusion of chilled lactated Ringer solution into the portal vein (this technique was modified for use in clinical kidney transplants and other organs). The first technique of in situ cooling was by extracorporeal hypothermic perfusion. The catheters were inserted via the femoral vessels into the aorta and vena cava as soon as possible after death. A heat exchanger was used to control the temperature.[69] The thoracic aorta was cross-clamped to limit the perfusion to the lower part of the body. The organs were then quickly resected in a bloodless field and then the tissue was dissected in the cold on the back table. This method of organ preservation was used from 1962 to 1969 before the acceptance of brain death and was the primary mode used in both the initial liver trials of 1963 and the later trials of 1967.[69] Of note, the preliminary stages of this approach provided the basis for subsequent in situ techniques that are used today.

After the failure from the trials of 1963 and during the moratorium following, the group at University of Colorado worked to improve the pitfalls of organ preservation that remained given that it was necessary to obtain livers from non–heart beating donors. To help surmount this difficulty, the University of Colorado group developed an ex vivo perfusion system in 1966 and 1967 that permitted reliable preservation in experiments with canine livers for as long as a day. This system combined the use of hypothermia, hyperbaric oxygenation, and low-flow perfusion with fresh diluted blood.[70]

ANIMAL MODELS: DEMONSTRATION OF HEPATIC TOLEROGENICITY

Despite the failures of the human liver clinical trials of 1963, during the liver moratorium the feasibility and potential of liver transplantation was best reflected in the growing kennel population of long-surviving canine liver recipients (Fig. 1-12), none of which was treated with more than a 4-month course of azathioprine[71] or a few doses of ALG.[64] In presenting the results of 143 canine liver replacements to the Society of University Surgeons in February 1965, it was emphasized that "Although the early recovery after liver homotransplantations has many hazards … the frequency and rapidity with which dogs could be withdrawn from immunosuppression without an ensuing fatal rejection is remarkable… The consistency of this state of host-graft nonreactivity and the rapidity with which it seemed to develop exceeds that reported after renal homotransplantations."[71]

A year later the French surgeon Henri Garnier along with Gaston Cordier reported that a significant percentage of untreated outbred pig liver recipients did not reject their allografts.[72] These observations were promptly confirmed

FIGURE 1-12 ■ Canine recipient of an orthotopic liver homograft, 5 years later. The operation was on March 23, 1964. The dog was treated for only 120 days with azathioprine and died of old age 13 years after transplantation.

by Calne at the University of Cambridge program,[73] John Terblanche and J.H. Peacock at the University of Bristol, England,[74] and Starzl at the University of Colorado.[75] Calne and his colleagues at the University of Cambridge further demonstrated that the tolerance self-induced by the liver extended to other tissues and organs from the liver donor, but not from third-party pigs.[76]

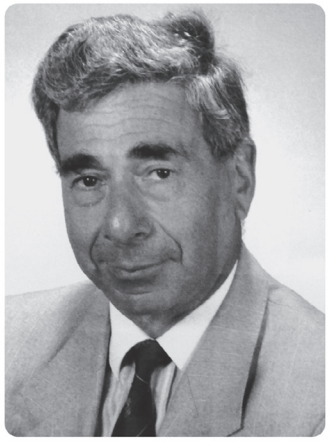
HUMAN TRIALS: THE HUMAN LIVER TRANSPLANT TRIALS RESUME IN 1967

After the significant advances were made with immunosuppression regarding ALG, and with the improvements in organ preservation, once again the idea of liver transplantation became viable, and the liver program at the University of Colorado was reopened in July 1967, ending a 4-year self-imposed moratorium. The program was reinforced by the addition of a powerful colleague, Carl Gustav Groth, a 2-year National Institutes of Health (NIH) fellow and Fulbright Fellow from Stockholm (Fig. 1-13). With a PhD in rheology (the study of the flow of matter), Groth's knowledge of blood flow and the issues of blood coagulation proved vital to helping the University of Colorado group overcome the clotting issues that had plagued earlier transplants and had led to several fatalities.[77] Groth became a key member of both the donor and recipient teams at the University of Colorado.

With this hurdle overcome, the team was ready to attempt the operation in the summer of 1967, and Starzl performed the first successful liver transplant in 1967 on an 18-month-old child named Julie Rodriguez, who was diagnosed with hepatoblastoma. With the triple-drug cocktail[16] that had been so successful in the kidney transplant trials, the young girl survived for more than a year before ultimately succumbing to metastatic recurrence 400 days after her transplant. The child's vivacious and charming personality lead Starzl to remark that Julie "became a metaphor for courage and human progress,"[53] and her successful transplant soon led to several more transplants that summer. Despite the advances, however, the 1-year survival rate of these transplants remained below 50%, and although it was a significant improvement, the high mortality rate would lead to liver transplantation remaining controversial for another decade. Yet, in spite of the controversy, the University of Colorado program was soon joined by similarly visioned clinicians at other programs, aimed at advancing the field of liver transplantation.

In February 1968 the liver transplant program at the University of Colorado was bolstered by the opening of Calne's clinical program at the University of Cambridge, England.[22] On May 2, 1968, Calne (with Moore, visiting unexpectedly at Cambridge, acting as first assistant)[78] attempted the program's first transplant (Fig. 1-14). Although the first patient transplanted by the program exsanguinated in a fashion similar to the experience at the University of Colorado, this was followed by several successful liver transplants, aided by a fruitful collaboration with the hepatologist Roger Williams at King's College Hospital in London, in what became known as the Cambridge-King's Program.[78,79] By 1969 a total of 33 human liver transplants had been performed throughout the world, including 25 performed at the University of Colorado by the Starzl group and 4 performed at Cambridge-King's Program by the Calne group. The importance of having another contemporary in the field was crucial for its

FIGURE 1-13 ■ The first three human recipients to have prolonged survival after liver replacements in July and August 1967. The adult, Carl Groth, was then a National Institutes of Health–supported fellow from Stockholm, Sweden.



Sir Roy Y. Calne

University of Cambridge
Cambridge, England
1965 – Present

St Mary's Hospital
Westiminster Hospital
London, England
1962 – 1965

Brigham Hospital
Boston, MA
1960 – 1961

First Liver Transplant 1968

Developed: 6– MP,
azathioprine & cyclosporin

FIGURE 1-14 ■ Roy Calne began with studying immunosuppressive drugs in canine kidney models. In 1960 he moved to Boston to work with Joseph Murray and collaborated with George Hitching and Gertrude Elion to develop 6-mercaptopurine (6-MP) and later azathioprine for use in transplantation. Returning to England in 1962, Calne practiced first in London and then moved to the University of Cambridge in 1965. He began performing liver transplantation at Cambridge in 1968, and together with Thomas E. Starzl he helped define the field. In 1979 Calne initiated the cyclosporine clinical trials in liver transplantation that would change the face of transplantation. He was knighted in 1981.

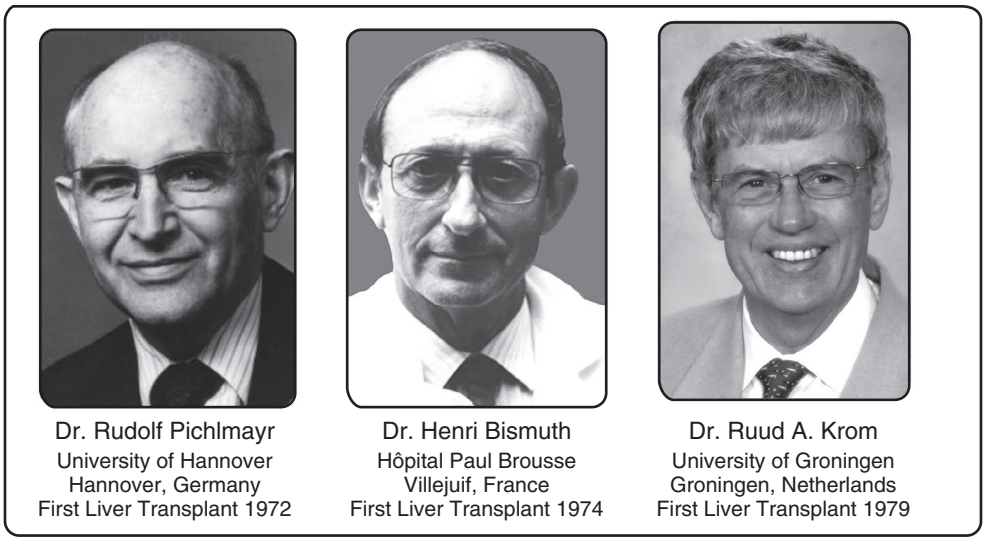


FIGURE 1-15 ■ Rudolf Pichlmayr in Hannover, Henri Bismuth in Paris, and later Ruud Krom in Groningen were the three other programs along with the University of Colorado and the Cambridge-King's program that were actively performing liver transplants in the 1970s and early 1980s. These three surgeons were instrumental in helping to develop the field through their collaborations with Thomas E. Starzl and Roy Calne.

advancement, as described by Starzl: "The fate of liver transplantation would depend on an unspoken trans-Atlantic alliance between Cambridge and Denver without which further efforts could not have continued, much less succeeded, on either side of the ocean. These mutually supportive moral and scientific bonds pulled liver transplantation into the mainstream of medical practice." By 1969 enough successes from the experience of these 33 transplants allowed publication of the first textbook of liver transplantation, *Experience in Hepatic Transplantation*.[23]

By the early 1970s the two active liver transplant programs of the University of Colorado and Cambridge-King's were joined by three other programs (Fig. 1-15) that would also make important contributions to liver transplantation over the next decade: the University of Hannover led by Rudolf Pichlmayr performed their first liver transplant in 1972; the group from Hôpital Paul Brousse in Villejuif, France, led by Henri Bismuth performed their first transplant in 1974; and the group in Groningen led by Ruud Krom, which followed with their first transplant in 1979. (Of note, that first patient from Groningen is still alive after 35 years.) Each of these programs reported a similar phenomenon—the nearly miraculous benefits of liver transplantation when it was successful, but with the caveat that the mortality rate was too high to allow its practical use. Nonetheless, much of the framework of liver transplantation in place today was developed through the transatlantic alliance of these five mutually supportive centers during the frustrating period between 1969 and 1979.[49,80]

HUMAN TRIALS: ADVANCEMENTS TO THE RECIPIENT OPERATION

Although the overall procedure for a liver transplant today is remarkably similar to the operation performed in 1967, almost all of the elements of the initial transplant procedure have undergone refinements over the last 40 years. Some examples of these refinements include the following:

- The incidence of bile duct complications was reduced to 30 % with the use of a choledochocholedochostomy with a T-tube stent.[81] In time, this would be further refined and T tubes were no longer necessary.
- The systematic use of pump-driven venovenous bypasses greatly diminished intraoperative bleeding; however, improvements in anesthesia and intraoperative fluid management have made bypass a selective option.[57,58]
- The use of arterial grafts allowed arterialization of the liver in cases of complex vasculature. The use of venous grafts was introduced in the 1970s[82] and eliminated extensive thrombosis of the portal vein and superior mesenteric vein as a contraindication to transplant.[83]
- The piggyback operation (Fig. 1-16) that keeps intact the recipient retrohepatic vena cava was first used in 1968 at both the University of Cambridge program[22] and the University of Colorado program[23] for pediatric recipients. The adult procedure was popularized by Andreas Tzakis at the University of Miami program.[21]
- The shortage of appropriate-sized donors for very small pediatric recipients was greatly ameliorated by the use of partial liver segments.[84,85]
- Management of coagulopathy was facilitated by the thromboelastogram to follow minute-by-minute clotting changes in the operating room. With better control of bleeding, the scarring from previous surgery or prior portosystemic shunts were removed as adverse factors in transplant.[86]

ORGAN PRESERVATION: IN SITU PERFUSION

The in situ perfusion technique was incorporated starting in 1970 and gained more exposure following the passage of brain death laws that allowed for controlled

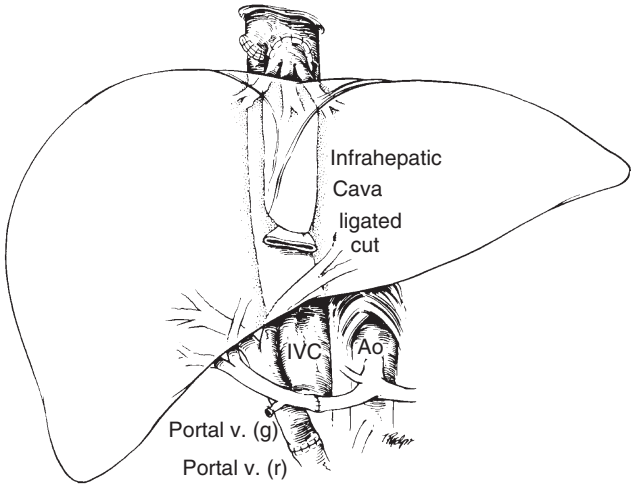


FIGURE 1-16 ■ Transplantation of a liver piggybacked onto an inferior vena cava (IVC), which is preserved through its length. Note that the suprahepatic vena cava of the homograft is anastomosed to the anterior wall of the recipient vena cava. The retrohepatic vena cava of the homograft is sutured or ligated, leaving a blind sac into which empty numerous hepatic veins. *Ao*, Aorta; *g*, graft; *r*, recipient; *v.*, vein. (From Tzakis A, Todo S, Starzl TE. Orthotopic liver transplantation with preservation of the inferior vena cava. *Ann Surg.* 1989;210:649-652.)

organ procurement. The in situ perfusion of organs developed out of the beginning stages of the hypothermic and core cooling methods. Eventually in situ cold infusion techniques were perfected that allowed the removal of all thoracic and abdominal organs, including the liver, without jeopardizing any of the individual organs.[54] With in situ cooling for multiple organ procurement, limited dissection of the aorta and great splanchnic veins is performed, cannulating both. After placing an aortic cross-clamp above the celiac axis, cold infusates are run through these cannulas and they are used to chill the organs in situ. Modifications of this procedure were made for unstable donors and donation after cardiac death donors. By 1987 the techniques of multiple organ procurement were interchangeable among the various centers worldwide.

IMMUNOSUPPRESSION: THE NEW AGE OF CYCLOSPORINE

The immunosuppressant cyclosporine would revolutionize liver transplantation, and yet it came close to not coming into production at all. Cyclosporine was introduced by the company Sandoz in Basel, Switzerland, coming from their routine study of fungi from soil samples brought in from around the world. Sandoz began screening soil samples in 1970 looking for the cytostatic activity among the fungi that might indicate an antibacterial or anticancer property. In late 1971 a fungal extract containing cyclosporine was submitted to the Sandoz laboratory for testing its cytotoxic activity,[87] and it was Jean-Francois Borel who was tasked with characterizing cyclosporine's immunological properties. Borel showed cyclosporine caused a marked reduction of antibody formation in mice.

In 1976 Borel presented his finding in a lecture at the spring meeting of the British Society for Immunology in London,[87] which was of major significance to the development of cyclosporine because it stimulated the interest of many clinicians, particularly Calne of the Cambridge-King's program and his junior associate David White, an immunologist. White and Calne reviewed a sample of cyclosporine and began their own clinical studies using a rat transplant model and confirmed it to be a powerful immunosuppressant and one that could be administered orally. However, the enthusiasm was not shared by all, and Sandoz was not convinced of the commercial potential of cyclosporine given its small market. The company proposed discontinuing the project, but Calne and White traveled to Basel to make the case to the company directors, and the company ultimately relented.[88]

During the 12 years spanning the period from the restart of liver transplantation in 1967 until the discovery of cyclosporine, the 1-year survival for liver transplantation remained stalled at an upper limit of 35%, despite continual attempts to improve it. This frustration ended when cyclosporine became available in 1979,[89] and it was first used initially by the Cambridge-King's group as a monotherapy drug. The improvements in transplant outcomes were sudden, and by 1982 the Cambridge-King's group passed the 50% 1-year survival mark for liver transplant, leading to several other transplant programs opening in England and across Europe. The results of cyclosporine were taken up by Starzl at the University of Colorado, but as with past immunosuppression cocktails, Starzl combined cyclosporine with prednisone or ALG as a double-drug combination.[90] Of the first 12 liver recipients treated with cyclosporine and prednisone in the first 8 months of 1980,[91] 11 (92%) lived for more than a year and 7 of them were still alive over 12 years later. At last, with the use of cyclosporine, liver transplantation was able to achieve the success rates that could allow mainstream support.

REGULATORY DEVELOPMENT: NATIONAL INSTITUTES OF HEALTH CONSENSUS COMMITTEE AND "THE STAMPEDE"

In December 1981 the promising developments regarding liver transplantation with cyclosporine were reported to C. Everett Koop, who was the surgeon-in-chief at Children's Hospital of Philadelphia (CHOP). Koop had helped establish the biliary atresia program at CHOP by bringing the pioneering Japanese surgeon Morio Kasai to CHOP in 1959-1960 as a research fellow—and liver transplantation represented a crucial therapeutic option for biliary atresia. But more importantly, less than 2 months after hearing about these results, Koop was appointed U.S. Surgeon General. Koop initiated steps leading to a Consensus Development Conference for liver transplantation at the NIH in June 1983. In addition to Starzl's program, which had moved to the University of Pittsburgh, the conference also included the four veteran European centers (Cambridge-King's, Paris,

University of Hannover, University of Groningen). This consensus committee concluded that liver transplantation had become a "clinical service" as opposed to an experimental procedure.[92]

After the success brought about by cyclosporine and the impact of the NIH Consensus report, there was a worldwide stampede to develop liver transplant centers. In 1989, only 6 years after the NIH report, a 17-page article in the *New England Journal of Medicine*, spread over two issues, began with the following opening statement: "The conceptual appeal of liver transplantation is so great that the procedure may come to mind as a last resort for virtually every patient with lethal hepatic disease."[49]

ORGAN PRESERVATION: COLD STORAGE

Another major advancement for liver transplantation was the development of cold storage with preservation solutions. Working with kidney grafts, the idea of static cold storage was first proposed in 1969 by Geoffrey Collins from UCLA, working in the laboratory of Paul Terasaki. He proposed cold storage after flushing out the kidneys with a simple electrolyte solution containing a high concentration of potassium designed to mimic the intracellular environment and also a high concentration of glucose to increase osmolarity and minimize cell swelling.[93] After the kidney was flushed, the organ was placed in a sterile bag and kept on ice without perfusion. This fluid was further modified by removing magnesium and substituting mannitol for glucose, and this modified Collins solution became known as Euro-Collins. Because of the simplicity of the method and the success of Euro-Collins solution, cold storage of kidneys was adopted by many kidney centers worldwide,[94] although it was not suitable for preserving liver grafts for transplant.

With the idea of cold static storage now a practice, Folkert Belzer (Fig. 1-17) now at the University of Wisconsin, along with James H. Southard worked to improve upon the strategy, turning their attention to ways to prevent the cold-induced cellular injury that limited Euro-Collins solution. They experimented with different preservation solutions and perfusion solutions to create the initial University of Wisconsin (UW) solution in 1979 and then patiently made adjustments on more than a dozen different ingredients,[27-29] improving the solution so that in 1987 it was first employed successfully in liver transplantation. This advance would change the whole strategy underlying liver transplantation.

Dr. Folkert Belzer
University of Wisconsin
Madison, WI

U.W. Solution Composition

Potassium	125 mmol/L
Sodium	30 mmol/L
Magnesium	5 mmol/L
Lactobionate	100 mmol/L
Phosphate	25 mmol/L
Sulphate	5 mmol/L
Raffinose	30 mmol/L
Adenosine	5 mmol/L
Allopurinol	1 mmol/L
Glutathione	3 mmol/L
Insulin	100 units/L
Dexamethasone	8 mg/L
Hydroxyethyl starch	50 g/L
Bactrim	0.5 mL/L

Osmolality 320 mmol/kg pH 7.4

FIGURE 1-17 ■ Folkert Belzer along with James H. Southard developed University of Wisconsin (U.W.) preservation solution as a way to avoid the cold-induced cellular injury that limited Euro-Collins solutions. After first developing the solution in 1979, they patiently made adjustments to the formula, improving the solution, so that in 1987 it was suitable for use in liver transplantation. This improved preservation solution allowed donor procurement from longer distances.

IMMUNOSUPPRESSION: FURTHER ADVANCEMENTS USING TACROLIMUS

Following Sandoz's commercial success with cyclosporine, the Fujisawa Pharmaceutical company began testing microorganisms and fungi from the soil and identified the macrolide FK506 in 1984 as a potential immunosuppressant. The first experimental reports appeared in 1987, and to investigators at the University of Pittsburgh,[95] the drug appeared very effective and free of many side effects[96]; however, to investigators in England, the drug appeared excessively toxic. The discrepancy likely was explained by an inability to test levels and an unclear understanding of the drug pharmacokinetics.[96] The program at the University of Pittsburgh was licensed to study tacrolimus, initially restricting it to patients with chronic rejection or having severe side effects from cyclosporine.[97] In the first trial, tacrolimus was successful in salvaging 7 out of 10 chronically rejecting grafts. In January 1989 a phase I trial of 110 new patients treated with tacrolimus showed a 1-year survival of 93%.[98]

A multicenter trial of 20 centers examining tacrolimus initially suffered from toxicity from high starting doses, but the investigators were able to salvage the trial after adjusting the trial based on the learning curve of the drug dosing. A randomized trial at the University of Pittsburgh was notable in that 47 of 75 patients randomized to the cyclosporine control arm were switched to the tacrolimus study arm to salvage their rejection, at the recommendation of the multi-institutional Patient's Rights Committee given the evidence of the superiority of tacrolimus.[97] These study results led to the substitution of tacrolimus for cyclosporine as the benchmark immunosuppression (Fig. 1-18). The Food and Drug Administration followed, with fast track approval of tacrolimus for use in liver transplantation in November 1993.[95,97]

ORGAN SUPPLY: MARGINAL DONORS

As early as 1987, Leonard Makowka and his colleagues at the University of Pittsburgh[100] identified the impending organ shortage and reported the feasibility of systematically using livers from older donors, donors with biochemical or histopathological evidence of liver injury, and those whose terminal course was characterized by

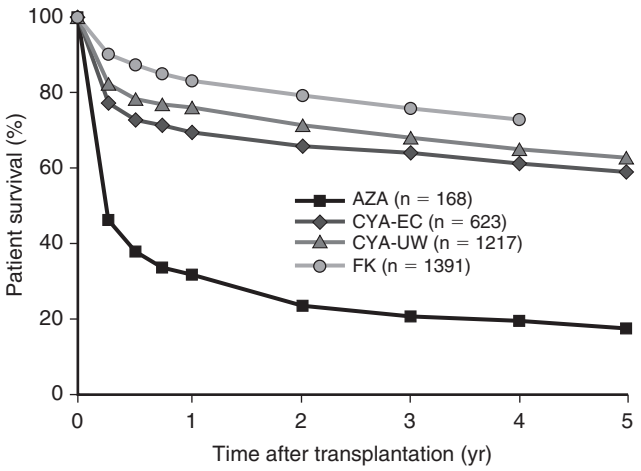


FIGURE 1-18 ■ Stepwise improvements in patient survival after liver replacement. These were associated with the advent of increasingly potent immunosuppressive drugs. Most of the difference between the CYA-EC and CYA-UW lines was because of the availability of FK for the rescue of cyclosporine failures. The data shown here were presented to the American Surgical Association in April 1994. *AZA,* Azathioprine; *CYA-EC,* cyclosporine before the availability of University of Wisconsin solution; *CYA-UW,* cyclosporine after the availability of University of Wisconsin solution; *FK,* tacrolimus.

management errors, physiological abnormalities, or the administration of potentially damaging pharmacological agents. Criticized at first, this form of expanding the donor pool became widely accepted once the magnitude of the supply problem was fully appreciated. The use of marginal donors has become so mainstream that what was once considered marginal is now more often than not considered standard.

Several efforts, many often contentious, have been made to define what constitutes a marginal donor, and how to decide who gets the liver.[101] The Donor Risk Index was defined by Sandy Feng of the University of California, San Francisco, along with colleagues from the University of Michigan[102] in 2006. This group used powerful statistical techniques and the data pooled nationally from large clinical trials and databases to identify significant donor parameters. An index was created that could quantify the risk of a particular donor based on these known pretransplant parameters and quickly provide that risk to the transplant surgeon in real time.[102]

As the organ supply issues become greater, and as the technical capabilities of transplantation and posttransplant management continue to be refined, the question as to what defines a marginal donor will invariably be adjusted further.

ORGAN SUPPLY: SPLIT-LIVER PROCEDURES

Split-liver transplantation evolved from the advancements of hepatobiliary surgery that have improved parenchymal transection and an improved understanding of liver segmental anatomy. Split-liver procedures involve dividing the liver into two segments, making more efficient use of deceased donor liver allografts by sharing one between two recipients. The first ex situ split-liver transplant was reported by Pichlmayr[103] from the University of Hannover in 1988, and similar procedures were reported very soon after in Paris by Bismuth's team[84] and at the University of Chicago by Christopher Broelsch.[104,105] The first in situ liver transplant was performed by Xavier Rogiers at the University of Hamburg in 1995.[106,107] The in situ technique used the lessons learned from living donor liver transplantation to create the two separate segments that could be used as liver allografts.[107]

Initially the results were inferior to those obtained from whole livers, but after a learning curve and adopting lessons from living donor transplantation, the results with livers split between adult and pediatric recipients have been comparable to standard deceased donor transplantation. There are two main types of split livers. The first is the classic split into an extended right graft and a left lateral segment suitable for creating grafts for pediatric patients. The second type results in a right and left segment that can be suitable for two adults.[107]

The current role for split livers is controversial. Although the evidence shows the outcomes are similar to those of whole livers, the current regulatory environment does not reward the efforts and expenses incurred by centers that pursue these option to bring it to the mainstream.

ORGAN SUPPLY: LIVING DONOR TRANSPLANTATION

Living donor liver transplantation evolved from the reduced liver graft procedures done in deceased donors and involves resecting liver segments (ranging in size from a left lateral segment to an extended right lobe segment) from volunteer adult donors and transplanting them into a pediatric recipient. The first successful living donor liver transplant, from an adult to a pediatric recipient, was performed by Russell W. Strong and Stephen V. Lynch of the University of Queensland in Brisbane, Australia, in July 1989.[108] The living donor transplant operation for pediatric recipients was subsequently popularized by Broelsch and associates from the University of Chicago, who reported their experience of living donation along with their experience of split livers and reduced-size deceased donors at the 1990 American Surgical Association conference.[105]

For adult-to-adult living donor transplantation, to obtain an adequate liver mass, the size of the transected liver segment was first increased from a left lateral segment, to a full left lobe, and then to the right lobe operation, which is the most common procedure today. This first right lobe living donor transplant was carried out by the program at Kyoto University in Japan,[109] when unexpected anatomical findings were encountered in the donor. The first series of right lobe transplantation in the United States was performed by the team of Igal Kam from the University of Colorado in 1997.[109] Shortly

thereafter, several other centers across the United States initiated adult-to-adult living donor transplants. Since this time, more than 3500 right lobe transplantations[111] have been performed in more than 60 U.S. centers, with patient and graft survival equivalent to that of whole-organ deceased donor transplantation or the various kinds of partial liver transplantation, including the adult-to-child living donor transplant.

Despite its utility, living donor liver transplantation has been used with caution by many transplant surgeons because of concerns of donor mortality. Living donor liver transplant donor deaths have occurred at some of the largest and most experienced living donor liver programs in the United States. These deaths occurred under a media microscope that never existed during the early liver transplant trials of the 1960s, and the intense media exposure magnified each event exponentially. A review of living donor liver transplantation in the United States showed the incidence of early mortality in donors was 0.2%[112] with seven liver donors having died in the United States by 2013, during either the operative procurement or in the immediate postoperative period.

Although much attention has focused on living donation in the United States, most of the later development in the field has occurred in programs throughout Asia, largely because of need related to a lack of organ supply from deceased donors. Living donor transplantation flourished early on in Japan, leading to the creation of several very large programs in Fukuoka, Kyoto, and Tokyo. The greatest success has been in Korea, particularly the program of Sung-Gyu Lee at the Asan Medical Center in Seoul, South Korea, which alone performs more living donor liver transplants each year than all of the centers in the United States combined.

ORGAN SUPPLY: XENOTRANSPLANTATION

Xenotransplantation is the transplantation of living tissue or organs from one species to another. It has long been hoped to be a solution for the supply issues facing liver transplantation. At the same time, xenotransplantation is associated with a number of concerns, including immunological problems and xenogeneic infections, as well as ethical, legal, and social concerns. Regardless of these issues, it is not an area that has had great success

The first clinical attempts in xenotransplantation of livers involved chimpanzees between 1966 and 1973.[113] There were three attempted transplants of chimpanzee livers into three children, and all were unsuccessful with all dying within 14 days of transplant.[114] Of interest, the clinical course and histopathological examination of the xenograft livers on autopsy were indistinguishable from allotransplantation transplants at that time.

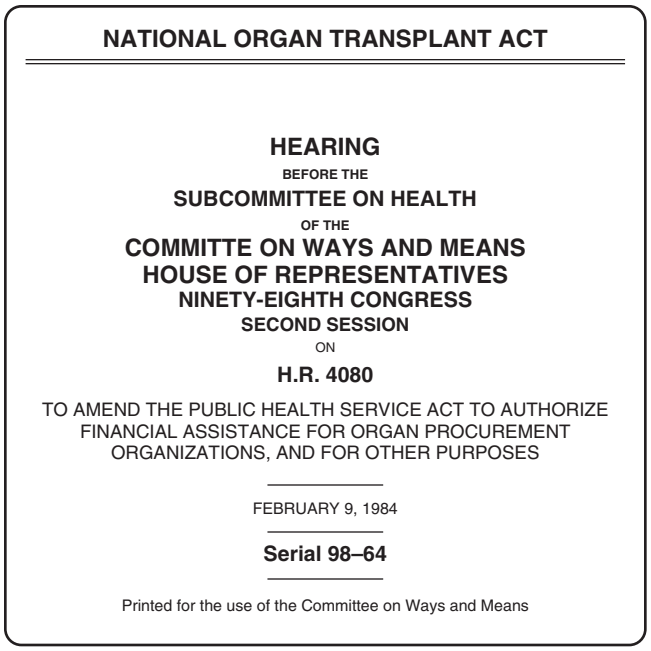
With the development of improved immunosuppression, two more xenotransplants were attempted by Starzl at the University of Pittsburgh program between June 1992 and January 1993 using the more phylogenetically distant baboon livers.[115] The recipients were patients with human immunodeficiency virus (HIV) infection and advanced hepatitis B, specifically chosen because animal livers are refractory to infection by either virus, and they survived for 70 days and 26 days, respectively. In these baboon xenotransplants, a four-drug immunosuppression cocktail was used, and neither cell-mediated nor humoral rejection was implicated as the cause of death in the recipients. However, there was evidence of continuous complement activation in both, and neither xenograft functioned optimally, with both developing intrahepatic cholestasis within the first postoperative week. Because of the heavy immunosuppression needed, both patients developed infections that led to their deaths, and the first patient also had a fatal brain hemorrhage at 70 days.[115] It was suspected that synthetic products created from the baboon liver might have been incompatible with the human metabolic environment. Further trials of xenotransplantation involving chimpanzees and baboons have been avoided because of the anthropometric qualities of the donor and the concerns that these animals pose a high risk for zoonotic infections that might enter the human population, given the evidence of human diseases that originated from nonhuman primates such as HIV-1 and HIV-2.[116]

It has been hoped that lower mammalian donors such as pigs may be suitable. Studies using the genetic knockout of clone pigs missing the α1,3-galactosyltransferease gene,[117] which is required for the 1,3-galactose sugar chains that induce human preformed antibodies, show it avoided the hyperrejection from the immediate innate immune response. The first porcine-to-human xenotransplantation was performed by Makowka at the Cedars-Sinai program in Los Angeles in October 1992. It was intended as a bridge for a human liver in a patient with acute liver failure, but the patient died of cerebral swelling 32 hours after transplant, and 2 hours before the human transplant was to begin.

Later trials of porcine-to-human xenotransplantation have focused on using them ex vivo, as extracorporeal support instead of implanting the liver, to bridge sick patients until a human liver becomes available. Marlon Levy at the Baylor University Medical Center in Dallas reported the first successful ex vivo porcine xenoperfusions used in this fashion.[118] Nonetheless, concerns of xenogeneic infections have developed out of this situation, because pigs carry an endogenous retrovirus called porcine endogenous retrovirus that is capable of infecting human cell lines.[113] There have been no reports of porcine-to-human transmission of porcine endogenous retrovirus from these ex vivo porcine systems.

REGULATORY DEVELOPMENT: NATIONAL ORGAN TRANSPLANT ACT OF 1984 AND BEYOND

The rapid developments in organ transplantation following the introduction of cyclosporine, as well as the report from the NIH consensus committee, led to many issues



NATIONAL ORGAN TRANSPLANT ACT

HEARING
BEFORE THE
SUBCOMMITTEE ON HEALTH
OF THE
COMMITTE ON WAYS AND MEANS
HOUSE OF REPRESENTATIVES
NINETY-EIGHTH CONGRESS
SECOND SESSION
ON
H.R. 4080

TO AMEND THE PUBLIC HEALTH SERVICE ACT TO AUTHORIZE FINANCIAL ASSISTANCE FOR ORGAN PROCUREMENT ORGANIZATIONS, AND FOR OTHER PURPOSES

FEBRUARY 9, 1984

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FIGURE 1-19 ■ The National Organ Transplant Act was sponsored by Representative Al Gore and Senator Orrin Hatch and was approved on October 19, 1984. The act was important in codifying guidelines regarding transplantation, including prohibiting the sale of human organs. Many of the administrative bodies and tools used today, including the Organ Procurement and Transplantation Network, organ procurement organizations, the United Network for Organ Sharing, and the Scientific Registry of Transplant Recipients, were laid out in the act.

that needed regulation and oversight. Before the passage of the National Organ Transplant Act (NOTA), there was not a clear understanding of property rights for transplant and there were concerns of a developing commercial marketplace for organs.

The NOTA was sponsored by Representative Al Gore and Senator Orrin Hatch (Fig. 1-19), and it was approved on October 19, 1984.[119] The act provided for the establishment of the Task Force on Organ Transplantation, and it outlawed the sale of human organs. Many of the administrative bodies in place today were outlined in the act. One mandate was the formation of the Organ Procurement and Transplantation Network (OPTN),[120] which would establish and oversee organ procurement organizations (OPOs). Another mandate was the development of the Scientific Registry of Transplant Recipients (SRTR) with which patient and graft survival could be assessed from center to center.[121]

Following passage of the NOTA, the Department of Health and Human Services awarded the contract to administer the OPTN and the OPOs to a private nonprofit organization, the United Network for Organ Sharing (UNOS). The SRTR was created in 1987 to support ongoing evaluation of the scientific and clinical status of solid organ transplant. The SRTR contract was transferred to the University of Michigan–based Arbor Research Collaborative for Health in 2000. In 2010 the University of Minnesota–based Minneapolis Medical Research Foundation was awarded the contract for the SRTR.

REGULATORY DEVELOPMENT: EQUITABLE ORGAN ALLOCATION AND THE MELD SCORE

As liver transplantation moved from being experimental to a "clinical service, and as it became more successful, the increased demand was met with shortages of organ supply. To help manage this supply-demand mismatch, the transplant field in the United States in 2002 began using the Model for End-Stage Liver Disease (MELD) score, based on an equation using three laboratory-based parameters, to prioritize equitable organ allocation. The MELD score was implemented in response to the OPTN Final Rule, a mandate to deemphasize waiting time and focus on disease severity and waiting list mortality.[122] Compared to the prior system that used the Child-Turcotte-Pugh score and location of the patient (i.e., home, hospital, intensive care unit) to allocate organs, the MELD system was thought to be more standard and equitable, more difficult to manipulate, less dependent on waiting list, and instead focusing on the idea of the "sickest first." Exception points were provided in certain situation such as for hepatocellular carcinomas that met the Milan criteria.

The system is not perfect, and its weaknesses have been widely recognized, including a lack of specificity for different liver diseases and particular biases associated with each laboratory parameter. Nonetheless, the MELD score has set a standard and has allowed for the idea of a newer system that reflects these weaknesses to one day be incorporated.

ORGAN PRESERVATION: EXTRACORPOREAL MACHINE PERFUSION SYSTEMS

Extracorporeal machine perfusion systems are an example of history repeating itself in the modern day.[123] Machine organ perfusion was part of the first studies of organ transplant, before the development of better preservation solution that allowed cold storage at 4° C. Unfortunately, the organs from marginal donors that make up so many of the transplants in today's transplant centers are more susceptible to damage from cold storage. The successful development of hypothermic pulsatile machine perfusion for kidney allografts, as well as interest in expanding the use of marginal donors, has led to efforts to create a similar system for livers. James Guarrera and colleagues from Columbia University, New York, devised a hypothermic machine perfusion system for liver (Fig. 1-20), and the initial trials reported in 2010 have shown benefit. These machine perfusion systems also allow delivery of metabolic substrates and therapeutic agents to the allograft and make assessments that can predict graft function.[123,124] The main limitation is devising a portable system that can accommodate the size and perfusion demands of a liver. Another machine perfusion strategy involves a normothermic perfusion system that

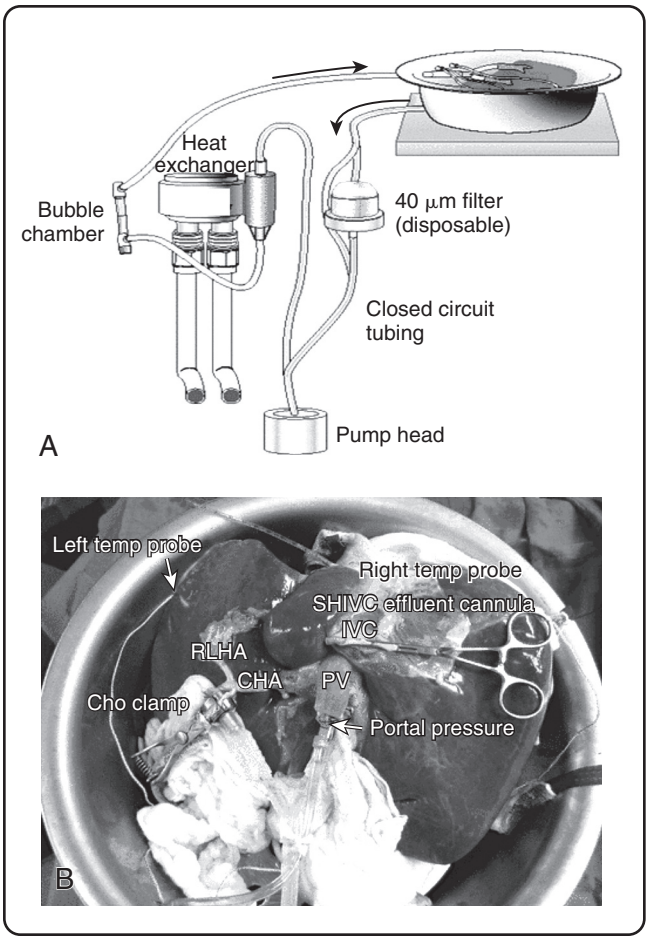

FIGURE 1-20 ■ The successful development of hypothermic pulsatile machine perfusion for kidney allografts, as well as interest in expanding the use of marginal donors, has led to efforts to create a similar system for livers. James Guarrera and colleagues from Columbia University, New York, devised a hypothermic machine perfusion system for liver, and the initial trials reported in 2010 have shown benefit. These machine perfusion systems allow delivery of metabolic substrates and therapeutic agents to the allograft and also allow assessments that can predict graft function. *CHA*, common hepatic artery; *IVC*, inferior vena cava; *PV*, portal vein; *RLHA*, replaced left hepatic artery; *SHIVC*, suprahepatic inferior vena cava; *temp*, temperature. (From Guarrera JV, Henry SD, Samstein B, et al. Hypothermic machine preservation in human liver transplantation: the first clinical series. *Am J Transplant.* 2010;10:372-381.)

pumps oxygenated blood through the liver at body temperature,[125,126] and initial trials at the program at King's College have been very successful.[127]

SUMMARY

The history of liver transplantation is a story that spans more than 6 decades. It is a story of bold clinicians overcoming obstacles and setbacks, learning from their failures, and through a collaborative effort accomplishing what conventional wisdom—and many experts of the day—thought was impossible. It is a story of those first brave patients at the beginning who were willing to go forward when there were no guarantees of success. And it is now a story of hundreds of thousands of lives worldwide that have been saved.

The history of liver transplantation is a complicated story to tell—but it's a really good one.

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CHAPTER 2

SURGICAL ANATOMY OF THE LIVER

John F. Renz • Milan Kinkhabwala

CHAPTER OUTLINE

The increasing organ shortage observed since the previous edition of *Transplantation of the Liver* mandates expert knowledge of partial allograft transplantation by the practicing clinician. The maturation of hepatobiliary surgery has expanded the role and safety of major hepatic resection,[1] permitting the expanded application of partial-liver allografts derived from living or deceased donors to adults and children.[2,3] In this past decade, partial-liver allografts have become the most common allograft for pediatric patients with superior results observed in infants,[4] while the application of partial-liver allografts to adults from living and deceased donors has expanded.[5-8] Fundamental to the successful outcome of major hepatic resection or partial-liver transplantation is the avoidance of technical complications. This requires maximizing functional hepatic mass while minimizing iatrogenic injury. Currently several nomenclature systems are used within the literature,[9,10] which can be a source of confusion. In this context a concise anatomical review with direct application to clinical transplant surgery is particularly relevant.

EMBRYOLOGY

The hepatic diverticulum, a ventral outpouching of the distal foregut observed early in the fourth week of gestation (3-mm embryo), is the origin of the hepatobiliary system. This outgrowth of proliferating endodermal cells infiltrates the embryonal ventral mesentery and extends into the septum transversum to form the early liver primordium.[11,12] The rapidly proliferating primordium expands into the left and right vitelline veins (omphalomesenteric veins) to stimulate extensive remodeling into separate liver chords and portal sinusoids from the primordium mass,[9,11,13]creating separate right and left intrahepatic portal circulations.[9] The vitelline veins undergo further differentiation into an intrahepatic component containing hepatic chords and portal sinusoids, a cranial component delivering blood from the embryonic liver to the heart, and a caudal component carrying blood from the yolk sac to the liver. Later endodermal cell proliferation yields hepatic cords and biliary epithelia that coalesce to create sinusoids, whereas hemopoietic tissue, Kupffer cells, and interstitial connective tissue originate from the splanchnic mesenchyme of the septum transversum.[12]

The hepatic veins originate from the vitelline venous system. The cranial component of the left vitelline vein initially involutes, shunting all returning blood to the heart through the cranial component of the right vitelline vein, known as the *embryonic common hepatic vein*. The common hepatic vein functions as an early single outflow source from the liver to the heart and persists as the later right hepatic vein. The vitelline venous system of the left side of the liver later reconstitutes channels that mature into left and middle hepatic veins to augment venous return from the liver to the heart and define the permanent anatomical arrangement. Vitelline venous system development is manifested by the surgical findings of a distinct right hepatic vein emptying directly into the vena cava as compared with the middle and left hepatic veins that typically empty via a common channel.[13,14]

The development of the extrahepatic main portal vein is one of the most complex processes observed in embryology.[9,13,14] Origination of the extrahepatic main portal vein begins with fusion of left and right vitelline venous elements returning blood from the gut–yolk sac complex. The objectives are to create a single inflow source to the liver from the bilateral vitelline veins while preserving the anatomical relationship of the main portal vein to the developing duodenum. As the yolk sac regresses, the omphalic portions of the vitelline veins disappear while

the mesenteric branches proliferate, increasing in length and complexity to serve the intestinal tract.[15] Between the fourth and sixth weeks (4.5- to 9-mm embryo), caudal elements of both vitelline veins unite through intravenous channels and undergo segmental involution to form a composite, S-shaped vessel, located posterior to the first portion of the duodenum, that drains both vitelline venous beds as a single vessel to the liver.[9,13,14]

The intrahepatic left portal vein is also a composite vessel originating from a communication between the vitelline veins and a segment of the left umbilical vein.[14] The umbilical veins are originally paired; however, the left umbilical vein is invaded by hepatic tissue and hypertrophies, whereas the right atrophies before contact with the liver. Umbilical blood initially flows through a meshwork of intrahepatic sinusoids, but as volume increases, these sinusoids coalesce to receive the proximal portion of the developing left portal vein and form a single vessel shunting blood through the liver, the ductus venosus.[14,15] The ductus venosus receives branches from the liver before joining the hepatic veins to drain into the inferior vena cava.[13] After birth the ductus venosus closes to form the ligamentum venosum.

The biliary and arterial systems develop later, along the latticework provided by the established portal venous system. The right biliary and arterial branches follow the portal system exactly, whereas the left biliary and arterial systems divide into equal-size branches on either side of the intrahepatic portion of the umbilical vein.[9]

The embryonal liver develops rapidly to occupy most of the abdominal cavity. By 9 weeks' gestation, the liver accounts for approximately 10% of the embryo's total weight with relatively equal hepatic mass on each side of the falciform ligament. The initial equality in volume between topographical lobes is lost by 12 weeks as the topographical right lobe hypertrophies to spawn the caudate lobe (initially recognizable at 6 weeks) and become the dominant hepatic mass.[11,12]

The ventral mesentery forms the gastrohepatic ligament[16] and the fibrous visceral peritoneum of the liver. This was first described by Glisson in 1659,[17] as a peritoneal sheath that envelops the organ, except for a "bare area" on the superoposterior surface of the right lobe where the organ is in direct contact with the inferior vena cava, diaphragm, and superior aspect of the right adrenal gland. Glisson's capsule involutes into the parenchyma as intrahepatic septa or trabeculae that support vascular structures and serve as surgical landmarks.[18,19]

Functional milestones in embryonic development include intrahepatic hematopoiesis during the sixth week, hepatocyte bile formation at the twelfth week, and excretion of bile into the duodenum by the sixteenth week.[11] The third trimester marks the cessation of hematopoiesis with a concomitant decrease in liver growth to account for approximately 5% of the newborn's body weight.[12,18]

TOPOGRAPHICAL ANATOMY

Topographical anatomy of the liver dates to early Babylon (3000-2000 BC), where the liver was described according to external landmarks. This anatomical system dominated through the late nineteenth century but is currently only of historical interest. The principal landmarks defining topographical anatomy include the falciform ligament, umbilical fissure, gallbladder fossa, and transverse hilar fissure.[18,20] These landmarks delineate four lobes (Fig. 2-1): left (medial to falciform), right (lateral to falciform), quadrate, and caudate (spigelian).[21]

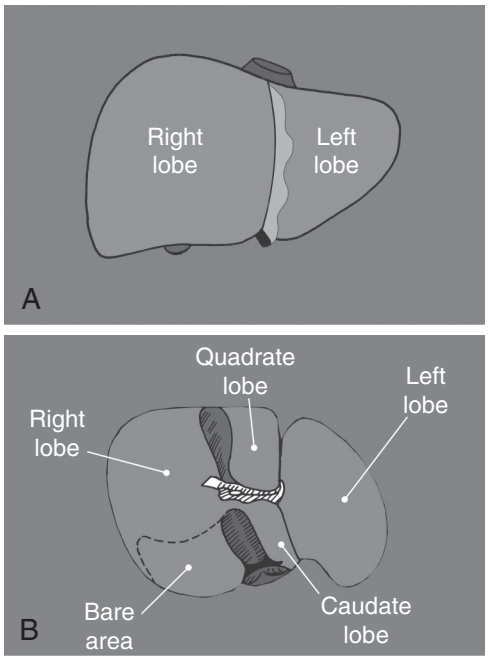

FIGURE 2-1 ■ Topographical anatomy of the liver. The landmarks defining topographical anatomy include the falciform ligament, umbilical fissure, gallbladder fossa, and transverse hilar fissure. These delineate four hepatic lobes: left, right, quadrate, and caudate (spigelian). **A,** Anterior view. **B,** Posterior view.

The liver is supported in position through peritoneal reflections continuous with Glisson's capsule that attach to the duodenum, stomach, diaphragm, and anterior abdominal wall. These peritoneal reflections include the falciform ligament, right and left triangular ligaments, and right and left coronary ligaments, as well as the lesser omentum. The falciform ligament extends from the ligamentum teres superiorly along the anterior liver surface in continuity with both the diaphragm and anterior abdominal wall above the umbilicus.[18] The ligamentum teres is a remnant of the vestigial umbilical vein. Normally obliterated, it may recanalize in disease conditions like cirrhosis, decompressing the portal circulation through collaterals of the periumbilical superficial venous plexus. This shunts portal blood to the systemic circulation through superficial venous plexuses, producing the characteristic "caput medusa." As the falciform ligament continues toward the diaphragm, the peritoneal sheets composing the ligament separate to adopt a triangular shape that broadly covers the entry of the hepatic veins into the suprahepatic vena cava.[19]

At the level of the suprahepatic vena cava, the peritoneal reflections progress laterally to become the anterior layers of the left and right coronary ligaments. The coronary ligaments anchor the superior surface of the liver through anterior and posterior reflections to the

diaphragm. As the right and left coronary ligaments extend laterally, each unites with the posterior reflections to form the respective right and left triangular ligaments. The right coronary ligament may continue and fuse to the superior pole of the right kidney to form the hepatorenal ligament.[18]

The lesser omentum is a continuous fold of peritoneum arising from the posterior reflection of the left triangular ligament. The lesser omentum extends from the liver onto the lesser curvature of the stomach and first 2 cm of the duodenum to form the gastrohepatic and hepatoduodenal ligaments, respectively. The hepatoduodenal ligament forms the anterior border of the epiploic foramen of Winslow and contains the porta hepatis.

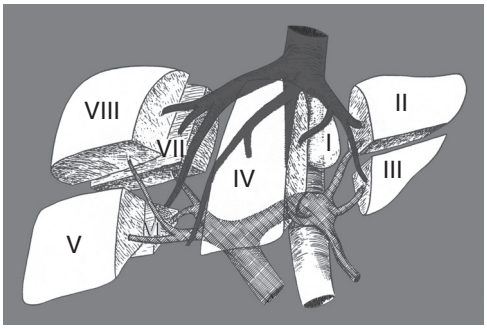

FIGURE 2-2 ■ Segmental liver anatomy. The segmental anatomy of the liver as described by Couinaud. Each anatomical segment *(Roman numeral)* receives a unique portal pedicle *(light gray)* consisting of a portal venous branch, hepatic arterial inflow, and bile duct. Venous drainage occurs via a major hepatic venous outflow branch *(dark gray)*.

LOBAR ANATOMY

Galen (130-201 AD) postulated the hepatic arterial and portal venous systems terminated as minute connections that reconstituted into hepatic veins draining to the inferior vena cava.[21] Galen's concept of separate arterial and portal venous systems reconstituting into hepatic veins resurfaced in 1888, when Hugo Rex studied hepatic corrosion casts from mammals.[22] Rex concluded that the right and left branches of the portal vein functioned as unique vascular systems, dividing the liver into separate halves. In 1897 James Cantlie extended these findings to humans, proposing a functional division of the liver into two lobes ("Cantlie's line") of relatively equal size based on the branching of the portal vein (and followed by the hepatic ducts).[23] Cantlie's line has no visible surface topography but rather is a virtual plane that bisects the gallbladder fossa and the suprahepatic vena cava. This plane roughly overlies the course of the middle hepatic vein and can be demonstrated in clinical practice by devascularization of the hemiliver (right or left).

Cantlie's description of functional anatomy shifted the entire quadrate lobe (topographical term), as well as a large component of the caudate lobe (topographical term), into the anatomical boundaries of the left lobe rather than the right. This classification system, founded on intrahepatic functional anatomy rather than surface topographical landmarks, was the underpinning of a modern surgical revolution in anatomically based hepatic resections.[24] Tiffany[25] reported the first liver resection performed in the United States in 1890 (although the accuracy of this publication is widely disputed), and Professor William Keen of Jefferson Medical College confidently and somewhat prematurely proclaimed to members of the Pennsylvania State Medical Society on May 17, 1899, "after my experience with these three cases [liver resections], I should hardly hesitate to attack almost any hepatic tumor without regard to its size."[21]

Cantlie's reference to hepatic lobes created two definitions for the same term and was the source of continuing confusion.[9] Europeans continued to describe hepatic lobes based on topographical anatomy, whereas North American surgeons adopted *lobectomy* as the hemiliver defined by Cantlie. One must be certain as to the reference system in use (topographical anatomy or Cantlie's anatomical classification) when applying the term *lobe* or *lobectomy*. A more appropriate scheme is to refer to Cantlie's anatomical lobes as hemilivers, thus describing a right or left hepatectomy.

The anatomical system of Cantlie was later expanded by the North American anatomists Healey and Schroy,[26] who based their nomenclature on biliary anatomy, rather than on Cantlie's description of portal venous anatomy, while retaining the term *lobe*. The right lobe was divided into anterior and posterior segments by a right segmental fissure, whereas the left lobe was divided into medial and lateral segments by a left segmental fissure.[9] The left segmental fissure corresponds to the falciform ligament, whereas the segmental "fissure" that divides anterior and posterior sectors of the right lobe is not easily discerned by surface landmarks, though one can infer its location based on the plane of insertion of the extrahepatic right portal pedicle. Healey and Schroy's classification scheme led to the descriptive but imprecise term *hepatic trisegmentectomy* for extended right hepatectomy, and the often used term *left lateral segment* for the topographical portion of the liver containing modern segments II and III.[27]

MODERN SEGMENTAL ANATOMY

The most sophisticated classification of intrahepatic anatomy is by Couinaud,[28] who in 1954 founded his anatomical description on the portal venous system. Portal vein distribution within the liver was subdivided into eight "segments." Individual segments each receive a "portal pedicle" consisting of a portal venous branch, hepatic arterial branch, and a bile duct radicle with segmental drainage through a dedicated hepatic venous branch. The eight functional segments embrace the hepatic veins that provide outflow to the inferior vena cava (Fig. 2-2).

The hepatic veins travel in planes termed *fissures* or *scissurae*, dividing the liver into four sectors (see Fig. 2-1). The left portal fissure contains the left hepatic vein, the main portal fissure contains the middle hepatic vein (in the plane of Cantlie), and the lateral-most (right) portal fissure contains the right hepatic vein. Three of the four

sectors contain smaller fissures that subdivide each into two segments to form a total of seven segments. Only the caudate lobe (segment I) is a functionally autonomous segment supplied by both the left and right branches of the portal vein and hepatic artery with drainage directly into the inferior vena cava.[28] Clinically this relationship is well demonstrated in patients with Budd-Chiari disease who compensate for major hepatic vein outflow obstruction by development of alternative outflow tracts via veins draining directly from segment I into the retrohepatic vena cava.

Biliary drainage of segment I occurs via small anterior radicles draining directly into the posterior surface of the biliary confluence. A well-defined segment 1 duct consistently drains into the proximal left hepatic duct between the hepatic duct bifurcation and the umbilical fissure. It is important to recognize and control this duct during resectional surgery and for partial liver allografts involving the left lobe. Segments II and III correspond to the posterior and anterior segments of the topographical left lobe, respectively. Segment IV, the largest segment and the only one derived from an undivided hepatic sector, extends from the left portal fissure to the main portal fissure (Cantlie's line) and includes the entire volume of the quadrate lobe.

The right portal fissure divides the right lobe into an anteromedial sector and a posterolateral sector, each of which is subdivided into anterior and posterior segments. The two anterior segments of the right lobe include segment V (inferiorly adjacent to the gallbladder fossa) and segment VIII (superiorly). The two posterior segments of the right lobe include segment VI (inferiorly, adjacent to the right kidney), and segment VII (superiorly). The posterior segments VI/VII are located posterior to the peritoneal reflection and are therefore retroperitoneal structures that are not visible at laparotomy without mobilizing the right lobe of the liver (see Fig. 2-2).[28]

The recognition of the segmental anatomy of the liver was a significant advancement for hepatic surgery. In 1982 Bismuth[24] integrated Couinaud's classification scheme into a formal anatomical approach to hepatectomy that has been widely adopted by hepatobiliary surgeons to standardize techniques and nomenclature. Rather than perform atypical resections based on the size or location of a lesion, hepatic resections could be performed along functional planes that would minimize intraoperative blood loss and postoperative necrosis of devitalized tissue, in addition to potentially improving oncological control of malignancy after resection. This classification has revolutionized hepatic surgery by providing a foundation for the development of highly selective anatomical resections as well as innovations in transplantation using surgically created partial-liver allografts.

APPLIED SURGICAL ANATOMY

Couinaud's anatomical classification permitted the theoretical construction of partial-liver allografts based on the known regenerative capacity of the liver (Fig. 2-3), which

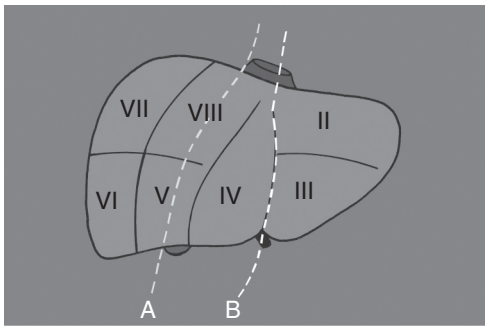

FIGURE 2-3 ■ Surgical division of the liver along Cantlie's line *(dashed line A)* yields a left hemiliver (segments I to IV or II to IV) and right hemiliver (segments V to VIII) allograft that can be used in adult-to-adult living donor and split-liver transplantation between two adults. Division along the falciform ligament *(dashed line B)* yields a segment II/III allograft, also termed a *left lateral segment allograft* or *topographical left lobe*, and remnant segments I, IV to VIII allograft, also termed a *right trisegment allograft* or *topographical right lobe*.

was realized in clinical practice during the 1980s. The successful application of partial-liver allografts mandates detailed anatomical considerations because these procedures predispose to unique surgical complications. Fundamental to the application of these techniques is an understanding of intrahepatic vascular and biliary anatomy. Although the incidence of vascular complications has declined with the widespread application of microsurgical techniques,[29-34] a relatively high incidence of biliary complications persists.[3,7,35]

Four distinct allografts have been used routinely in partial-liver transplantation (see Fig. 2-3). These include the right hemiliver (Couinaud segments V to VIII), the left hemiliver (Couinaud segments II to IV), the topographical left lobe (Couinaud segments II to III), and the topographical right lobe (Couinaud segments IV to VIII).

Anatomy of the Hepatic Hilum

All partial-liver allograft preparation includes a hilar dissection. The objective is to specifically isolate vascular and biliary supply with minimal disruption to surrounding structures. Figure 2-4 depicts the anatomical relation of the proper hepatic artery, common hepatic duct, and portal vein. The conventional anatomical relationship of the hilum is a posterior portal vein, anteromedial proper hepatic artery, and anterolateral common bile duct. Following bifurcation of the proper hepatic artery, the right hepatic artery typically courses posterior to the common hepatic duct (see Fig. 2-4). Arterial variations within the hilum are common,[36,37] particularly in the setting of superior mesenteric artery–derived arterial supply. In classic descriptions the proper hepatic artery originates distal to the gastroduodenal artery and receives aortic inflow from the celiac trunk. When arterial inflow to the liver originates from the superior mesenteric artery rather than the celiac artery, anatomy is termed *replaced*. Thus the entire proper hepatic artery may be replaced, or the right hepatic artery may independently originate from the superior mesenteric, rather than the proper hepatic, to be replaced. Replaced arterial anatomy is readily identifiable preoperatively by

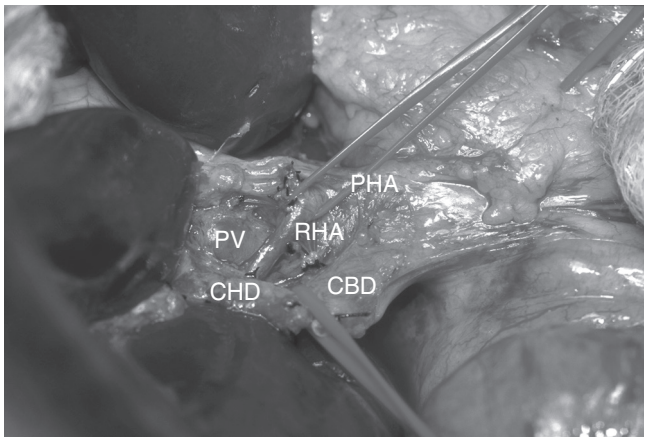

FIGURE 2-4 ■ Intraoperative hilar dissection. The three principal elements of the porta hepatis—the common hepatic duct (CHD), the portal vein (PV), and the proper hepatic artery (PHA)—are demonstrated in this intraoperative photograph. The anterolateral CHD is retracted (lower vessel loop) just before the origin of the cystic duct signaling the beginning of the common bile duct (CBD). The bifurcation of the anteromedial PHA to form the right hepatic artery (RHA) is retracted medial (upper vessel loop). The RHA *(center)* is immediately anterior to the PV and courses posterior to the CHD in celiac-derived hepatic arterial supply.

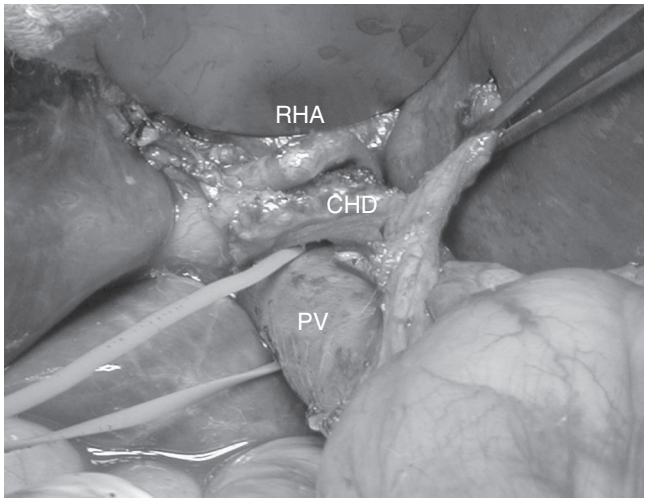

FIGURE 2-5 ■ Anatomy of the hilum. The main portal vein (PV) is dissected and encircled with a vessel loop. The cystic duct is retracted with the forceps and the right hepatic artery (RHA) lies above the common hepatic duct (CHD). Note that the course of the RHA anterior to the CHD is rare except in the setting of replaced arterial anatomy.

computed tomography, magnetic resonance arteriography, or angiography and is clinically relevant to hepatobiliary surgery and transplantation (Fig. 2-5).

Couinaud Segment II/III Allograft

Division of the hepatic parenchyma at the falciform ligament yields a segment II/III allograft, commonly referred to as a *left lateral segment* or *topographical left lobe graft* for pediatric recipients.[38-40] The segment II/III allograft can be further reduced to a "monosegment" allograft (segment III) for very small infants and neonates.[41]

Dissection of the portal triad in segment II/III donor hepatectomy originates at the base of the round ligament

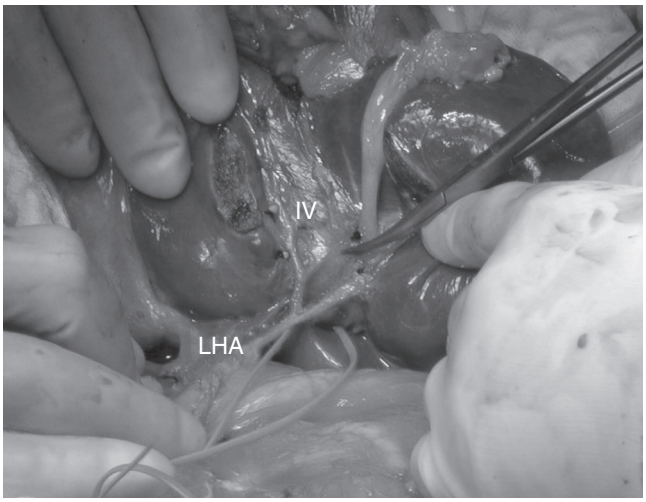

FIGURE 2-6 ■ Segment IV arterial branches originating from the left hepatic artery (LHA).

with isolation of the left hepatic artery and left portal vein. The left hepatic vein is isolated and encircled with a vessel loop. With vascular control achieved, parenchymal transection typically occurs within 1 cm to the right of the falciform ligament and progresses to within 1 cm of the left hepatic duct in the umbilical fissure.[7,42]

At its origin the left hepatic artery enters the base of the umbilical fissure anteromedial to the left portal vein. The left portal vein travels for a variable distance in a horizontal direction outside the liver along the inferior aspect of segment IV before entering the base of the umbilical fissure, in a similar pathway as the left hepatic duct. The left hepatic artery originates anteromedial and inferior to the origin of the left portal vein but ascends to be anterosuperior to the left portal vein by the point of parenchyma entrance. Although extrahepatic, the left hepatic artery sends a major and several minor branches to segment IV. Accompanying the left hepatic artery is the left portal vein with branches to segments I and IV along its intrahepatic and extrahepatic course.

Left Lobe Arterial Anatomy

Principal segment IV arterial branches may originate proximal, near the origin of the left hepatic artery, or distal at the level of the umbilical fissure (Fig. 2-6). Furthermore, principal segment IV arterial branches may originate independently, distal to the origin of the left hepatic artery, to create parallel arteries across segment IV with superior branches servicing segment II (Fig. 2-7).[42,43] Segment IV penetrating arteries provide significant inflow and should be preserved whenever possible. When allografts are split to produce an extended right lobe graft (segment IV to VIII) and a smaller lateral segment graft (segment II/III), major segment IV arteries may require reconstruction to preserve viability of segment IV after implantation.

Arterial supply to the left lobe (and by extension to segment II/III allografts) may originate from the left gastric artery ("replaced left hepatic artery"). Replaced left arteries course transversely across the gastrohepatic ligament from the left gastric artery on the lesser curvature

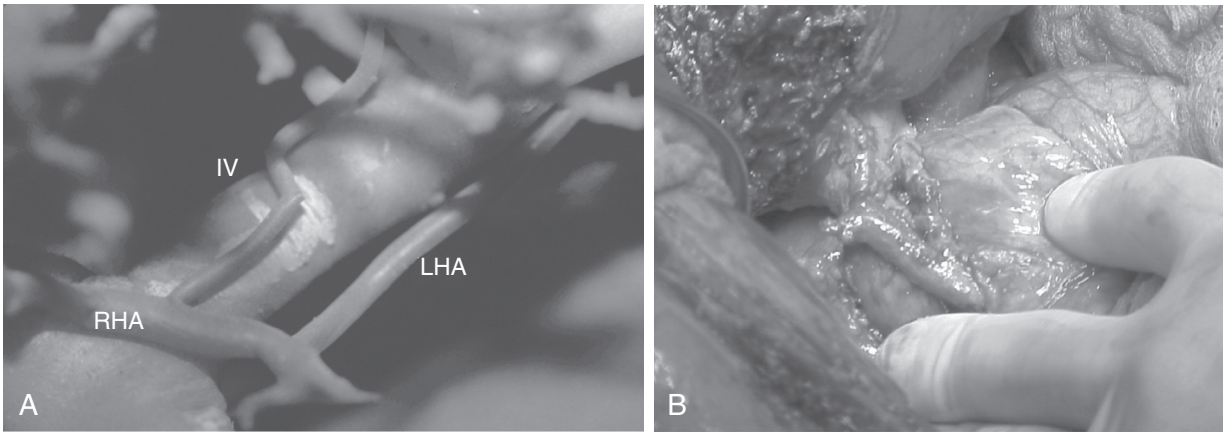

FIGURE 2-7 ■ Independent segment IV hepatic artery. A large segment IV artery, diameter greater than 1 mm, originates distal to the origin of the left hepatic artery (LHA) and courses anterosuperior to the left portal vein to supply segments IV and II. **A,** Corrosion cast. **B,** Intraoperative photograph. *RHA,* Right hepatic artery.

of the stomach to enter the inferior surface of segment III just anterior to segment I (caudate lobe) in approximately 15% to 23% of deceased donors.[36,37,44,45] This anatomical variant can be the principal arterial supply to the segment II/III allograft as a replaced vessel or augment arterial supply to the allograft as an accessory vessel.

Left Lobe Ductal Anatomy

Arterial and biliary structures are located superior to the extrahepatic portion of the left portal vein with the orientation of the portal pedicle at the umbilical fissure preserved as the structures penetrate the hepatic parenchyma. The left hepatic artery is anterosuperior to the left portal vein, whereas the orientation of the left hepatic duct system, with respect to the left portal vein, is variable. The anatomical relationship of the left hepatic duct to the left portal vein at the umbilical fissure is anterosuperior (35%), superoposterior (35%), and midline on the left portal vein (20%). Separate ducts from segments II and III that unite greater than 1 cm lateral to the umbilical fissure to form the left hepatic duct occur in approximately 10% of study specimens.[42,46] In this anatomical variant the segment II duct remains posterosuperior while the segment III and IV ducts course anterosuperior to join just before the hilum (Fig. 2-8, *C*).

The segment II and III ducts join to form a common channel (the left lateral segment duct), which is typically formed within the umbilical fissure. The segment II/III duct then receives biliary drainage from segment IV and segment I to form the main left hepatic duct. The anatomy of the segment II/III duct, as well as segment IV ducts that cross the plane of the umbilical fissure, is highly variable.[42,46] The most commonly observed biliary pattern (55%) is the union of segment II and segment III ducts within 1 cm of the umbilical fissure (see Fig. 2-8, *A*). For this variant the segment II/III duct receives a single segment IV duct between the umbilical fissure and the hilum to form the left hepatic duct. The union of segment II and segment III ducts was at the umbilical fissure in 5% of specimens, lateral to the umbilical fissure within segment IV in 50% of specimens, and medial to the umbilical fissure in 45% of specimens. Healey and Schroy[47] have described the union of segment II and segment III bile ducts within the umbilical fissure in 50%, lateral to the umbilical fissure in 42%, and medial to the fissure in 8% of autopsy specimens.

The second most frequent anatomical pattern (30%) is creation of the segment II/III duct close to the umbilical fissure followed by the union of two parallel ducts from segment IV to form the left hepatic duct (see Fig. 2-8, *B*). Typically, one segment IV duct is on the umbilical portion of the left portal vein and one is close to the union of the right hepatic duct. Thus biliary radicles originating in segment IV cross the umbilical fissure to drain the anteroinferior component of segment III in approximately 30% of specimens. Healey and Schroy[47] reported a 20% incidence of segment IV ducts crossing the umbilical fissure in a study of 100 autopsy specimens. Segment IV biliary radicles crossing the umbilical fissure are a potential source of parenchymal leaks. Segment IV biliary radicles that cross the umbilical fissure are consistently located anterior to the left portal vein and the segment II/III duct (see Fig. 2-8, *B*). They are terminal in nature without a distinct connection to the principal segment III duct; however, their significance in biliary drainage is trivial, and they are readily amenable to suture ligation.

The third biliary pattern is a single segment III duct, which receives a duct from segment IV and joins segment II close to the hepatic hilum (see Fig. 2-8, *C*). This pattern was identified in 10% of specimens. In this anatomical variant there is absence of a distinct segment II/III duct.

The least observed biliary pattern (5%) is defined by segment II and segment III ducts joining lateral to the umbilical fissure to form a very short segment II/III duct that immediately receives the segment IV duct to become the left hepatic duct (see Fig. 2-8, *D*). In our analysis a single segment II/III duct had formed within 1 cm lateral to the umbilical fissure in 90% of specimens. Russell et al,[48] in a review of 838 cholangiograms and 15 liver autopsy specimens, likewise described the union of segment II and segment III bile ducts immediately lateral to the plane of the falciform ligament in most specimens.

The union of segment II and segment III ducts occurs within a connective tissue sheath to form a bile duct plate

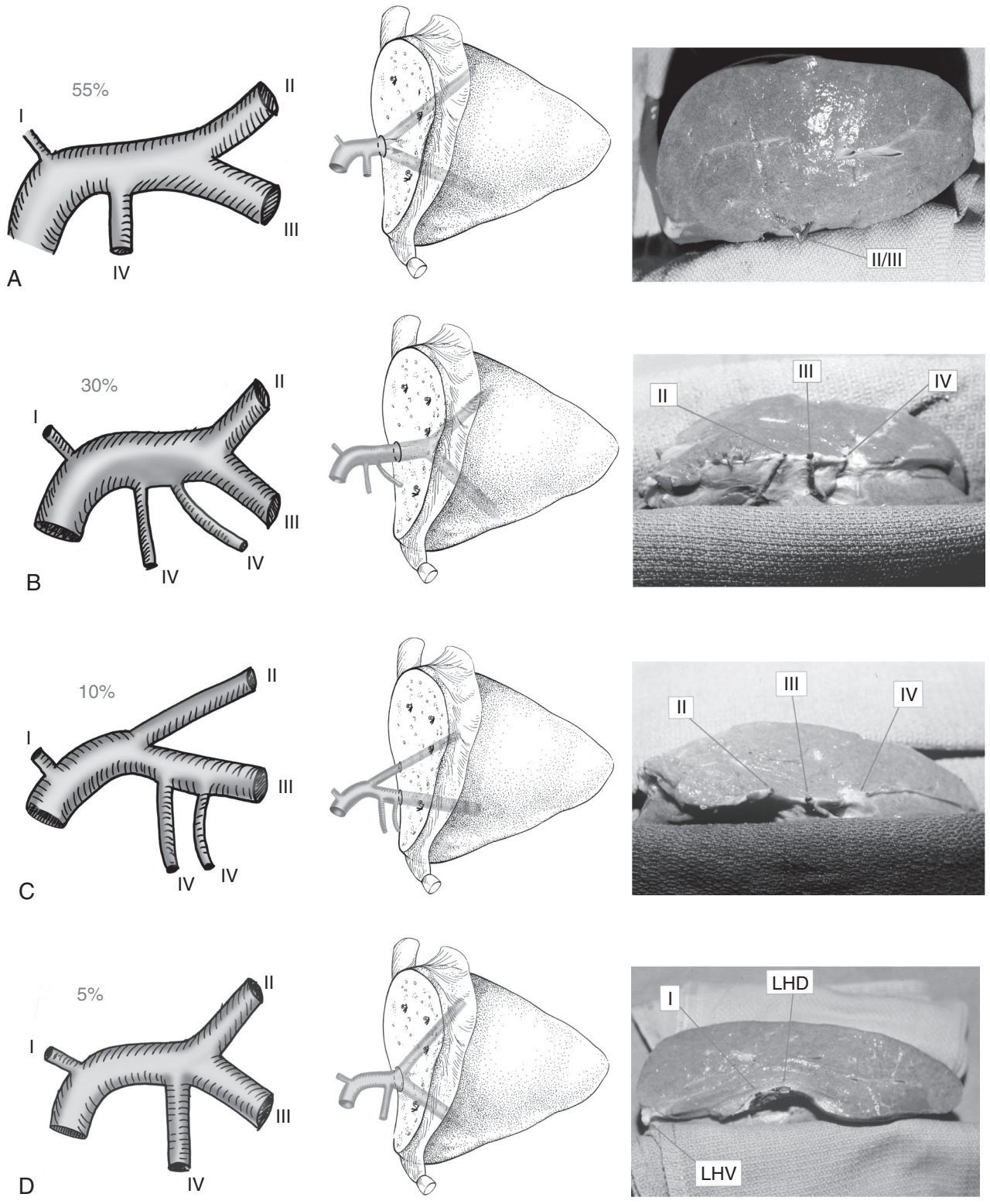

FIGURE 2-8 ■ Biliary variation within segments II and III. **A** to **D,** The four biliary variants of segments II and III. Each variant is depicted as an illustration *(left)*, in relation to the segment II/III allograft *(center)*, and by actual photograph *(right)* within the panel. **B,** Segment IV biliary radicles crossing the umbilical fissure to drain the anterior aspect of segment III. Segment IV radicles are located anterior to the principal duct of segment III outside of the biliary connective tissue sheath and may be the source of posttransplantation biliary leaks if not identified.

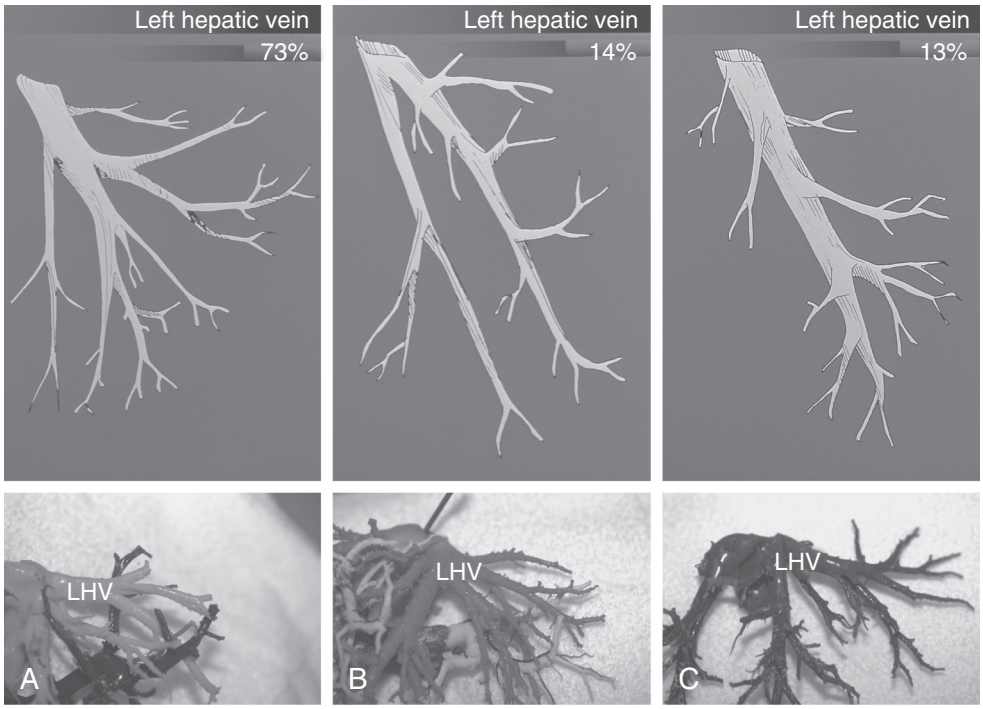

FIGURE 2-9 ■ **A** to **C,** Anatomical variation of the left hepatic vein (LHV) in schematic form with an accompanying corrosion cast.

that can be identified clinically (see Fig. 2-8). The connective tissue plate at the origin of the segment II/III duct is analogous to the hilar plate at the main biliary confluence. An essential element to identification of biliary anatomy is recognition of the bile duct plate as a connective tissue interface that envelops the ducts and guides dissection.

Left Lobe Hepatic Venous Anatomy

The anatomy of the left hepatic vein can be broadly described by three distinct anatomical patterns (Fig. 2-9). The most common pattern, observed in 73% of specimens, is the union of segment II and segment III veins to form a principal left hepatic vein at the superior umbilical fissure (see Fig. 2-9, *A*). This pattern receives significant tributaries draining the posterior aspect of segment IV as it approaches the inferior vena cava. The second most frequently observed pattern, observed in 14% of anatomical specimens, involves separate large veins, each draining an individual segment, that unite to form the left hepatic vein at the level of the inferior vena cava (see Fig. 2-9, *B*). In this pattern each venous channel receives tributaries from the posterior aspects of segment IV before uniting just before the inferior vena cava. The third anatomical pattern, identified in 13% of specimens, is a union of segment II and segment III draining veins within the parenchyma of the segment II/III allograft to form the left hepatic vein medial to the umbilical fissure. In this pattern the left hepatic vein is a large single vessel that empties directly into the inferior vena cava without receiving significant tributaries from segment IV (see Fig. 2-9, *C*). The middle and left hepatic veins fuse to form a common channel before the vena cava; however, dissection at or slightly within the parenchyma will delineate a plane of separation between the venous structures. Rarely, segments II and III will independently drain into the inferior vena cava. Recognition of separate segment II and segment III hepatic veins is critical to maintaining adequate venous outflow from the allograft and requires both orifices to be incorporated on a common caval patch.[42]

Hemiliver Allografts

For transplantation of two adults from one adult deceased donor or living donor liver transplantation between two adults, the liver is divided along Cantlie's line to create two relatively equal-sized hemilivers (see Fig. 2-3). Left hemiliver allografts of approximately 400-mL volume can be created with (segments I to IV) or without the caudate lobe (segments II to IV) for recipients who are children, teenagers, and adults who typically weigh less than 60 kg. Right hemiliver allografts (segments I, V to VIII, or V to VIII) have a typical volume of approximately 800 to 1000 mL and are generally suitable for candidates who weigh less than 80 kg.[49-52] The applied surgical anatomy for these procedures focuses on hilar anatomy at the bifurcation, as well as the relationship of the middle and right hepatic veins.

Arterial Anatomy and Reduced-Size Grafts

Bifurcation of the proper hepatic artery into the right and left hepatic arteries occurs outside the hepatic parenchyma, permitting direct isolation of each vessel. Classic descriptions emphasize distinction; however, the region of the hilar plate and the junction of segments IV and V is best understood as a network of vascular supply involving both left and right hepatic arteries. Following bifurcation of the proper hepatic artery, the right hepatic artery courses posterior and lateral to the common hepatic duct to enter the right hemiliver directly. As described earlier,