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Liver Transplantation

A CURRENT PROBLEMS IN SURGERY® CLASSIC

Liver Transplantation
A 31-Year Perspective

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YEAR BOOK MEDICAL PUBLISHERS, INC.
Chicago • London • Boca Raton • Littleton, Mass.

The contents of this book appeared as the February, 1990, March, 1990 and April, 1990 issues of *Current Problems in Surgery*, a monthly monographic journal for surgeons published by Year Book Medical Publishers, Inc.

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2 3 4 5 6 7 8 9 0 Y C 94 93 92 91 90

Library of Congress Cataloging-in-Publication Data

Starzl, Thomas E. (Thomas Earl), 1926-
Liver transplantation/Thomas E. Starzl, Anthony J. Demetris.
p. cm.
Includes bibliographical references.
Includes index.
ISBN 0-8151-7931-6
1. Liver—transplantation. I. Demetris, Anthony J. II. Title.
[DNLM: 1. Liver Transplantation. WI 770 S798L]
RD548.S79 1990
617.5'56—dc20 90-12421
DLC CIP
for Library of Congress

ISBN: 0-8151-7931-6

Sponsoring Editor: Nancy E. Chorpenning
Assistant Director, Manuscript Services: Frances M. Perveiler
Production Project Coordinator: Gayle Paprocki
Proofroom Supervisor: Barbara M. Kelly

To Joy and Jackie

FOREWORD

Occasionally in medicine a single individual makes a contribution of such magnitude and significance that it clearly represents a new direction in the field. Such is the case in this monograph devoted to transplantation of the liver which originally appeared in **Current Problems in Surgery**. Dr. Thomas Starzl and his colleagues, formerly of the University of Colorado and now of the University of Pittsburgh, have, by their many seminal contributions, had a great influence on the entire field of transplantation; but it is transplantation of the liver which has gained these scientists their widest recognition.

The operation began as an idea only 30 years ago and the seemingly painful and slow steps which subsequently led from early clinical trials to the current stage of development are remarkable. Today, the procedure is performed in a number of medical centers around the world, in all age groups of patients, and for a wide variety of indications—a tribute to the remarkable efforts and the persistence of Dr. Starzl and his group.

In this volume, Dr. Starzl and Dr. Demetris cover all aspects of hepatic transplantation, including the technical points of the replacement operation, the prevention of rejection, and the complications both of the operation and of the postoperative immunosuppressed state. In the closing parts of this treatise, the authors review the newly emerging technique of multiple organ transplantation, auxillary transplantation, and the practical limitations of the procedure, including organ donation and economic factors.

This contribution is authoritative and excellent, and will surely become a classic in the field.

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ACKNOWLEDGMENTS

We wish to thank Mrs. Terry Mangan for managing the Pittsburgh editorial duties. Her ever-pleasant attitude, diligence and persistence kept the authors "on track," when it was easy to lose enthusiasm. Without her contributions, it is likely the text would not have been completed. We are especially grateful for her ability to locate figures and references given only "free associations" and her willingness to persevere at odd hours, after her duties as a home manager had begun.

Thomas E. Starzl, M.D., Ph.D.
Anthony J. Demetris, M.D.

CONTENTS

INTRODUCTION

Liver transplantation has had intellectual as well as practical ramifications in all aspects of hepatology. In 1955, when the concept of transplanting a whole liver was first mentioned in the medical literature,[1] the specialty of hepatology still had ambiguous boundaries and purposes. This account will show how such a seemingly fanciful idea as transplanting a liver became a practical reality and thereby helped shape the specialty of hepatology during the succeeding 30 years. During the same period, transplantation fostered changes in practically every aspect of hepatology and liver surgery to the extent that it is no longer possible to have a liver disease center without hepatic transplant capability.

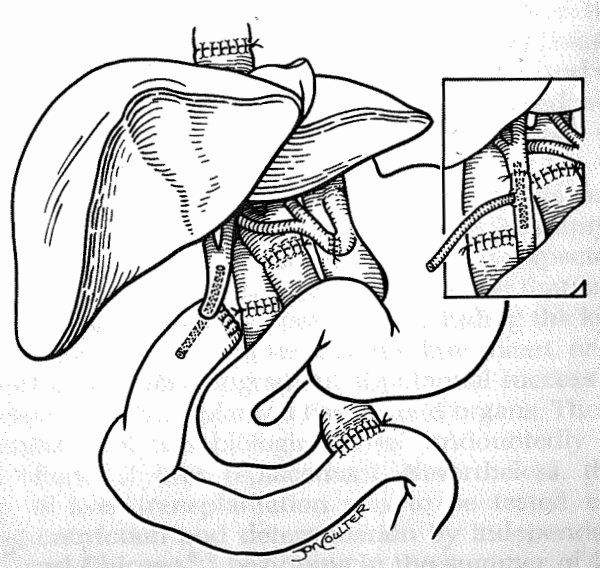


FIG 1.
Orthotopic liver transplantation (liver replacement). Biliary tract reconstruction usually is with choledochojejunostomy (to a Roux limb) or *(inset)* with a choledochocholedochostomy, which is stented with a T tube.

The liver can be transplanted as an extra (auxiliary) organ at an ectopic site or in the normal (orthotopic) location after removal of the host liver (Fig 1). This review will be preoccupied with the orthotopic procedure. However, there has been renewed interest in the auxiliary operation, which will be discussed separately at the end of this monograph. In addition to the potential clinical value of auxiliary hepatic transplants, efforts to define the optimal way of revascularizing auxiliary liver grafts opened a new field of physiologic and biochemical research by demonstrating that splanchnic venous blood possesses specific liver supporting (hepatotrophic) qualities.[2, 3]

As we develop the subject of orthotopic transplantation, we will provide a running historical perspective since even the earliest major publications on this subject are less than 30 years old, and many are still of current interest. However, particular attention will be paid to the massive literature that has developed since June 1983, when the conclusion was reached by a Consensus Development Conference that orthotopic liver transplantation had become a service as opposed to an experimental procedure.[4]

DEVELOPMENT OF THE REPLACEMENT OPERATION

The distinction between creative and delusional thinking usually becomes clear only in retrospect. The idea of liver replacement first surfaced in 1956 with a publication by Dr. Jack Cannon, who was working at the new Department of Surgery, University of California, Los Angeles (UCLA).[5] Because it was suspected at that time that the liver might play a role in rejection, Cannon apparently hoped that a hepatic homograft would be more kindly received than other transplanted organs since presumably it would not contribute to its own destruction. There was no journal devoted to transplantation in 1956, and abstracts or brief articles in this field were published in an appendix to *Plastic and Reconstructive Surgery*, which was called *Transplantation Bulletin*. Cannon's article in *Transplantation Bulletin* was less than one page long. It did not have a title, and descriptions of the procedure or even of the animal species used were omitted. Cannon referred to "several successful operations" but without survival of the recipients.

Even for nonhistorians, Cannon's one-page article may have the special fascination of a solitary dot on a nearly empty canvas on which a complex mural was to quickly and unexpectedly appear. There was no identifiable reason in 1956 to hope that any whole organ could be transplanted successfully, including the kidney, much less more complicated grafts such as the liver, heart, or lung.

The most unattainable ingredient of potential success was prevention of rejection of transplanted tissues and organs. The seeming insurmountability of this biologic barrier undoubtedly discouraged research efforts at liver replacement. Nevertheless, the technical feasibility of liver transplantation was to be tested in dogs with increasing conviction and determination by independent teams in Boston[6, 7] and Chicago,[8, 9] beginning in the summer of 1958. The canine model proved to be a difficult one technically, and systematic investigation of liver replacement was hampered seriously by the fact that this operation could be done successfully in only a few laboratories in the world. In recent times, improvements in the clinical operation have been incorporated into the dog procedure.[10, 11]

The technical requirements for liver transplantation in dogs are almost too complex for simple categorization. However, two cardinal requirements for perioperative survival emerged from this work more than 30 years ago. The first was adequate preservation of the homograft during its procurement and the period of devascularization.[8] The second was decompression with veno-venous bypasses of the obstructed recipient splanchnic and systemic venous beds during the anhepatic period when the host liver was being removed and the new liver was being inserted.[6,8]

We will consider these principles as they have been applied clinically under the general headings of donor and recipient operations and then discuss the more conventional surgical components of liver transplantations including recipient hepatectomy, graft revascularization, biliary tract reconstruction, and hemostasis.

DONOR HEPATECTOMY AND INITIAL COOLING

Hypothermia and Core Cooling

Steps in the development of liver graft procurement and preservation have been few. However, these steps have had an importance beyond their application for liver replacement, since the principles involved are germane to the preservation of other whole organs. The first innovation of core cooling by infusion of chilled lactated Ringer's solution into the portal vein may have been the most important.[8] Before core cooling was used, survival of dogs after liver transplantation was virtually never obtained, but afterward, success became almost routine.[8]

At an even earlier time, it was appreciated by cardiac surgeons that hypothermia protected ischemic tissues and organs below the level of aortic[12] and renal pedicle[13] crossclamping. To our knowledge, Lillehei and associates were the first to use hypothermia in transplantation.[14] They immersed dog intestinal grafts in iced saline before autotransplantation or homotransplantation. Later, the extent of hypothermic protection from ischemia was quantified by Sicular and Moore, who reported that enzyme degradation in hepatic slices was greatly slowed by refrigeration.[15]

The cooling of organs with fluids infused via the vascular system was such an obvious expedient that failure to do it can only be described as surprising. Even more inexplicable was failure to core cool kidney transplants. This was not done until long after the initial research with canine liver transplantation had been completed. Then, as a direct result of our experience with the dog livers, we introduced core cooling of kidney grafts into clinical practice. At first, we had protected human renal homografts by inducing total body hypothermia of living volunteer donors, but before long, we replaced this cumbersome and potentially dangerous method with infusion of chilled fluid into the kidney immediately after its removal.[16]

Today, core cooling is the first step in the preservation of all whole organ grafts, and it is most often done with the organs in place by some variant of the in situ technique originally described by Marchioro and associates.[17] These investigators used a heart-lung apparatus that contained a heat exchanger to cool the carcass of dogs before beginning organ removal and to maintain hypothermic perfusion thereafter. This method (Fig 2) for the immediate or continuous in situ hypothermic perfusion of cadaveric livers and kidneys was used clinically long before the acceptance of brain death conditions[18]; the technique has had a renaissance recently for procurement of thoracic organs.[19,20] Ackerman and Snell[21] and Merkel and col-

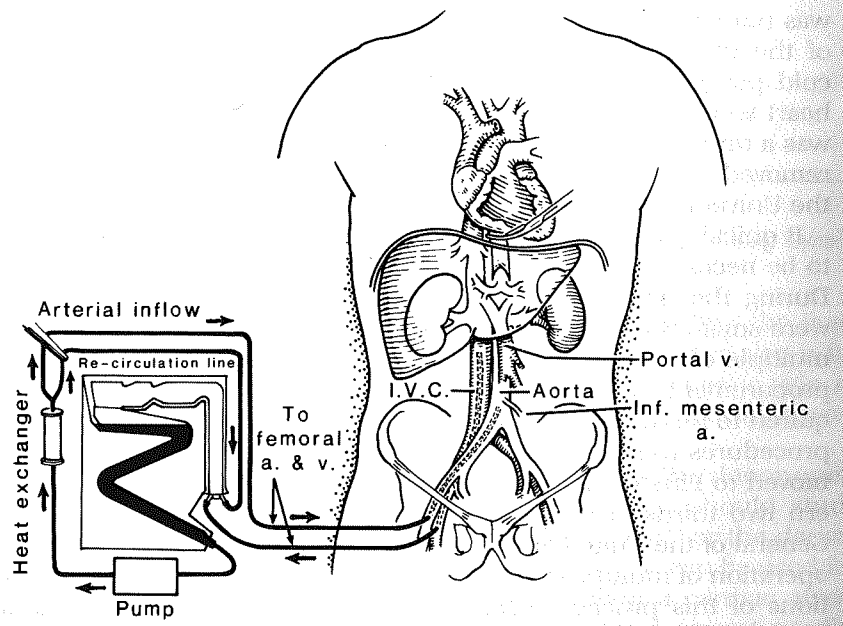


FIG 2.
First technique of in situ cooling by extracorporeal hypothermic perfusion. The catheters were inserted via the femoral vessels into the aorta and vena cava as soon as possible after death. Temperature control was provided with a heat exchanger. Crossclamping of the thoracic aorta limited perfusion to the lower part of the body. This method of cadaveric organ procurement was used from 1962 to 1969, before the acceptance of brain death. The preliminary stages of this approach provided the basis for subsequent in situ infusion techniques. (Redrawn from Starzl TE: *Experience in Renal Transplantation.* WB Saunders Co, Philadelphia, 1964.)

leagues[22] popularized much simpler methods of in situ cooling of cadaveric kidneys with cold electrolyte solutions infused into the distal aorta.

Core Cooling for Multiple-Organ Procurement

An extension of these primitive in situ cold infusion techniques has allowed removal of all thoracic and abdominal organs, including the liver, without jeopardizing any of the individual organs.[23] The techniques of organ procurement and preservation used clinically came from the laboratory procedures as described earlier. However, much further development was required for the procurement of multiple organs from human cadaveric donors that were expected to provide kidneys, hearts, pancreases, and other tissues as well as livers.

In the first trials of multiple-organ procurement, in situ cooling was not used. The individual organs were skeletonized, and after all of the dissection was completed, the kidneys were removed and cold perfused on the back table. At a second stage, the liver and heart were removed simultaneously. The removal of all four organs was a rare event, and the first time the kidneys, liver, and heart were removed from a single donor was on April 17, 1978 during a visit by the University of Colorado team to the University of Minnesota.

It quickly became obvious that in situ cooling of organs was going to be necessary if extrarenal organ transplantation were to flourish. During the times when the numbers of liver or heart transplants were small, the annoyance caused for renal transplant surgeons by multiple-organ procurement was relatively minor. As multiple-organ procurement became routine, a major educational effort was required to recruit the cooperation of kidney transplanters. The in situ procedures were developed in Denver, and when the Colorado team moved to Pittsburgh, these were demonstrated throughout the eastern two thirds of the United States. At the request of the Surgeon General of the United States, Dr. C. E. Koop, a description of the new operation of multiple-organ procurement was published.[23] Modifications of this procedure have been made for unstable donors and even for donors whose hearts have ceased to beat.[24] In less than 5 years, multiple-organ procurement, using techniques that are interchangeable not only from city to city but from country to country, had become standardized in all parts of the world.

A complete midline abdominal and thoracic incision is made (Fig 3). The aorta at the diaphragm is encircled so that it can be crossclamped when the core cooling is begun. The distal aorta is used as an entry site for the fluid infusion (Fig 4). By coordination of the fluid infusion and the crossclamping of the great vessels and by dissection and ligation of appropriate arterial branches, the cold infusate

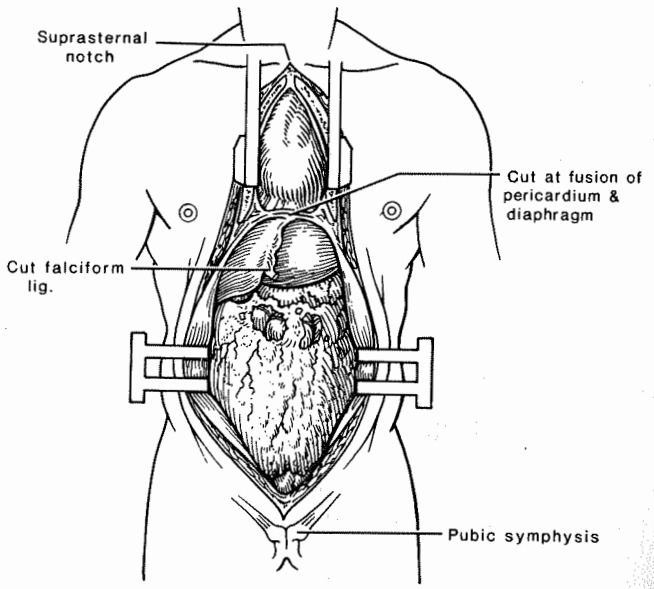


FIG 3.
Total midline incision used for cadaveric donors. (Redrawn from Starzl TE: *Surg Gynecol Obstet* 1984; 158:223–230.)

can be made to go selectively to those organs (including the liver) that are to be used (see Fig 4). The portal vein of the liver also is infused after a catheter is placed into it through the splenic vein or other major tributary (see Fig 4). Core cooling of the thoracic organs is accomplished with the same principles.[23]

There is little point in providing further details of the donor operation. Those interested in procurement procedures should study the description of the originally described technique[23] or the derivative method called the *rapid flush technique,*[24] which can be used for unstable donors or even for donors who develop a cardiac arrest (see the next section). With the rapid flush method, almost no dissection is performed initially. The organs are quickly chilled and washed free of blood in situ by aortic infusion and infusion through a distal portal branch such as the inferior mesenteric vein. They can then be removed swiftly in a bloodless field.

Liver Procurement In Non-Heart-Beating Donors

When liver transplantation was first performed experimentally and clinically, it was thought that the liver would be exquisitely sensitive to warm ischemia.[8] This perception has changed in the ensuing

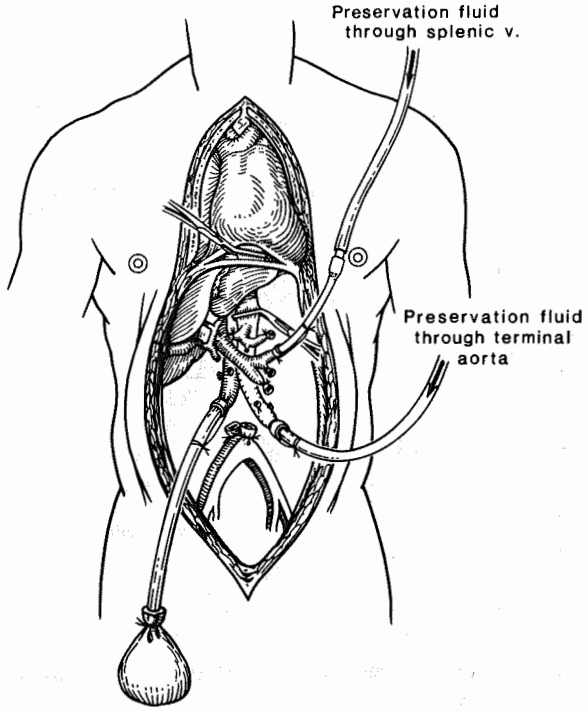


FIG 4.
Principle of in situ cooling used for multiple organ procurement. With limited preliminary dissection of the aorta and of the great splanchnic veins (in this case the splenic vein), cold infusates can be used to chill organs in situ. In this case, the kidneys and liver were to be removed. Note the aortic crossclamp above the celiac axis. (From Starzl TE, Hakala TR, Shaw BW Jr, et al: *Surg Gynecol Obstet* 1984; 158:223–230.)

years, particularly with the demonstration by Huguet and associates that the human liver can tolerate at least 1 hour of warm ischemia with relative impunity.[25] Studies in normal dogs have shown that the portal triad usually can be crossclamped for at least 2 hours without mortality, providing there is perfect decompression of the obstructed portal venous drainage.[26]

If a cardiac arrest occurs in a patient considered to be a good donor, it is possible to quickly open the abdomen, encircle the proximal aorta at the level of the diaphragm, and cannulate the terminal abdominal aorta or one of the iliac arteries (Fig 5). Within 5 or 10 minutes, core cooling can be started with an infusion of cold solution. The aorta is crossclamped near the diaphragm. The inferior vena cava is decompressed by incising it. The liver becomes blanched and free of blood with surprising rapidity. Within 2 or 3

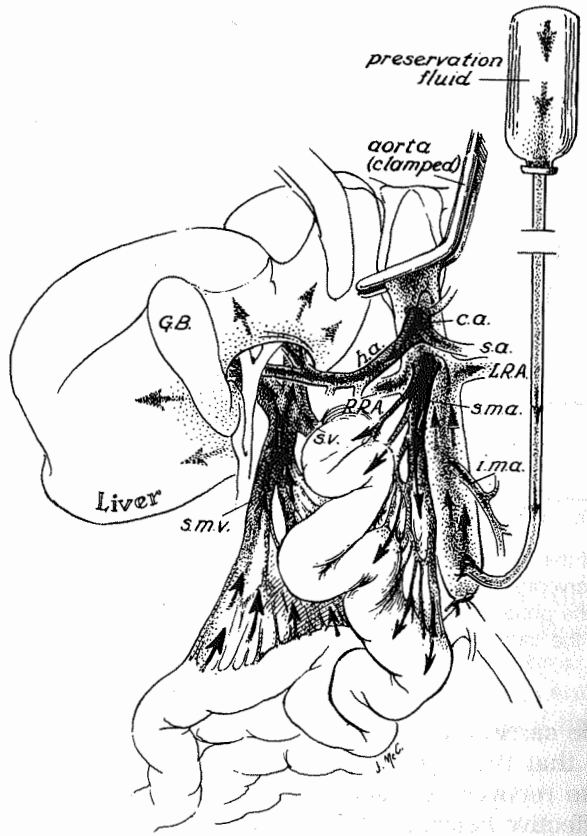


FIG 5.
If there is not time to insert a splanchnic venous catheter for infusion, the rapid infusion of cold fluid into the aorta alone will promptly cool the liver since the superior mesenteric venous blood contributes to the hepatic cooling (see Fig 6). All that is necessary is to insert the catheter into the distal aorta and to crossclamp the aorta at the diaphragm. (From Starzl TE, Iwatsuki S, Shaw BW Jr, et al: *Transplant Proc* 1985; 17:250–258. Used by permission.)

minutes, the liver becomes palpably cold. At the same time, the intestines become blanched from the superior mesenteric artery infusion, and blood in the portal vein that has passed through the splanchnic capillary bed becomes clear and hemoglobin free (Fig 6). Thus, full perfusion of the liver eventually is assured even though the chilled fluid is instilled only into the aorta (see Figs 5 and 6).

In adults, 2 or 3 L of cold solution rapidly infused into the distal aorta are required to bring the liver into a cryoprotective range of less than 28°C. After this has been achieved, the rest of the procure-

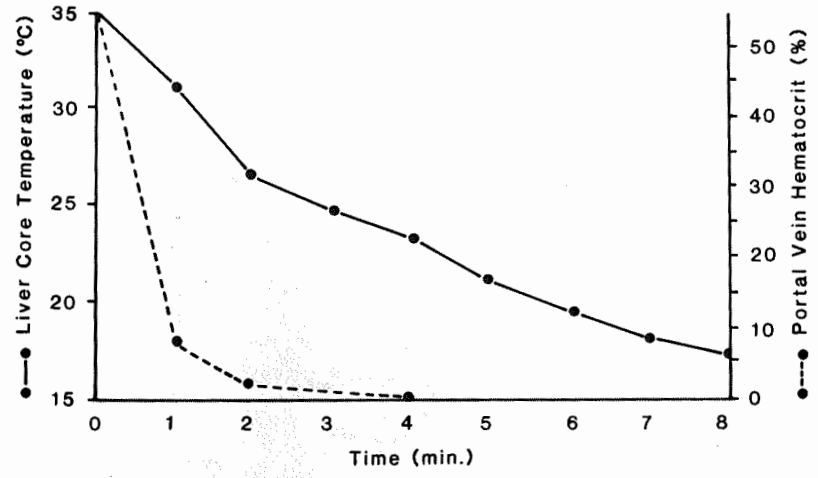


FIG 6.
Core cooling of the liver with aortic infusion alone. Note that the body (and liver) temperature becomes cryoprotective within 2 or 3 minutes after beginning the aortic infusion. The hematocrit of the portal venous blood is quickly diluted, meaning that the liver is being perfused with the increasingly asanguinous cold blood returning from the splanchnic venous bed.

ment can be carried out at a more leisurely pace. This is facilitated by the fact that there is now a bloodless field. We have used this technique to recover satisfactory livers from many donors with absent or ineffective heartbeat.[27] The method has been used with considerable success in Sweden, which did not have "brain death" laws until recently.[28] Our experience and that of the Swedish workers under these circumstances have been almost as good as with the standard procurements in cadaveric donors with beating hearts. However, a high level of skill is required to prevent the loss of these organs, and discriminating judgment is necessary about which organs have a good chance of being satisfactory. Only surgeons experienced in procurement of donor organs will be capable of this kind of work.

Donor Anomalies

In at least one third of the human donors, arterial anomalies will be encountered whereby some or all of the liver is supplied by branches of the left gastric artery, superior mesenteric artery, or direct branches from the aorta instead of by ramifications of the common or proper hepatic artery (Fig 7). Special techniques that allow essentially all such livers to be used have been developed.[29–35] Most

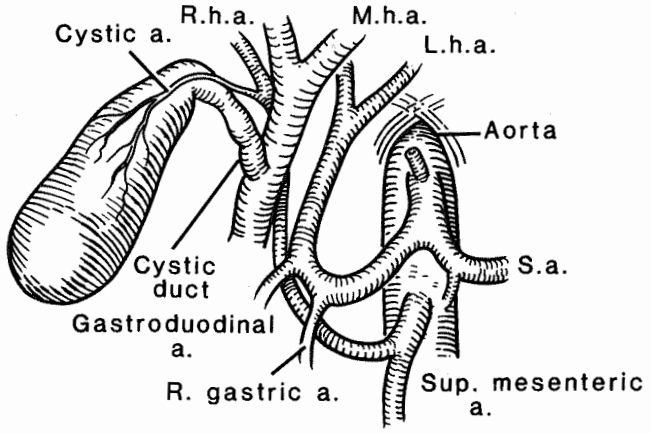


FIG 7.
A common anomaly in which a right hepatic artery originates from the superior mesenteric artery. This right artery always is posterior to the portal vein.

of these techniques have in common the conversion of multiple vessels into a single trunk by back-table dissection and anastomoses (Figs 8–10). Uniting the celiac axis and superior mesenteric artery as shown in Figure 10 may leave an excessively long vessel and a bulge at the site of the fold-over anastomosis. Consequently, if this princi-

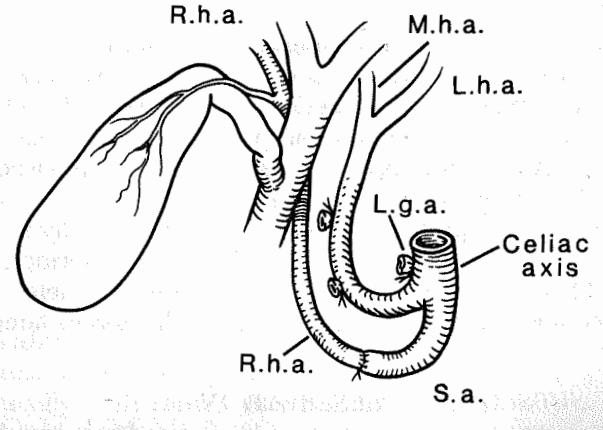


FIG 8.
With the anomaly in Figure 7, the splenic artery can be anastomosed to the anomalous right hepatic artery, thereby converting the origin of the blood supply to a single vessel based on the celiac axis. (Redrawn from Starzl TE: *Experience in Hepatic Transplantation.* Philadelphia, WB Saunders Co, 1969.)

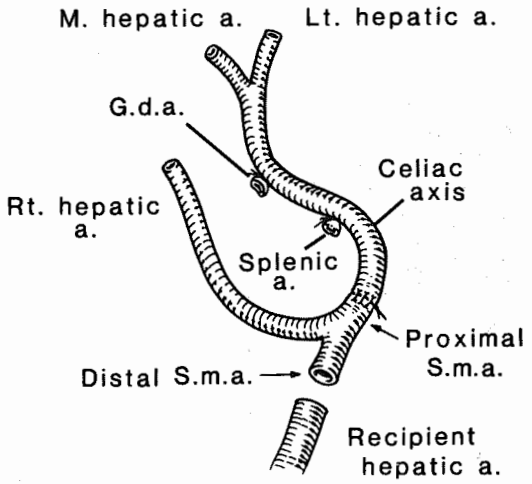


FIG 9.
Alternative methods to reconstruct the anomaly shown in FIgure 7. The proximal (left) or distal (right) end of the superior mesenteric artery containing the anomalous right hepatic artery is anastomosed to the graft celiac axis. The open end is sewed to the recipient celiac axis.

ple is employed, an end-to-end celiac axis to superior mesenteric artery anastomosis may be preferable (see Fig 8 or 9).

Vascular Homografts

An integral part of the donor operation should be procurement of free grafts of the iliac arteries and veins, since these can be used to reconstruct anomalies or damaged vessels of livers (Fig 11), kidneys, and other organs. At the time of procurement, these grafts are placed in a solution developed at the University of Wisconsin (UW solution), where they can be used for at least 1 or 2 days or possibly longer. When arterial grafts are needed, they are usually based below the recipient renal arteries. They can be brought anterior to the pancreas (Fig 12) or behind the pancreas through tunnels created by finger dissection (Fig 13). Vein grafts will be discussed later.

MEANS OF SUBSEQUENT PRESERVATION

In dogs, the liver can be transplanted successfully as long as 6 to 12 hours after cooling with lactated Ringer's solution and storage at 4°C.[36] Further extension of this period and improvement of safety have depended on one of two prototype strategies, derived from research done mainly with kidneys and applied secondarily to livers.

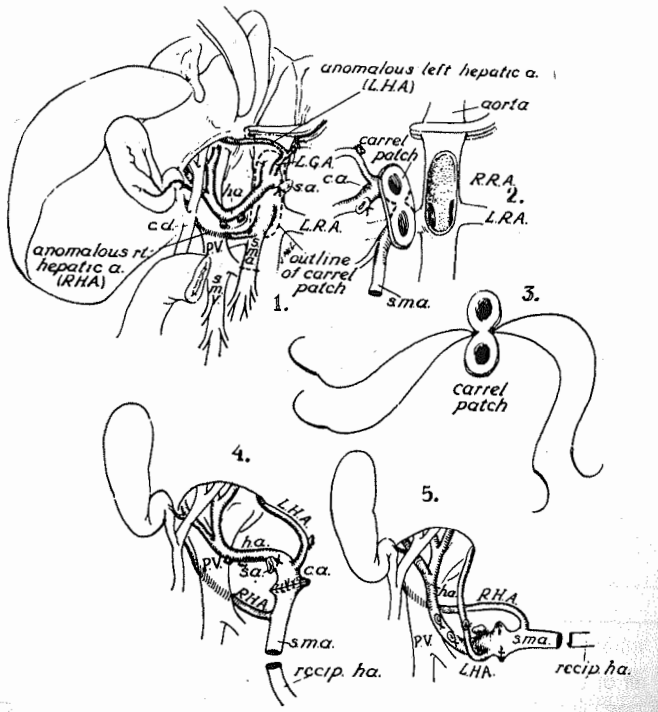


FIG 10.
Same principle as the reconstruction of Figure 9 *(left)*. However, the origin of the superior mesenteric artery and celiac axis are folded together, leaving the distal end of the superior mesenteric artery for anastomosis to the recipient. There is a small left hepatic artery in this case originating from the left gastric artery. This latter anomaly is very commonly found in association with a right hepatic artery of superior mesenteric arterial origin. (From Gordon RD, Shaw BW Jr, Iwatsuki S, et al: *Surg Gynecol Obstet* 1985; 160:474–476. Used by permission.)

Ex Vivo Perfusion After Initial Cooling

With one approach, a continuous circulation has been provided with a cold perfusate primed with blood and oxygenated within a hyperbaric oxygen chamber.[37] This method, which originally was used for kidneys by Ackerman and Barnard,[38] has permitted the successful preservation of dog livers for as long as 2 days[37] and was applied clinically with remarkable success in several human cases in the pre–brain death era.[39] When Belzer and associates were able to eliminate the hemoglobin and hyperbaric chamber components for kidney preservation,[40] their asanguinous perfusion technique for cadaveric renal grafts become a worldwide standard. However, efforts were unsuccessful to use continuous asanguinous perfusion for livers.[41]

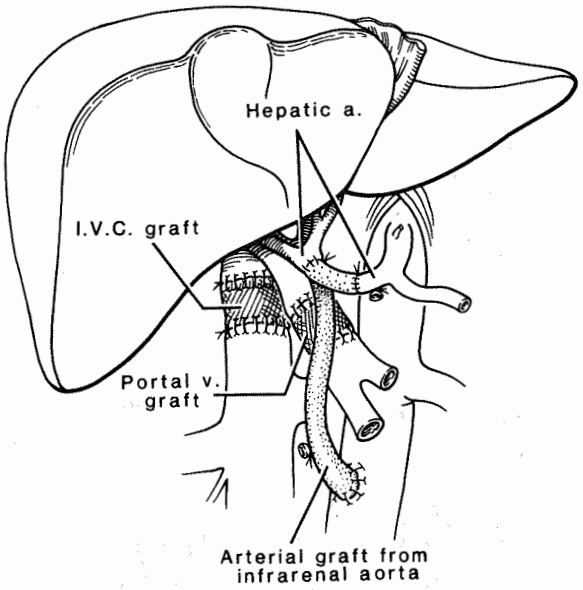


FIG 11.
By 1979, all of the demonstrated grafts had been used clinically. The use of vascular grafts has been life saving, and liver transplantation should never be attempted without an emergency assortment of these grafts. (Redrawn from Starzl TE, Halgrimson CG, Koep LJ, et al: *Surg Gynecol Obstet* 1979; 149:76–77.)

Slush Techniques

The alternative strategy for the subsequent preservation of kidneys, livers, and other organs has been the instillation of special solutions (Table 1) such as those described by Collins and co-workers[42] or the plasma-like Schalm solution.[43] The original Collins solution or modifications of it have been used for almost 20 years for the so-called slush techniques of kidney preservation in which the organ is packed in an ice chest at 4°C after its infusion. The experimental work of Benichou and colleagues[36] and Wall and associates[44] with the Collins and Schalm solutions opened up the possibility in 1976 of clinical sharing of livers between cities but within narrow time limitations. The outer limit of safety for human livers was generally set at 8 hours in spite of the fact that dog livers could be maintained for much longer than this with the Collins and Schalm solutions.

The UW Solution for Slush Preservation

The development of the UW solution has been the first major development in liver preservation since that time.[45] The UW solution is a generic advance that also is applicable to the preservation of the

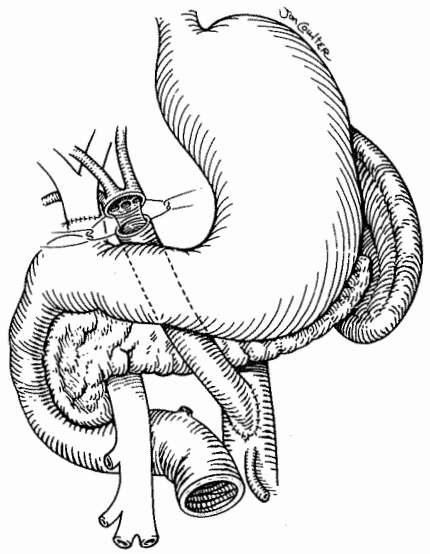


FIG 12.
An antepancreatic route for a vascular graft placed onto the infrarenal abdominal aorta. The graft is brought either to the right or left of the middle colic vessels, anterior to the pancreas, and beneath the pyloris. (From Tzakis AG, Todo S, Starzl TE: *Transplant Int* 1989; 2:121. Used by permission.)

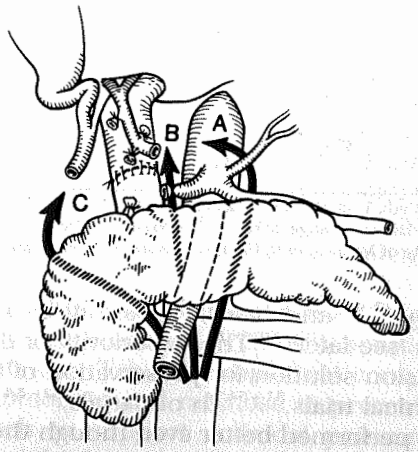


FIG 13.
Posterior routes by which the arterial grafts shown in Figure 11 can be brought from their aortic origin to the liver hilum behind the pancreas. The tunnels are created by blunt finger dissection. Route *A* is rarely used because it is potentially dangerous. (From Todo S, Makowka L, Tzakis AG, et al: *Transplant Proc* 1987; 19:2406–2411. Used by permission.)

TABLE 1.
Characteristics and Constituents of Test Solutions*†

	EC	LR	UW	UM1	UM2	UM3
Anions						
Bicarbonate (mM/L)	10	—	—	—	—	—
Chloride (mM/L)	15	109	—	—	20	5
Lactate (mM/L)	—	28	—	—	—	—
Phosphate (mM/L)	57.5	—	25	—	—	0.72
Lactobionate (mM/L)	—	—	100	—	—	90
Cations						
Calcium (mM/L)	—	1.5	—	—	—	0.6–1.4
Sodium (mM/L)	10	130	30	146	146	1
Potassium (mM/L)	115	4	120	4.3	24.3	124
Magnesium (mM/L)	—	—	5	—	4	7.8
Colloids and osmotically active agents						
Hydroxy ethyl starch (gm/L)	—	—	50	—	—	—
Proteins (gm/L)	—	—	—	65.2	90	65
Mannitol (gm/L)	—	—	—	—	3.75	—
Raffinose (gm/L)	—	—	17.8	—	—	48
Glucose (gm/L)	194	—	—	—	—	99
Others						
Adenosine (gm/L)	—	—	1.34	—	—	—
Glutathione (gm/L)	—	—	0.922	—	—	—
Insulin (units)	—	—	100	—	—	—
Allopurinol (gm/L)	—	—	0.136	—	—	—
Antibiotics and steroids						
Ampicillin (mg)	—	—	—	—	250	50
Sulfamethoxazole (mg)	—	—	40	—	—	—
Trimethoprim (mg)	—	—	8	—	—	—
Dexamethasone (mg)	—	—	8	—	—	—
Methyl prednisolone (mg)	—	—	—	—	250	500
Osmolality (mOsm/L)	375	273	320	308	—	301
pH	7.4	6.3	7.4	7.4	7.4	7.4

*From Todo S, Podesta L, Ueda Y, et al: *Clin Transplant* 1989; 3:253–259. Used by permission.
†EC = Euro-Collins; LR = Lactated Ringer's; UW = University of Wisconsin; UM1 = University of Minnesota I; UM2 = University of Minnesota II; UM3 = University of Minnesota III.

pancreas,[46] kidney,[47,48] and heart,[49] possibly by mechanisms common to all organs (see later).[50] The superiority of the UW solution to any previous infusion solution for preservation of the liver has been established in clinical trials.[51–54] In our trials,[52–54] the livers infused with UW solution performed better even though they were preserved on the average for almost twice as long as livers preserved with Euro-Collins solutions. The livers in UW solution permitted a higher rate of graft survival, and they had a lower rate of primary nonfunction, hepatic artery thrombosis and retransplantation. They appeared to be safe for at least 1 day and possibly longer.

When the UW solution was undergoing its first clinical trials, it was in such short supply that only a final portal flush was possible. In adult donors, 1 L of the UW solution was given on the back table via the portal vein just before packing the liver in ice. By this time, the liver had been cooled in situ with lactated Ringer's or Collins' solution and excised. In addition to a shortage of UW solution, the use of lactated Ringer's or Collins' solution for preliminary cooling was insisted on almost invariably by the local procurement team as a condition for the collaborative effort with the renal transplant surgeon.

The positive results clinically that have been reported with the UW solution were obtained with this mixed use of fluids in which only the final flush was with UW solution. However, the best practice probably is to use only UW solution for all infusions from the outset, a practice that became feasible (as of 1 June 1989) with the commercial availability of UW solution. The high cost of the UW solution ($400/L) is the principal disadvantage of this practice. Approximately 5 L of solution are required for a multiple organ procurement in adults, exclusive of the thoracic organs. Because it has been shown that the UW solution is superior to previously used solutions for the kidney[47,48] as well as the liver, there can no longer be any objection to this use of UW solution.

Although the extension with the UW solution of acceptable cold ischemia from 6 or 8 hours out to 1 day does not seem like a large gain, the effect has been phenomenal. Until 18 months ago, logistic problems dominated the use of cadaveric livers that had to be removed, transported to their destination, and revascularized with an overriding sense of urgency. With the longer preservation time that has been made practical with the UW solution, countrywide and worldwide networks of organ sharing have been set up. The consequences in the future should be a reduction in organ wastage, a greater flexibility for use of grafts that can be trimmed to the appropriate size for pediatric recipients, and more efficient recipient travel and preparation. The use of slower propeller planes instead of expensive jet planes for recipient and organ transplantation already has become feasible.

An explanation for the effectiveness of the UW solution has been provided by Belzer and Southard.[55] The UW solution contains more than 10 ingredients (see Table 1). Important components and their effects are (1) lactobionate and raffinose to prevent cell swelling, (2) hydroxyethyl starch to support colloidal pressure, (3) allopurinol and glutathione to inhibit oxygen free-radical generation, and (4) adenosine to enhance adenosine triphosphate (ATP) synthesis after reperfusion. In studies performed in our laboratory, the difference in the performance of different solutions may provide sketchy insight into the relative importance of some constituents.[56] These studies

have shown that an intracellular-like electrolyte solution (Collins) or a hyperosmolar colloid solution such as those developed at the University of Minnesota (see Table 1) do not allow long-term cold storage of the liver, even though these can be useful for the pancreas.[57, 58] Lactobionate and raffinose, two sugars that prevent imbibition of water by cells, have seemed to be the essential ingredients without which the effectiveness of UW solution is lost.[56] Others have come to the same conclusion.[59, 60]

Much remains to be learned about liver preservation, the effects of ischemia on hepatic function and the hepatic microvasculature, and the role of these factors in the early and late postoperative course of recipients. We will return to these subjects further on. In the meanwhile, a discussion of slush preservation would be incomplete without mentioning the potential dangers of the preservation solutions. For example, the bolus of potassium washed out during the reperfusion of a liver containing Collins' or UW fluid has caused a number of cardiac arrests. It also should be noted that other ingredients than potassium in present-day preservation solutions may impose a risk. Prien and associates have shown that bradycardia or even more serious arrhythmias are caused in recipients of kidneys preserved with UW solution if these organs are not washed out first.[61] They believe that the offending agent is adenosine, which is known to be arrhythmiagenic. Aside from this consideration, and the elimination of potassium, the preservation fluid should be washed out of liver grafts before they are placed into the recipient circulation to eliminate air bubbles entrapped in the graft.[62] Moen and co-workers have shown that sodium can be substituted for potassium in the UW solution.[60] This change will make safer the reperfusion of liver grafts by eliminating the potential bolus of potassium at the time of reperfusion.

RECIPIENT OPERATION

The component parts of the recipient operation are so dissimilar that a single surgeon operating from skin to skin may find it difficult to adjust to the changing pace. Removal of the diseased liver can be one of the most bloody and stressful experiences in a surgeon's life. Yet, the subsequent performance of the vascular anastomoses can be among the most delicate and sophisticated, especially in very small children. Obtaining perfect hemostasis subsequently is often a tedious third phase that, if not accomplished, will ruin all that has gone before. At the end, success depends on adequate biliary tract reconstruction. In some centers, various parts of the procedure are being done by independent and fresh teams. However, the total responsibility still rests with a single surgeon who must understand each part of the operation.

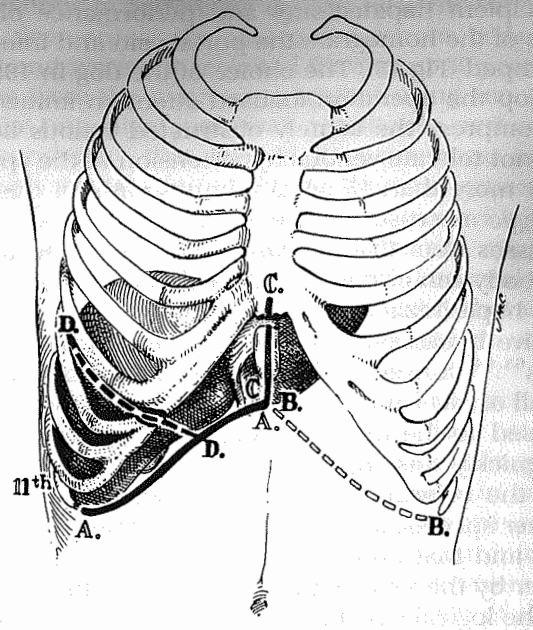


FIG 14.
The usual incision used for the recipient of an orthotopic liver graft. A right subcostal incision is always made, usually with an upper midline extension, and often with a left subcostal extension. Removal of the xyphoid process gives extra exposure of the suprahepatic vena cava. (From Starzl TE, Bell RH, Beart RW, et al: *Surg Gynecol Obstet* 1975; 141:429–437. Used by permission.)

A right subcostal incision is almost always used for the recipient operation (Fig 14), but its exact location is dictated by previous right upper quadrant incisions and by the size and configuration of the liver. An upper midline extension has been particularly valuable. If the upper midline extension is made, the xiphoid process usually is excised since better access to the hepatic veins and suprahepatic vena cava can be obtained. In the majority of cases, the patients end up with a bilateral subcostal incision, with a superior midline T extension (see Fig 14). Thoracic extensions are almost never needed.

Once the abdomen is entered, an effort is made to find a plane of dissection just outside of the liver capsule if there are major adhesions. Movement away from this plane invites disruption of varices that may be large enough to cause unpleasant or even lethal hemorrhage during the preliminary dissection.

Veno-Venous Bypasses

During recipient hepatectomy and performance of the vascular anastomoses of the homograft, the portal vein and inferior vena cava are crossclamped (Fig 15). The choice of the dog in 1958 as the species to develop the operation focused attention immediately on the need to decompress the acutely obstructed venous beds. The normal dog cannot tolerate venous hypertension of the splanchnic capillary bed for more than 15 or 20 minutes without the development of hemorrhagic necrosis of the intestinal mucosa. Passive veno-venous bypasses from the stagnant venous pools to the upper part of the dog's body can circumvent these lethal complications without the need for heparinization.[6, 8]

Such passive bypasses were used for several patients in the first clinical trials[63, 64]; however, either the bypasses clotted and did not function at all or, far worse, clots were released from the bypass tubing and passed to the lung, causing lethal pulmonary emboli.[64] In addition, it quickly was appreciated that the human can tolerate obstruction of the inferior vena cava and portal vein better than the dog, that other species, including the pig, were more like humans in this respect, and that even in the dog venous crossclamping could be made safer by the expedient of bile duct ligation several weeks in advance.[65] The logical conclusion from this last observation was that

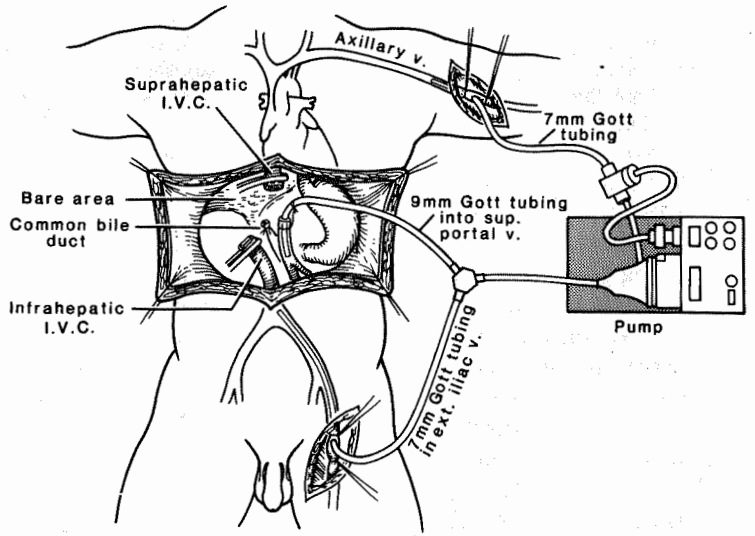


FIG 15.
Pump-driven veno-venous bypass, which allows decompression of the splanchnic and systemic venous beds without the need for heparinization. (Redrawn from Griffith BP, Shaw BW Jr, Hardesty RL, et al: *Surg Gynecol Obstet* 1985; 160:270–272.)

the stimulation of venous collaterals by liver disease diminished the magnitude of venous hypertension caused by acute venous obstruction. Efforts to decompress the obstructed venous beds were abandoned by 1964 and were not resumed for almost 20 years.

So persuasive were the arguments against using veno-venous bypasses that liver transplantation was repetitively performed in humans under conditions that limited its usefulness, increased its perioperative risk, and made training of the next generation of hepatic surgeons difficult. Liver transplantation was widely viewed as being too dangerous and difficult to be generally applicable. The mistake had been made of believing that a fundamental principle of surgical physiology worked out in animals, namely that veno-venous bypass was essential for effective liver transplantation, was not truly relevant in humans.

It was possible to carry out liver transplantation successfully without veno-venous bypasses,[66, 67] but the operation could be performed only by highly experienced surgeons and frequently with such a sense of urgency that training of new teams in any numbers was not possible. All too often, a virtuoso performance was required, and even when the anhepatic period was kept to a minimum, major declines in cardiac output and variable hypotension were common.[68] The fact that recovery usually occurred in the hands of skilled teams created a false impression about the expendability of the bypass. Usually there was gross swelling of the intestine during the period of occlusion. Subsequently, many patients suffered from third space sequestration and postoperative renal failure. The extent to which these complex physiologic events contributed to the high perioperative morbidity of the 1960s and 1970s was not fully appreciated until later.[67, 69]

How this deficiency in technique was rectified cannot be traced easily from the articles describing the work. The stimulus for reassessment was a persistent 5% to 10% intraoperative mortality that was due almost entirely to poor patient tolerance of the venous occlusions during the anhepatic phase. However, nothing decisive was done to rectify the situation until a tragedy occurred in Pittsburgh in May 1982 that utterly demoralized the transplant team. A popular male hemophiliac teenager with chronic active hepatitis died on the operating table from the combination of bleeding, third space fluid sequestration, and cardiovascular instability that was then common during hepatectomy and the sewing in of the new liver.

The program was closed for more than 1 month until June 15, 1982 when cardiac surgeon Dr. Henry T. Bahnson, Chairman of the Department of Surgery at the University of Pittsburgh, was requested to set up a pump-driven bypass for the next case. Bahnson grasped the essence of the problem instinctively, and he agreed immediately. That night, a liver replacement was carried out under veno-venous

bypass in a 6-year-old child with biliary atresia. The bypass was performed under 3 mg of heparin/kg with a roller pump and other conventional equipment used for open-heart surgery. This technique of a pump-driven bypass had been described in dogs 10 years earlier by Cutropia and associates,[70] but their article was unknown to us at the time. There was little trouble in reversing the heparin effect afterward. Those who were there that night were ecstatic about the ease and nonstressful nature of the transplantation under bypass conditions.

The ways in which liver transplantation was facilitated by veno-venous bypass were verified in a number of other cases.[67] By July 1982, abstracts describing the technique were submitted under the senior authorship of Bahnson to the Southern Surgical Association and to the American Association for the Study of Liver Diseases. Both were rejected. In the meanwhile, problems with reversal of the heparin effect had been encountered in several of the adult recipients. Veno-venous bypass under systemic heparinization had worked well in those patients with relatively "simple" diseases such as primary biliary cirrhosis and in recipients who had not had previous abdominal operations. The same was not true in patients with difficult pathology, exceptionally advanced disease, and especially in those who had undergone multiple procedures previously. Here, the bleeding from the raw surfaces was so great and the heparin effect reversed with such difficulty that the value of bypass technique was vitiated. In fact, two patients with veno-venous bypass under heparin died of hemorrhage when clotting could not be restored.

Two of Bahnson's young associates, Drs. Bartley Griffith and Robert Hardesty, had avoided systemic heparin in patients with pulmonary insufficiency who had been treated with pump-driven extracorporeal membrane oxygenators. Griffith and Hardesty recently had purchased an atraumatic centrifugal pump that they thought would permit the pumping of venous blood without anticoagulation. Work on the nonheparin bypass began in dogs in the laboratory on September 30, 1982. The project was assigned to Dr. Scot Denmark, a resident who was in his "lab year." Griffith and Denmark provided the bypass capability. The liver transplantations were performed by members of the transplantation service, including the second-year transplantation fellow Dr. Byers Shaw, Jr. By the end of 1982, most of the work that was reported by Denmark at the Surgical Forum of the American College of Surgeons in October 1983 already had been completed.[71] However, clinical trials of the nonheparin bypass were not started, in part because it was difficult to predict which patients really needed it. In addition, there still was uneasiness about the possibility of clot formation in bypass tubing and consequent pulmonary emboli.

During the Christmas season of 1982 and in January 1983, three

more deaths occurred on the operating table in much the same way as with the earlier hemophiliac patient. As a consequence, a policy decision was made at the end of January 1983 that veno-venous bypasses must be used for all adult recipients of liver transplants from that time onward (see Fig 15). It became obvious almost immediately that liver transplantation had become a far more reasonable procedure than in the past.[69,72] Kam and associates have shown subsequently that these techniques are easy to use and safe in many pediatric recipients, particularly those weighing more than 15 kg.[10]

Not all liver transplant surgeons believe that veno-venous bypasses are of overriding importance.[73–77] Calne and co-workers have described a venoarterial bypass, sometimes with an intervening oxygenator, that is used only when venous cross clamping causes cardiodynamic instability.[73] They contend that strain on the heart is relieved thereby. Even today, most infants and small children undergo liver transplantation without veno-venous bypass, and some surgeons routinely omit it for their adult recipients.[74–77] Nevertheless, veno-venous bypass converted liver transplantation to a procedure that can be carried out by many well-trained general or vascular surgeons. The consequence was that effective teams could be developed quickly, blanketing the United States and Europe almost overnight with a network of competent liver transplant services.

Recipient Hepatectomy

There is no single best way to remove a diseased native liver. In each case, an ad hoc decision is required on the best technical approach that the abnormal anatomy will permit. In some patients, efforts to mobilize the liver from the hepatic fossa can cause lethal hemorrhage unless the hepatic arterial and portal venous blood supply are ligated first. In the other recipients, it may even be impossible because of scarring from previous operations or because of the massive formation of varices to dissect individually the structures of the portal triad.

Finally, the method of hepatectomy, as well as the conduct of the rest of the operation, are determined largely by whether or not veno-venous bypasses are going to be used. If the bypass is omitted, it is important to limit the venous occlusion period as much as possible, hopefully to the time required for performance of the two vena caval and the portal anastomoses. Otherwise, damage to the splanchnic and systemic capillary beds may be excessive, with grossly obvious petechial hemorrhages and edema in the intestines and elsewhere. With occlusion of both the vena cava and the portal vein, hemorrhage from the thin-walled varices and from all other raw surfaces of the operative wound is predictably amplified. The bleeding often cannot be controlled by any mechanical means until decompression is accomplished by opening of the vena caval and portal venous

anastomoses of the new liver. Thus, if veno-venous bypasses are to be omitted, as much preliminary dissection as possible is desirable so that the occlusion period can be made as short as possible.

In contrast, the extent of preliminary dissection can be greatly decreased if a veno-venous bypass is to be used. The individual structures of the hilum usually are skeletonized, but no other areas need be invaded. When the bypass is ready for implementation, the hepatic artery and the common duct are ligated. The portal vein cannula for the veno-venous bypass is inserted, as is a femoral cannula, allowing both the splanchnic and systemic systems to be brought into the veno-venous circuit (see Fig 15). Entry into the superior vena caval system usually is via the axillary vein (Fig 16). In adults, 1 to 6 L of blood per minute are bypassed. Simultaneous obstruction of the portal vein and inferior vena cava should cause little change in blood pressure or other measures of cardiovascular function.

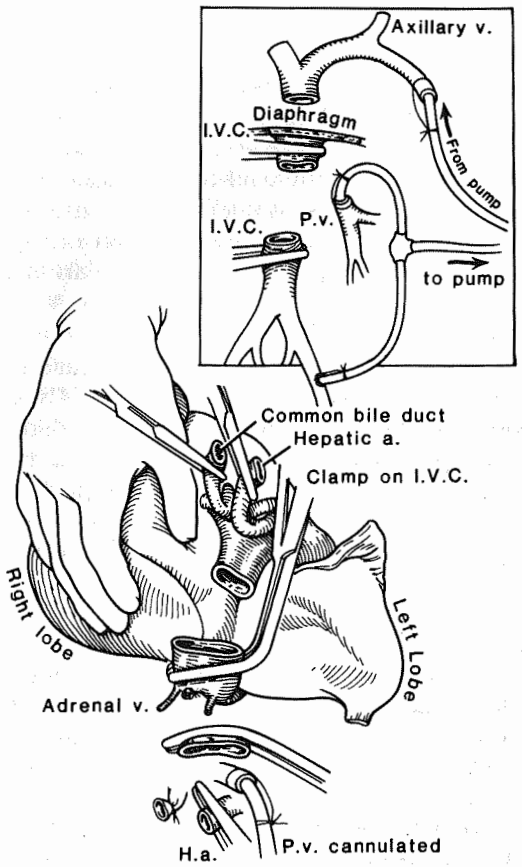


FIG 16.
Technique for removal of the liver from below upward. This is a particularly attractive approach if a veno-venous bypass is used as shown. (Redrawn from Starzl TE, Porter KA, Putnam CW, et al: *Surg Gynecol Obstet* 1976; 142:487–505.)

With the hemodynamic stability afforded by the veno-venous bypass, it is possible to systematically dissect all other structures that are holding the now-devascularized liver, including the infrahepatic vena cava. The triangular ligaments and the leaves of peritoneal reflection that make up the coronary ligament are cut if these have not been incised already (Fig 17). The bare areas are entered on both the right and left sides. After these maneuvers have been carried out, the right hepatic lobe can be retracted into the wound. If it has not been possible to encircle the inferior vena cava earlier, this can be done now just below or above the liver, and eventually at both locations. The liver can then be shelled out on the stalk defined by the vena caval connection (see Fig 17), and the vena caval cuff for eventual anastomosis can be developed (see Fig 17, inset).

Once the liver has been removed, it is possible using veno-venous bypass time to close most of the raw surfaces that were created dur-

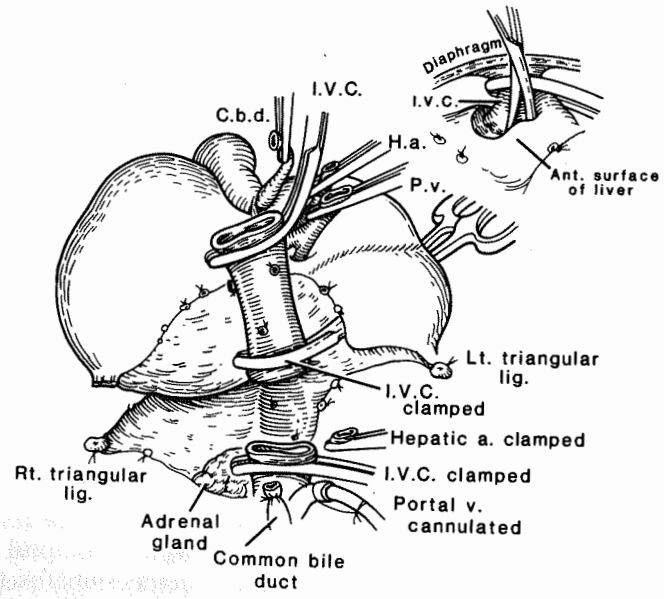


FIG 17.
Completion of removal of the liver from below upward, leaving the liver attached only by a stalk of vena cava at the diaphragm. (Redrawn from Starzl TE, Porter KA, Putnam, CW, et al: *Surg Gynecol Obstet* 1976; 142:487–505.)

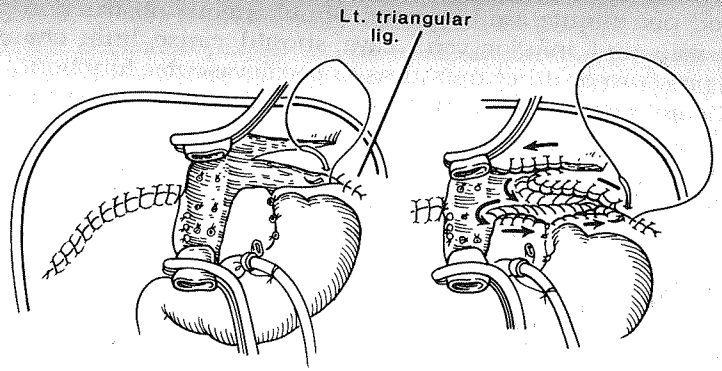


FIG 18.
Closure and hemostasis of the bare area after peeling out the liver. Under conditions of veno-venous bypass, there is plenty of time to do this so that the wound is dry when the anastomoses to the new liver are carried out. (Redrawn from Starzl TE, Iwatsuki S, Shaw BW Jr, et al: *Transplant Proc* 1985; 17:107–119.)

ing the hepatectomy (Fig 18). Closure is usually done with a continuous polypropylene suture, beginning at the tip of the right triangular ligament and continuing centrally in rows that eventually are connected.[78] The superior leaf of the coronary ligament can be the starting point, with continuation into the bare area itself and eventually to the inferior portion of the coronary ligament (see Fig 18). When these continuous suture lines are eventually incorporated into a single suture line, all of the right bare area may be eliminated if desired. The same principle is followed in dealing with the left triangular and falciform ligaments as well as other bare areas (see Fig 18).

The foregoing well-ordered strategy of hepatectomy is not always possible, particularly in patients who have undergone previous operations in the upper abdomen. In some cases, the only way to get the liver out is by placing clamps across the entire hilum. The lumens of the individual hilar structures can then be seen after transecting between the mass clamps, and these individual structures can be dissected downward toward the clamp (Fig 19).

Another drastic variation that may be especially helpful in children in whom the infrahepatic vena cava is inaccessible is to encircle and transect the vena cava above the liver. When this is done, one or two fingers are thrust downward into the retrohepatic vena cava to prevent massive hemorrhage (Fig 20). Then the liver can be peeled down from above.

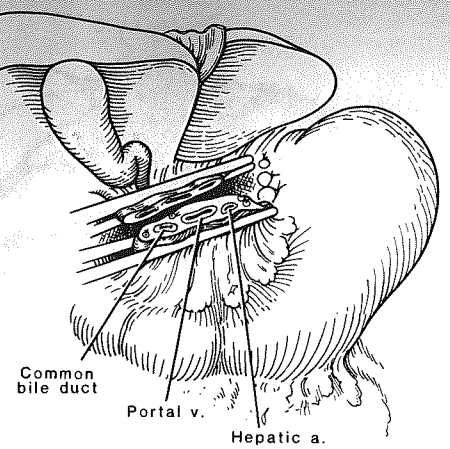


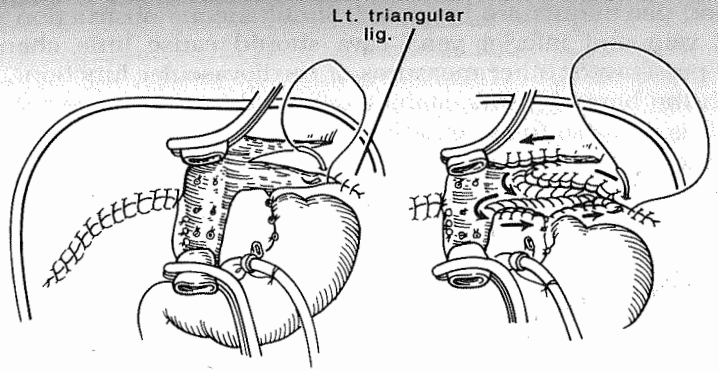
FIG 19.
Crossclamping of portal triad, which is sometimes necessary when preliminary dissection of the individual structures is too difficult. Once the triad has been clamped, the triad structures are seen head on and are dissected downward. A portal venous cannula for veno-venous bypass can then be inserted. (Redrawn from Starzl TE: *Experience in Hepatic Transplantation*. Philadelphia, WB Saunders Co, 1969.)

Preservation of the Vena Cava and the Piggyback Technique

An integral part of the standard orthotopic liver transplantation is removal of the inferior vena cava from above the renal veins to the diaphragm. Complete excision of this retrohepatic vena cava is not necessary, and Stieber and co-workers have pointed out that it may not be desirable.[79] They recommend leaving that portion of vena cava into which the right adrenal vein drains and then oversewing it.

In another modification, the full length of the recipient inferior vena cava is preserved, and the new liver is placed "piggyback" onto its anterior surface. A particularly appealing feature of the piggyback operation in children for whom veno-venous bypass might not be feasible is that vena caval occlusion can be avoided during the hepatectomy and sewing in of the homograft. The piggyback operation has been used for a number of years. In some of our first patients, this operation was employed,[80] and one of Calne's first five recipients had a piggyback operation.[81] However, the formal description and widespread use of the piggyback operation has been recent.[82] At the present time, about one fifth of our recipients are having the piggyback modification.

The essence of this operation is shown in Figure 21. By rotating



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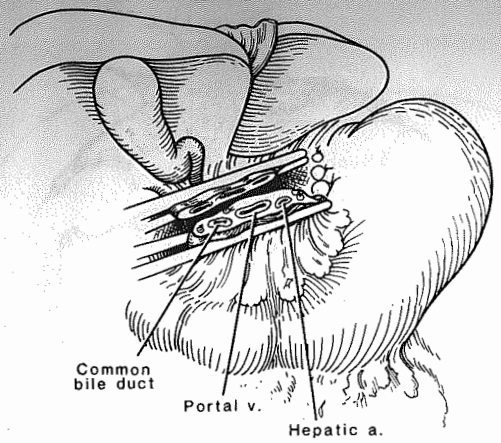

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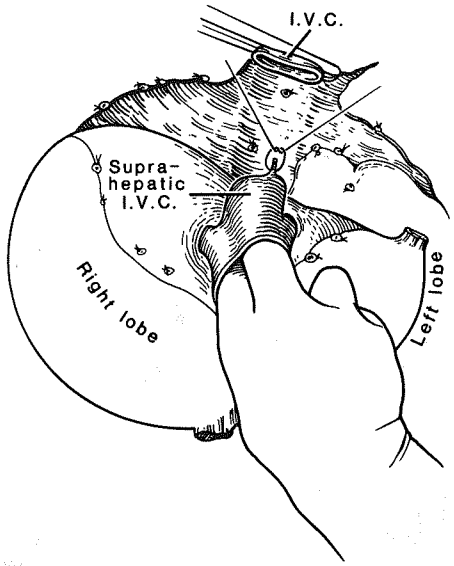


FIG 20.
Removal of the liver from above downward, preventing hemorrhage with a finger or fingers thrust down the lumen of the transected suprahepatic vena cava. The maneuver is indicated if it is difficult or impossible to safely encircle the inferior vena cava below the liver. This technique is almost specific for certain cases of biliary atresia with extensive subhepatic scarring in which the small size of these livers makes it possible to completely occlude the vena cava with a single finger. (Redrawn from Starzl TE, Iwatsuki S, Shaw BW Jr, et al: *Transplant Proc* 1985; 17:107–119.)

the liver out of the wound, either to the right or to the left, one can dissect the individual hepatic veins, ligate them, and divide them (Fig 22). The major hepatic veins are crossclamped and eventually used to fashion an orifice for the outflow anastomosis of the homograft (Fig 23). The right, middle, and left hepatic veins or, more commonly, the middle and left are joined by dividing the intervening septum.

If difficulty is encountered in dissecting the hepatic veins from an exterior approach, an alternative technique is to split the liver like a book. A tributary-free plane is identified at the upper portion of the liver, and with gentle blunt dissection, the finger is burrowed down the anterior surface of the vena cava (Fig 24). The liver is then divided with a knife from its anterior surface down to the finger using a knife (Fig 25).

The exact technique of the outflow anastomosis depends on which hepatic veins have been selected for this purpose. The lower end of the vena cava of the homograft is ligated or sutured (see Fig 21).

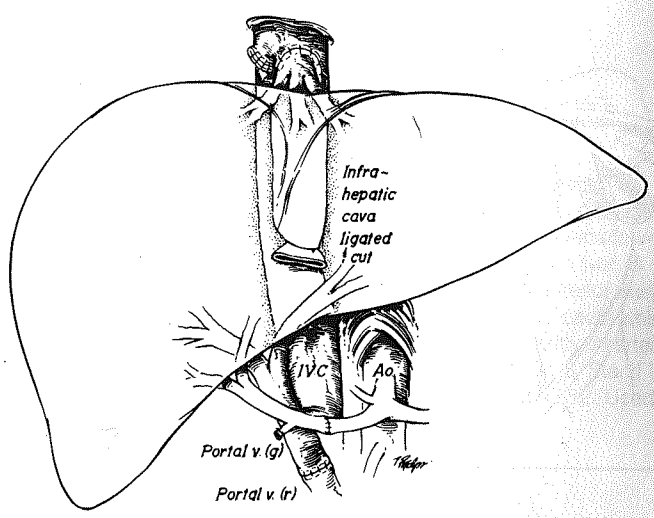


FIG 21.
Transplantation of a liver piggyback onto an inferior vena cava, which is preserved through its length. Note that the suprahepatic vena cava of the homograft is anastomosed to the anterior wall of the recipient vena cava. The retrohepatic vena cava of the homograft is sutured or ligated, leaving a blind sac into which empty numerous hepatic veins. (From Tzakis A, Todo S, Starzl TE: *Ann Surg* 1989; 210:649–652. Used by permission.)

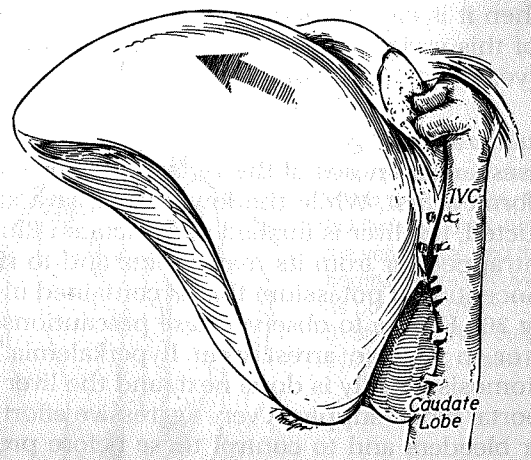


FIG 22.
Steps in preparation of the recipient vena cava for the piggyback operation. All of the small hepatic veins entering the retrohepatic vena cava are ligated and divided, and the large principal tributaries (right, middle, and left hepatic veins) are dissected free. (From Tzakis A, Todo S, Starzl TE: *Ann Surg* 1989; 210:649–652. Used by permission.)

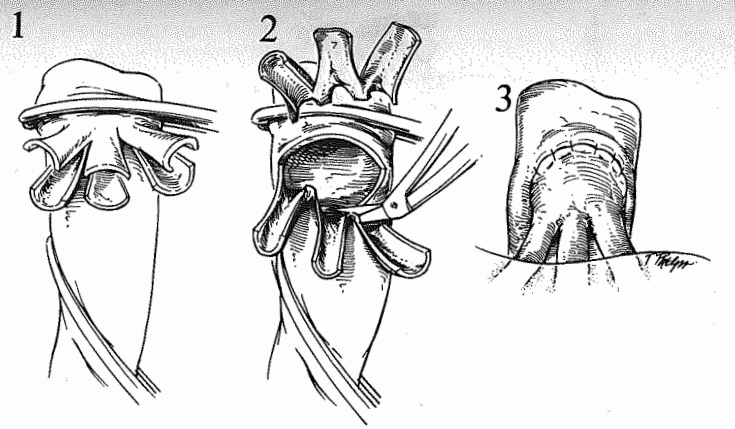


FIG 23.
Formation of the site for anastomosis. The three main hepatic veins can be connected as shown, or other combinations can be used, of which the most common is a left and middle hepatic cloaca. (From Tzakis A, Todo S, Starzl TE: *Ann Surg* 1989; 210:649–652. Used by permission.)

The applicability of the piggyback operation depends on finding favorable anatomic conditions as the recipient hepatectomy proceeds. If the liver is very cirrhotic, small, and firmly adherent to its retrohepatic vena cava, it is foolish to persist in efforts to save the vena cava. When it is easy to perform, there is little that can be said in criticism of this variant technique, which is being used in about 75 cases per year in our Pittsburgh program.[82]

Graft Revascularization

In most cases, anastomoses of the vena cava above and below the liver are performed first. While the lower vena cava anastomosis is being constructed, the liver is flushed with lactated Ringer's solution to remove entrapped air from its major veins and to rid the graft of the highly concentrated potassium that is contained in the preservation fluid (Fig 26). Failure to observe these precautions can result in air embolus or in cardiac arrest from hyperkalemia.[62] The portal venous anastomosis usually is done next, and the liver is revascularized with a portal blood supply. A very aggressive effort then is made to find major bleeders and to control these before proceeding with rearterialization. As already mentioned under donor hepatectomy, many options have been described for dealing with anomalies or other unusual anatomic features of the donor or recipient arteries. The objective in all is to obtain as large a caliber recipient vessel as possible, consistent with the size of the donor artery. This usually

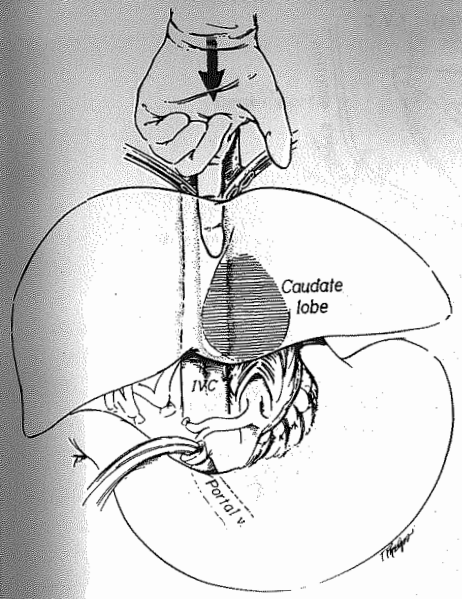


FIG 24.
Maneuver that facilitates cleaning the dissection of the retrohepatic vena cava and removing the liver. A vascular plane exists on the anterior surface of the retrohepatic vena cava, which is developed with a gentle inserted finger. (From Tzakis A, Todo S, Starzl TE: *Ann Surg* 1989; 210:649–652. Used by permission.)

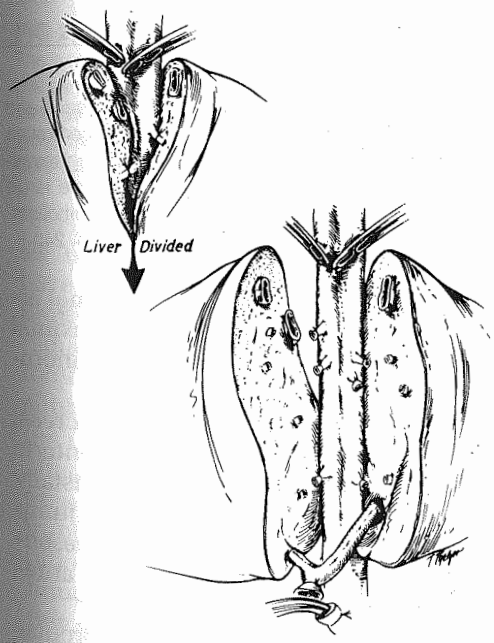


FIG 25.
After the plane is developed as shown in Figure 24, the liver is boldly transected, bringing into view the vena cava, and the right and left fragments are removed as quickly as possible. (From Tzakis A, Todo S, Starzl TE: *Ann Surg* 1989; 210:649–652. Used by permission.)

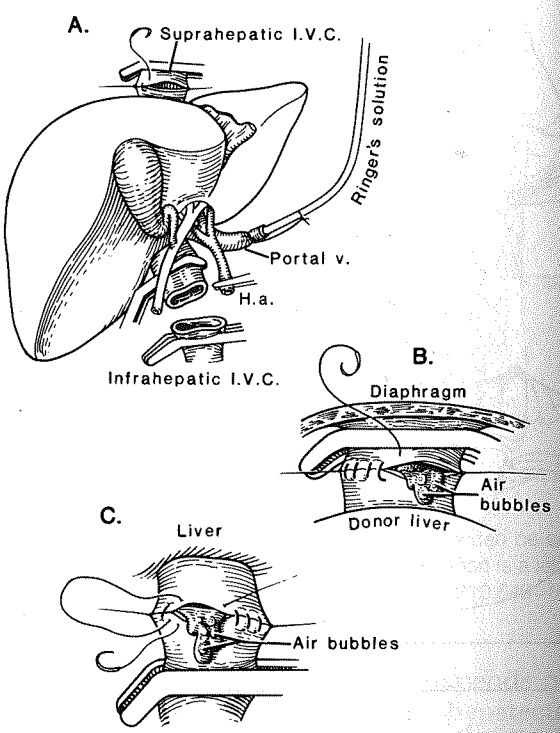


FIG 26.
Technique of washing out the homograft, which is performed with both the piggyback and standard operations. The organ is washed with a solution of low potassium concentration **(A)** to avoid the infusion of a bolus of potassium from the preservation fluid during revascularization. In addition, it is important to wash out air that may be trapped in the large hepatic veins (**B** and **C**). Failure to eliminate these bubbles could lead to air embolism. (Redrawn from Starzl TE, Schneck SA, Mazzoni G, et al: *Ann Surg* 1978; 187:236–240.)

requires making the anastomosis proximal to the gastroduodenal artery in recipients with normal arterial anatomy and often proximal to the splenic and left gastric arteries in those recipients with anomalies.

Vein grafts of the portal vein can be inserted above the pancreas, usually at the confluence of the splenic and superior mesenteric vein (see Fig 11). If a portal vein thrombosis extends too far distally to allow insertion of a vein graft superior to the pancreas, a jump graft can be placed on the anterior surface of the superior mesenteric vein below the transverse mesocolon. The graft is brought anterior to the pancreas and beneath the pylorous (Fig 27).

In restoration of the portal venous and hepatic arterial circula-

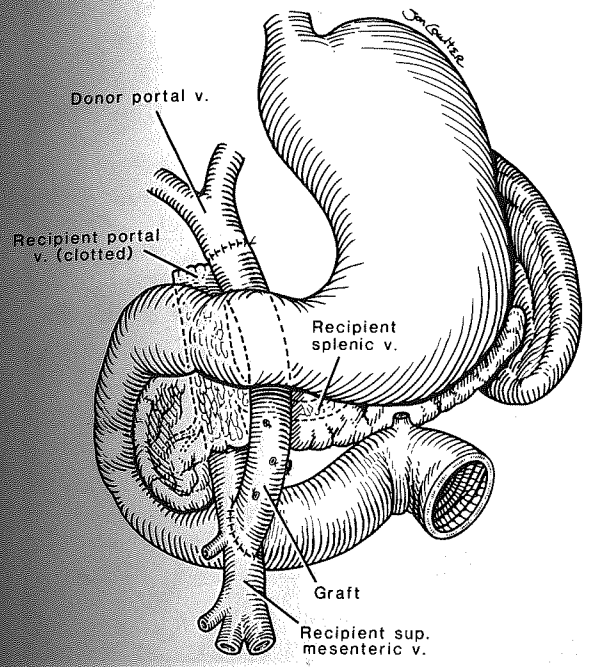
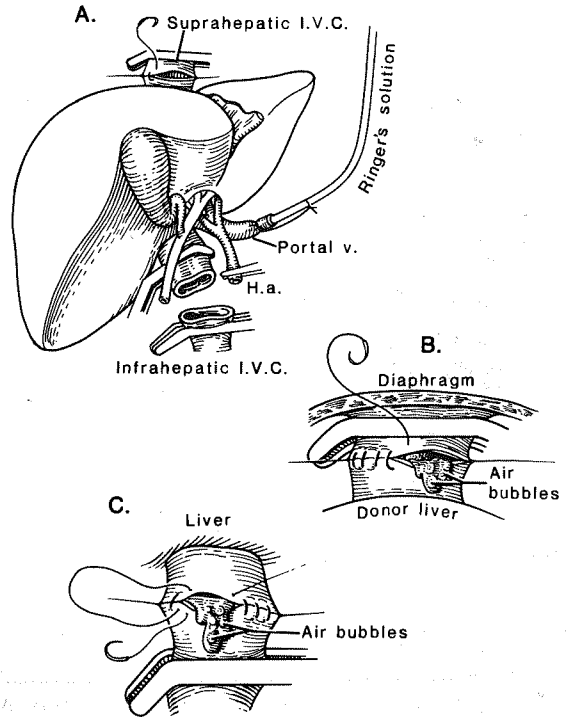


FIG 27.
The use of an antepancreatic portal vein graft from the superior mesenteric vein through the same pathway as shown for an arterial graft in Figure 12. The use of these grafts has eliminated portal vein thrombosis as a contraindication to transplantation, providing a good superior mesenteric vein is still open. (From Tzakis A, Todo S, Stieber A: *Transplantation* 1989; 48:530–531. Used by permission.)

tions, performance of a poor anastomosis with subsequent thrombosis usually will cause death or necessitate retransplantation. We have described special techniques to prevent flawed anastomoses, particularly in children who have small vessels.[83] These special techniques were designed to prevent anastomotic strictures.[83] The anastomoses are done in the usual way with a continuous polypropylene suture (Figs 28,A and B), but a so-called growth factor is left by tieing the sutures at a considerable distance from the vessel wall (Fig 28,C). After flow is restored through the hepatic artery or portal vein, the excessive suture recedes back into the vessels and distributes itself throughout the circumference of the suture line (Fig 28,D). If an additional suture is placed at the point where the two ends of the continuous suture line meet, thus preventing distraction of the lips at this point, the amount of hemorrhage at the time of flow restoration is surprisingly small. Suture materials other than polypropylene are



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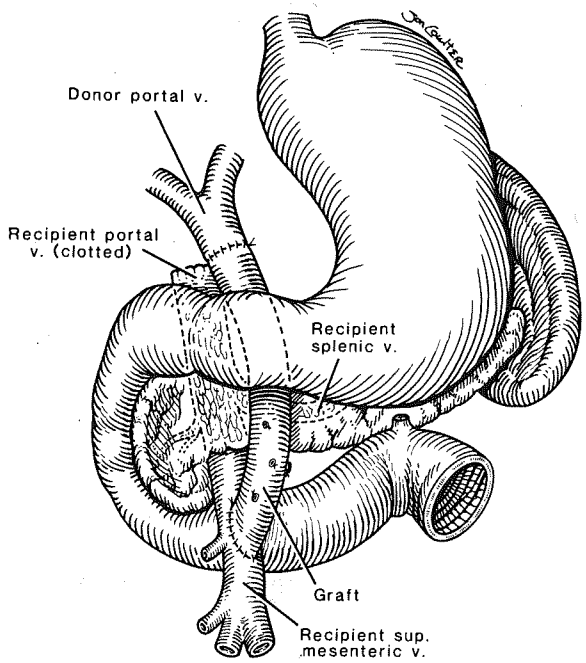

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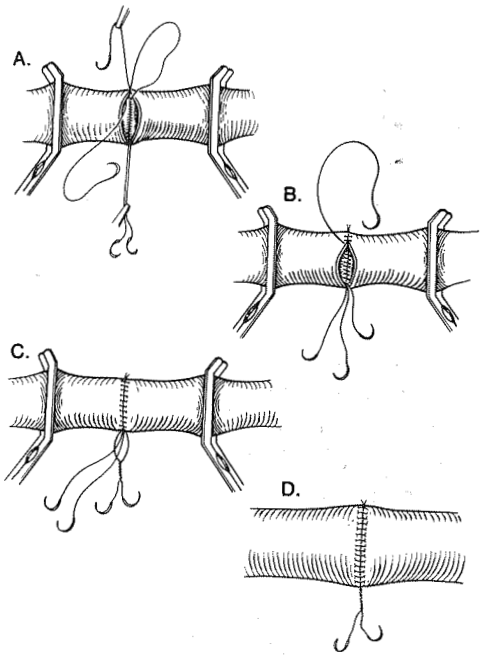

FIG 28.
Method of avoiding strictures of small vascular anastomoses. See text for explanation. (Redrawn from Starzl TE, Iwatsuki S, Shaw BW Jr: *Surg Gynecol Obstet* 1984; 159:164–165. Used by permission.)

not satisfactory for this technique. The polypropylene is so slippery that it is not caught by the adventitia and can easily work itself back through the entire circumference of the suture line.

Biliary Reconstruction

An acceptable technique of biliary tract reconstruction if the anatomic conditions permit is end-to-end anastomosis of the donor and recipient common ducts over a T-tube stent (see Fig 1).[67] Variants of this principle include a side-to-side choledochocholedochostomy after closure or ligation of the donor and recipient duct ends.[84] Alternatively, the homograft common duct can be anastomosed to a defunctionalized (Roux) limb of jejunum (see Fig 1) with equally good results.[67, 85, 86] Whichever method is used, there has been a 10% to 15% incidence of late bile duct obstruction that required correction by interventional radiologic techniques, secondary duct reconstruction, or in occasional cases with retransplantation.[85–89]

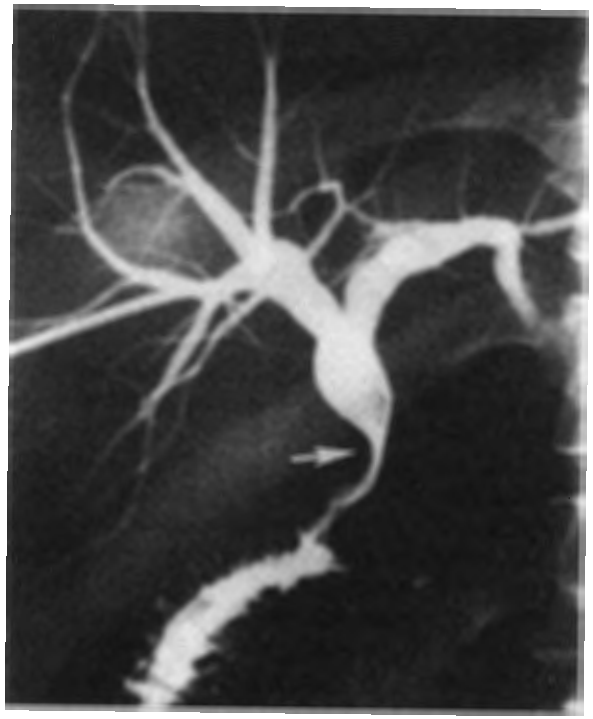

FIG 29.
Typical extrinsic mass effect on homograft common hepatic duct, which is caused by obstructing a cystic duct at both ends. This surgical complication results in obstructive jaundice and requires secondary excision of the resulting mucocele. (From Koneru B, Zajko AB, Sher L, et al: *Surg Gynecol Obstet* 1989; 168:394–396. Used by permission.)

One kind of biliary obstruction that is highly avoidable is caused by leaving an obstructed segment of the cystic duct with the graft. Usually, this occurs when the cystic duct enters the common duct at an anomalously low level, creating a double lumen at the site of duct transection. If the distal and proximal ends are occluded, a mucocele can form in the obstructed segment and lead to extrinsic compression (Fig 29).[90] The best way to avoid this is to completely resect the cystic duct at the time of transplantation. Alternative techniques are shown in Figure 30.

Rarely, there may be an indication to use a technique that incorporates a donor gallbladder conduit between the donor common duct and the recipient anastomotic site.[91, 92] This method (Fig 31), which was described by Waddell and Grover[91] and by Calne,[92] has had a high incidence of late sludge and stone formation. In our experience, almost one half of the biliary tracts reconstructed with the Waddell-Calne technique eventually developed the characteristic ob-

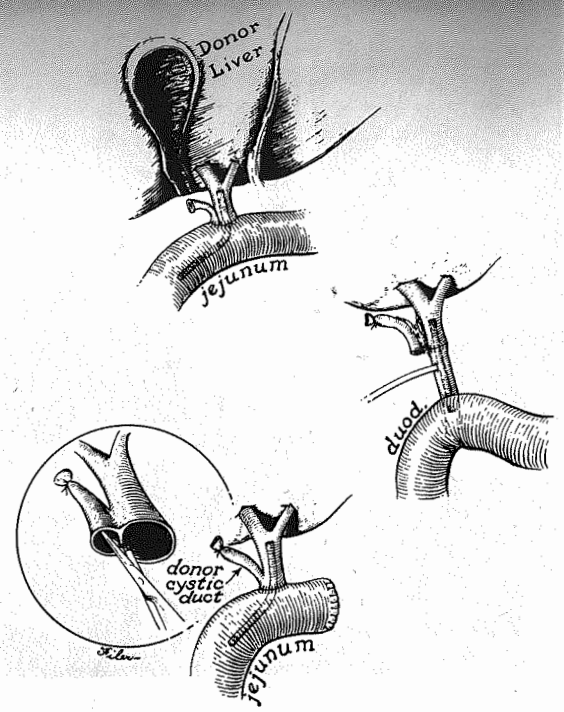

FIG 30.
The best way to prevent mucocele formation is to completely excise the cystic duct, but alternative techniques to prevent a blind cystic duct remnant are shown. (From Koneru B, Zajko AB, Sher L, et al: *Surg Gynecol Obstet* 1989; 168:394–396. Used by permission.)

struction shown in Figure 32.[93] It has been possible to rectify the situation by conversion to a choledochojejunostomy.

Need for Hemostasis

Complete hemostasis is mandatory before closing. The assumption that nature will take care of bleeding if effective liver function is provided by a homograft has proved to be a vain hope on many occasions. Often a coagulopathy will be present intraoperatively that can persist into the postoperative period.

The presence of the coagulation expert Dr. Kurt von Kaulla at the University of Colorado in the 1960s was a key element in the development of the transplantation programs there. Von Kaulla and associates studied the renal[94] and hepatic[95] recipients and characterized the clotting defects in both classes of patients. In the first three liver recipients, they demonstrated clotting factor defects, showed the seriousness of fibrinolysis as well as how to treat this problem.[63] They

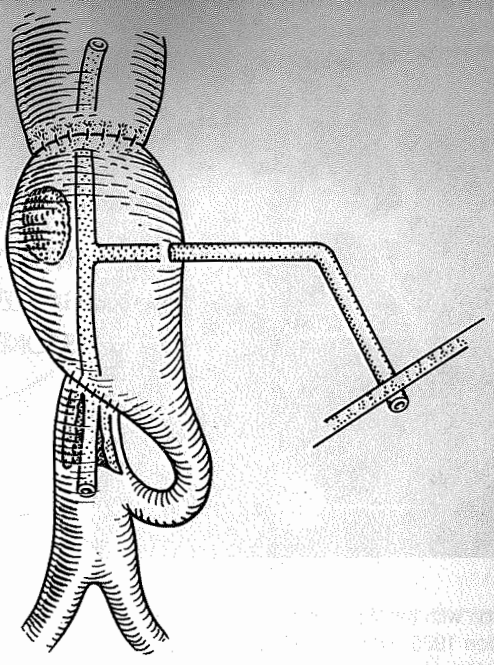

FIG 31.
The Waddell-Calne technique of gallbladder conduit biliary reconstruction. Note that the homograft common duct has alternative pathways of emptying, both through the gallbladder conduit. The choledochocholecystostomy is stented with a T tube brought out through the gallbladder. (From Halff G, Todo S, Hall R, et al: *Transplantation* 1989; 48:537–539. Used by permission.)

recommended the thromboelastogram to follow the minute-to-minute clotting changes in the operating room in much the same way as is recommended and practiced currently. Other studies showing consumption of clotting factors, including platelets within the graft itself[96, 97] and the development in some patients of a hypercoagulable state postoperatively, completed the picture. Flute of Cambridge provided confirmatory data.[98] Ultimately, this kind of information was acted on systematically for therapeutic correction by the anesthesiologists at the University of Pittsburgh in the early 1980s under the direction of Drs. Jessica Lewis, Frank Bontempo, and Yoo Goo Kang.[99–103] Now cautious correction of coagulation defects is an integral part of liver transplantation, greatly diminishing the hemorrhages of nightmare proportions that were common. As already emphasized, the other factor that has ameliorated the intraoperative bleeding problems has been the systematic use of veno-venous bypasses.

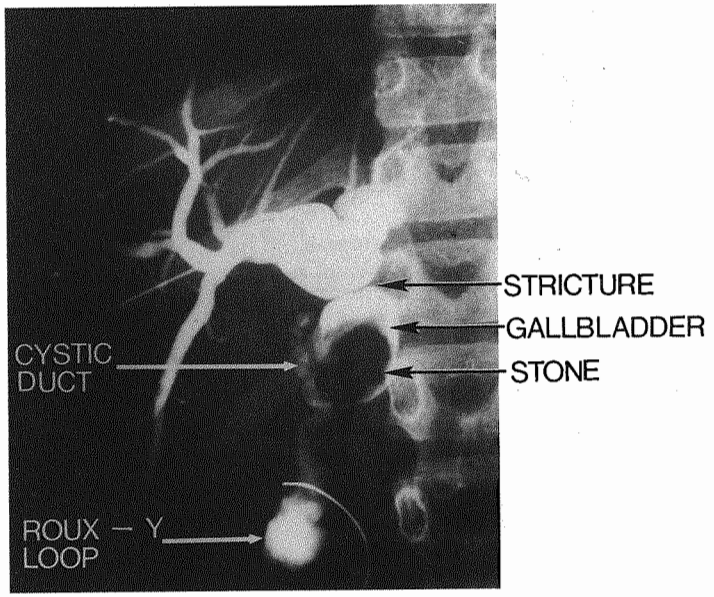

FIG 32.
Typical complication with the Waddell-Calne reconstruction. (From Halff G, Todo S, Hall R, et al: *Transplantation* 1989; 48:537–539. Used by permission.)

Many hours of tedious and exhausting effort may be necessary to obtain perfect hemostasis, but these efforts are eventually rewarded with a dry wound. After hemostasis has been accomplished, closed sump drains are placed in two or three locations above and below the liver, and the wound is closed with nonabsorbable sutures.

Modifications of This Standard Procedure

The piggyback operation, in which the graft is placed onto the anterior surface of the retained recipient inferior vena cava, was mentioned previously. The other structures are anastomosed in the usual way. The piggyback reconstruction gives an unusual degree of mobility to the liver and a greater freedom in tailoring vessel lengths. These may be important advantages if the donor liver is substantially smaller than the diseased native organ that was removed. The piggyback operation has also been especially helpful for four of our patients with situs inversus, of whom one has been reported (Fig 33). A patient with situs inversus also has had an orthotopic liver transplantation performed by Raynor and colleagues, with removal of the vena cava in the usual way.[104]

Size reduction techniques that permit the transplantation of part of a liver have been perfected in recent years in Paris,[105, 106] Hannover,[107, 108] Brussels,[109] and Chicago,[110, 111] allowing greater flexibil-

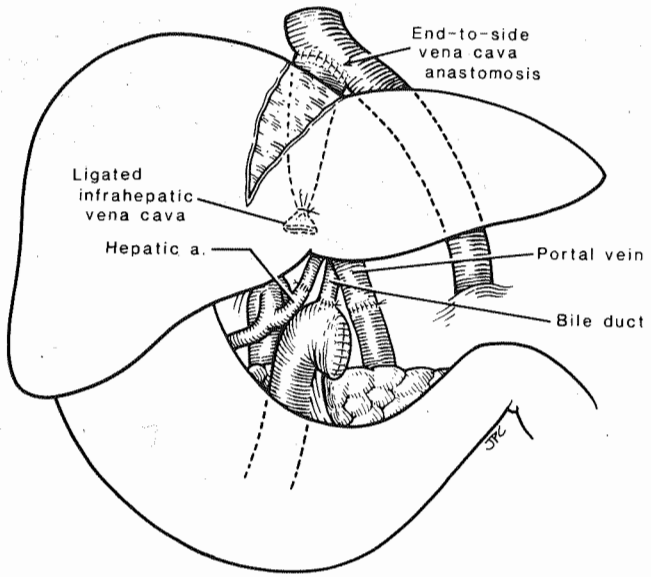

FIG 33.
Reconstruction after transplantation to a child with situs inversus. Note suprahepatic inferior vena cava of the graft was anastomosed to the anterolateral surface of the recipient inferior vena cava. The graft infrahepatic vena cava was ligated. (From Todo S, Hall R, Tzakis A, et al: *Clin Transplantation*, in press. Used by permission.)

ity in matching donor availability to recipient needs. Pediatric recipients have benefitted most from this development. The first known example of partial liver transplantation occurred on March 26, 1975 at the University of Colorado. The left lateral segment of an adult liver was transplanted into the orthotopic position in an infant with biliary atresia. Because of its historic interest, the case is described here.

The recipient, a 23-month-old boy weighing 8.2 kg, had a failed Kasai portoenterostomy and subsequent cholangitis. Absence of the retrohepatic inferior vena cava shadow was noted on a chest x-ray film. At the time of transplantation, the absence of the retrohepatic inferior vena cava was confirmed. The portal vein was in a preduodenal location. Multiple splenic nodules were situated in the upper left quadrant (splenosis), and intestinal malrotation was present. This constellation of anomalies is not rare in biliary atresia.[112] Removal of the 405-gm liver was difficult because of multiple dense vascular adhesions and portal hypertension. The liver graft was taken from a large adult male donor whose exact weight is not known. A right trisegmentectomy was done with an intact circulation, leaving the left lateral segment (weighing 700 gm) vascularized in the donor until the last possible moment. The graft was revascularized by connecting the donor left hepatic

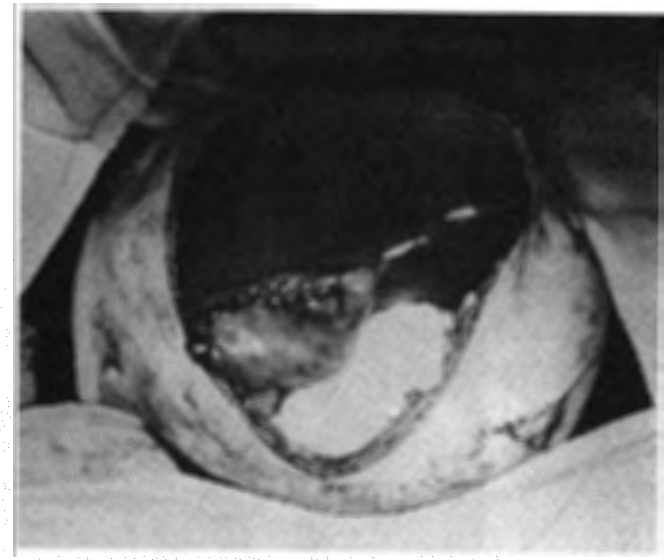

FIG 34.
The first-known effort at use of a cut-down liver. The lateral segment of a large donor was transplanted to a 7½-year-old child who was dying of biliary atresia. The head of the child is to the left, and the legs are to the right. The lateral segment was too large, and the wound could not be closed. This operation was first used successfully by Bismuth of Paris and has been used extensively in France, Germany, Belgium, and the United States (see text).

vein end to end to the venous cloaca into which the diseased liver had drained. The donor left hepatic artery and left portal branch were anastomosed end to end to the recipient's common hepatic artery and portal vein, respectively. The donor left hepatic duct was anastomosed to a previously created Roux-en-Y jejunostomy.

After revascularization, the liver segment had immediate return of normal color and consistency. However, the fragment was too large to permit closure of the abdomen (Fig 34). Consequently, Dr. John Lilly covered the wound by suturing a sheet of Silastic-Marlex mesh to the peritoneum and fascia of the abdominal wound. A persistent bleeding diathesis occurred intraoperatively and subsequently. The child died 36 hours later, and at autopsy, the liver was relatively normal except for scattered focal infarcts. There was a 450-mL hemoperitoneum. Pulmonary *l*-isomerism and patent ductus arteriosus were also noted.

In this 1975 case, the fragment of liver that was retained still weighed almost twice as much as the excised native liver, dooming the effort to failure. In addition to the senior author of this monograph, members of the surgical team included many young surgeons whose continued academic activities are reflected in their current University appointments: John R. Lilly (Professor, University of Colorado), C. W. Putnam, (Professor, University of Arizona), R. H. Bell (Associate Professor, University of Cincinnati), R. W. Beart (Professor, Mayo Clinic), M. Ishikawa (Professor, Tohoku University, Japan), and M. A. Haberal (Professor, Turkish Transplantation and Burn Foundation, Ankara).

EARLY GRAFT FUNCTION

The correction of preexisting liver function abnormalities begins intraoperatively if good graft function is obtained. When the graft fails completely to provide function, the only recourse is prompt retransplantation before cerebral edema and brain stem herniation occur.[113] Lesser degrees of graft injury can lead to renal failure, altered consciousness, a need for prolonged ventilatory support, ileus, and a host of other complications, which, even if they are not lethal, require protracted intensive care unit stays and generate astronomical hospital bills.[114] The penalties of primary dysfunction or nonfunction are so severe that much effort has been made to delineate the causes, to prevent these, to quickly quantitate the prospects of recovery, and to facilitate decisions about urgent retransplantation.

Since late 1987, the incidence of early graft failure necessitating retransplantation in the first 3 months or leading to death has been about 10%.[52] This incidence was down from 18% in the immediately preceding period.[52, 113] However, primary graft failure still occurs in 10% to 15% of cases.[52, 115, 116] There are four general reasons for graft failure, which are not necessarily mutually exclusive: (1) unrecognized liver disease in the donor, (2) a technically imperfect recipient operation, (3) ischemic injury of the graft, or (4) an immune event perioperatively. In Part II (*CPS*, March 1990) we will discuss the fourth factor, and will add a fifth factor, namely, endotoxemia, which is still speculative but too important to ignore as a possibility.

PREEXISTING DISEASE

When a liver has primary nonfunction in spite of a seemingly perfect operation, it may have been diseased in the donor even though the tests used to screen donors were acceptable. Undetected chronic disease has been distinctly uncommon in livers that have passed through the donor screening process.[117–119] However, a few indisputable examples in which the donor livers had diffuse fatty infiltration (Fig 35) or other serious abnormalities have been reported.[117, 120] Rarely, an unrecognized malignancy can be transferred with the donor liver.[121]

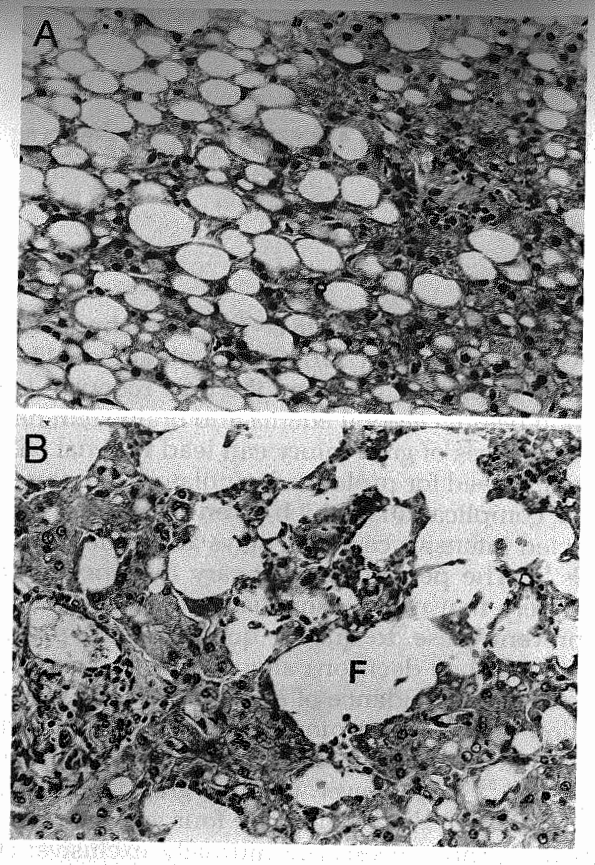

FIG 35.
Transplantation of a liver with severe macrovesicular steatosis involving more than 80% of hepatocytes, as is shown in **(A),** from a back-table biopsy predictably results in graft failure. After reperfusion **(B)** lysed hepatocytes release the fat (*F*, clear spaces), which contributes to microvasculature disruption with fibrin deposition and leukocyte sludging. (From Todo S, Demetris A, Makowka L, et al: *Transplantation* 1989; 47:903–905. Used by permission.)

The pathologist frequently is requested to evaluate a donor liver by frozen section before implantation because of gross physical alterations or suspicious agonal events in the donor. Gross inspection of the potential allograft by the pathologist is mandatory. Donor diseases recognized on frozen section in Pittsburgh have included metastatic carcinoma, diffuse regenerative hyperplasia, focal nodular hyperplasia, small noncaseating granulomas, severe steatosis, probable alcohol-induced injury, changes consistent with chronic active, persistent or nonspecific reactive hepatitis, and multiple small subcapsular infarcts. The livers with carcinomas, diffuse regeneration hyperplasia, and chronic active hepatitis have not been used. Those

with severe steatosis (see Fig 35) have also been routinely disregarded after several organs with similar changes were transplanted and failed.[120] Donor organs with nonspecific reactive hepatitis, small noncaseating granulomas, and other mild nonspecific changes are routinely used and have not caused problems. Usually, small focal nodular hyperplasia lesions are removed before implantation. In the absence of any of the obvious contraindications or severe ischemic injury, the pathologist is unable to predict the adequacy of organ function after transplantation based on frozen section light microscopy prior to the operation.

TECHNICAL FAILURE

Early retransplantation has been successful in less than one half of the cases when carried out in patients whose primary graft failure was caused by technical deficiencies.[113] This reflects in part the infections that quickly develop in or around a graft that is imperfectly transplanted as well as the rapidity of hepatic decompensation in many of the recipients.

Florid technical complications account for less than 10% of primary graft failures in adults compared with 30% in pediatric recipients.[113] With very small pediatric recipients, defined by a weight of less than 10 kg or by an age less than 1 year, technical complications have been a significant factor in a 35% 1-year mortality.[122] Vascular thrombosis has been a particularly troubling problem in these tiny recipients.[122–124]

Thrombosis of the hepatic artery or portal vein is usually classified as a technical error. Most technical errors are obvious, but subtle flaws in revascularization can be hard to diagnose. Suboptimal portal venous flow or reduced hepatic arterial flow has been found with electromagnetic flow meter studies.[125–127] In some of these cases, an unsatisfactory and ultimately correctable situation was not suspected before the flow determinations were obtained. A few patients have undergone emergency reconstruction of the thrombosed arteries.[126, 128]

When a graft fails because of arterial thrombosis, the pathologist may be able to find an underlying defect in the artery such as intraluminal mural flaps, devitalization of part of the wall, or intramural dissection. In a multivariate factor analysis in pediatric recipients,[129] the risk of arterial thrombosis was increased if the vessels were smaller than 3 mm, if the anastomoses had to be revised, or if aortic or iliac grafts were needed as "conduits" to the hepatic artery.

Portal vein thrombosis has been rare and usually occurs when the splanchnic venous bed of the recipient was altered by a previous operation, such as a portal-systemic shunt or splenectomy.[130] Unless

they are looked for, venous thrombi can be carried to the recipient in the portal vein of the liver graft, particularly if there has been a splenic injury in the donor.[131] Spontaneous resolution of a portal vein thrombosis has been reported.[132] However, early portal vein thrombosis usually requires retransplantation.[130] A few patients have been saved by immediate or delayed operation and secondary portal vein reconstruction.[67, 133] Two patients whose reconstructed portal vein thrombosed have had distal splenorenal shunts.[134–136] The first of these patients is still well 7 years after transplantation and 6 years after the shunt.[134, 135]

It is also true that hepatic artery thrombosis does not necessarily lead to graft loss. The event may be completely asymptomatic in 20% to 30% of cases.[123, 137, 138] Until Doppler ultrasound examinations were used routinely,[139] the diagnosis would not have been suspected in these recipients. In contrast, all of the syndromes that develop in symptomatic patients are serious and include primary nonfunction, regional septic hepatic infarction of a liver of which the viable portions may retain good function, bacteremia, abscess formation, rupture of the dearterialized ducts with bile peritonitis or with bile leakage, and biloma formation within the graft parenchyma (Fig 36).[74, 123, 137, 138, 140–143] Later, multiple intrahepatic biliary

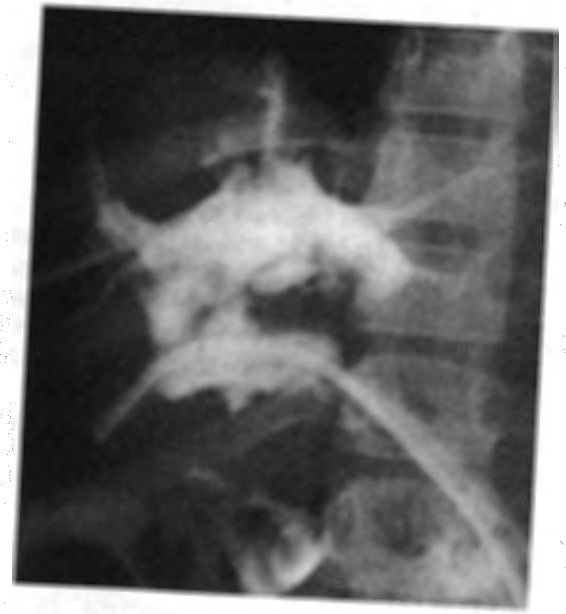

FIG 36.
Formation of a biloma within a dearterialized liver. Typically, patients with this complication have good liver function. It is possible to drain the biloma with a radiologically directed catheter, but retransplantation usually is necessary. (From Zajko AB, Campbell WL, Logsdon GA, et al: *Transplant Proc* 1988; 20[suppl 1]:607–609. Used by permission.)

strictures resembling the lesions of sclerosing cholangitis may form (Fig 37).[138, 141, 142]

The diagnosis of hepatic artery thrombosis has been made much more frequently since the availability of Doppler ultrasound. Before then, arteriography was needed as a definitive step, but this was not commonly done. Needle biopsy is a rather insensitive method for establishing the diagnosis of hepatic artery thrombosis.[144, 145] The histologic changes can be quite variable and core needle biopsies are subject to more sampling error than usual. The findings may range from completely normal to frank coagulative necrosis. Marked perivenular hepatocellular swelling, cholangiolar proliferation, often with bile plugs, and acute cholangiolitis similar to that seen with "preservation injury" may also be observed. The pathologist should routinely search for microorganisms when necrotic tissue in encountered, since these foci frequently become seeded with bacteria and fungi (Fig 38).

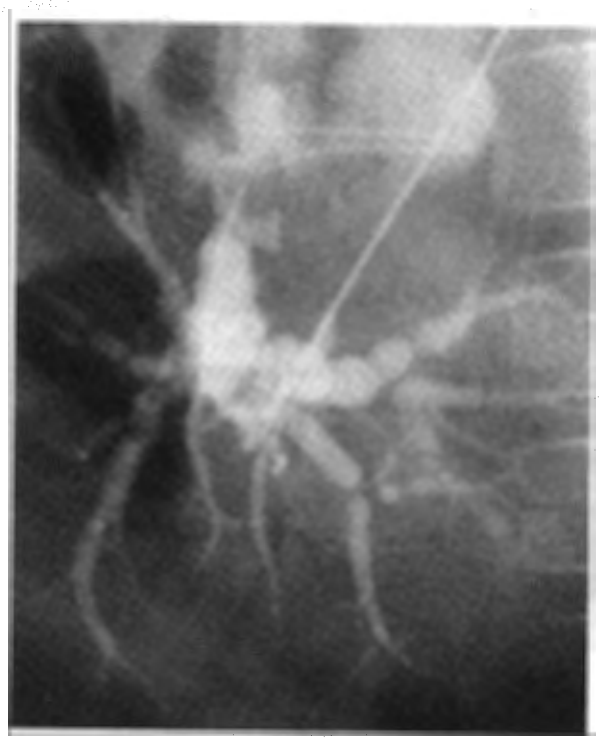

FIG 37.
Multiple strictures in a patient whose hepatic artery clotted early. The recipient survived but ultimately developed cholangitis from multiple strictured and obstructive sites. The resulting appearance of the duct system has some resemblance to sclerosing cholangitis. (From Zajko AB, Campbell WL, Logsdon GA, et al: *Transplant Proc* 1988; 20[suppl 1]:607–609. Used by permission.)

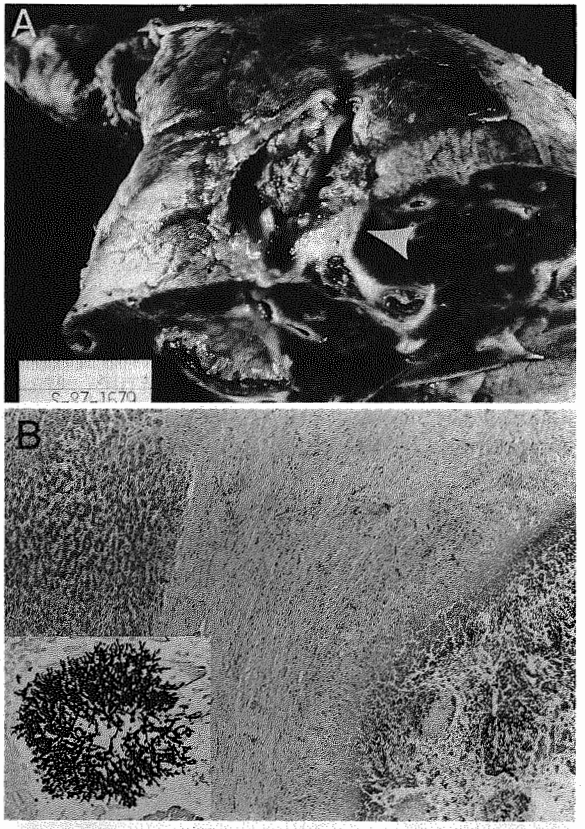

FIG 38.
A, gross examination of a failed allograft with hepatic artery thrombosis often reveals necrosis of the hilar structures, including the connective tissue *(arrowhead)*. **B,** microscopically, the large bile ducts are often necrotic, and the dead tissue becomes seeded with microorganisms, which was *Candida* in this case. (From Demetris AJ, Kakizoe S, Oguma S, Pathology of liver transplantation, in William JW [ed]: *Hepatic Transplantation.* Philadelphia, WB Saunders Co, 1990, pp 60–113. Used by permission.)

Since the hepatic artery is the sole direct supply of blood to the major bile ducts, intrahepatic ducts, hilar connective tissue, lymph nodes, and walls of the portal vein,[146] compromise to arterial flow frequently leads to selective necrosis of these structures (see Fig 38). In addition, an allograft may be more susceptible than nongrafted livers to this form of injury since it is devoid of the natural cascade type of arterial collaterals, at least in the early postoperative period. The areas prone to necrosis are not easily accessible to routine needle biopsy sampling. Therefore, biopsy monitoring of an allograft with a thrombosed artery may lead to a false sense of security.

"Medical" Factors Contributing to Vascular Thrombosis

Preoccupation about mechanical and technical causes of graft thrombosis is justified. However, so-called medical factors can contribute to or even make inevitable the thrombosis of a hepatic artery or portal vein. Overzealous correction of clotting defects during operation was shown long ago to predispose to vascular thrombosis in small children,[147] a lesson recently relearned with the use of fresh frozen plasma.[129] Polycythemia caused by transfusion is another iatrogenic risk factor.[148] The tendency of children to clot their vessels may be greater than in adults because of deficiencies in protein C and antithrombin and by defective fibrinolysis.[149]

An additional factor of unknown significance is the institution of cyclosporine therapy. This drug alters the prostanoid metabolism and other hemostatic processes of vascular endothelial cells.[150–153] Finally, a drastic reduction in hepatic blood flow is a well-known feature of rejection.[154] In a French clinical study, hepatic artery or portal vein thrombosis was associated with rejection more strongly than with any other definable factor.[155]

Microvascular Injury

Another factor making the new liver vulnerable to thrombosis during the perioperative and early postoperative periods is injury to the hepatic microvasculature from ischemia and cold preservation.[156–159] The denudation of the sinusoidal lining in preserved livers as assessed by light and electron microscopic studies is now known to be so extensive[159] that it is surprising that vascular thrombosis is not even more common than it is.

ISCHEMIC INJURY

It is not practical at present to measure in advance or even to estimate very accurately the ischemic injury during the events causing donor death, the procurement operation itself, and the period of formal cold preservation. The interval from cessation of donor circulation to cooling of the liver with preservation fluid is called *warm ischemia time.* The storage time after this plus the time to sew in the liver and restore its portal flow after removing it from an ice chest are termed *cold ischemia.* Under conditions of brain death pronouncement, and with modern techniques of multiple-organ procurement,[23,24] there is virtually no warm ischemia.

Thus, almost all clinical reports equate cold ischemia with global ischemia. If this simplistic view were correct, the degree of organ damage would be a direct reflection of preservation time. The expected association can be demonstrated easily in controlled animal experiments[36,44,56,157–160] but far less clearly in a clinical setting.