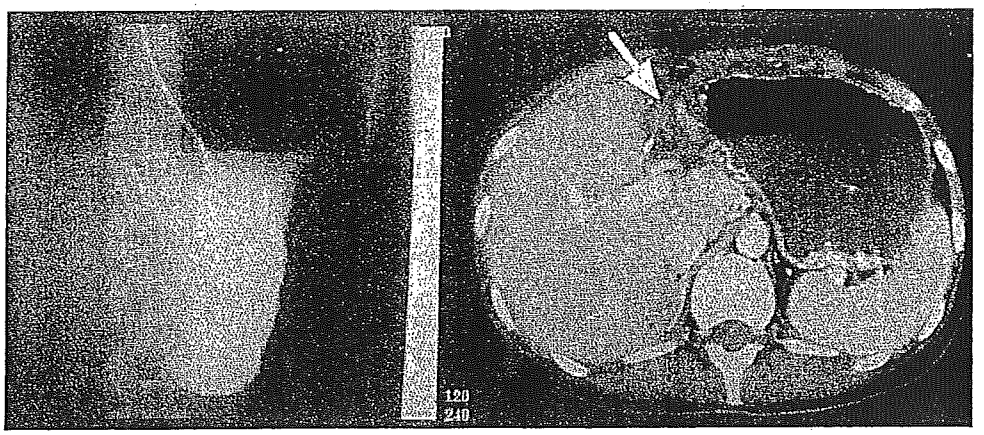

FIGURE 42-2
Adhesion of the gastric wall to the cut surface of liver after left lateral segmentectomy in pediatric living related liver transplantation. **Left,** Gastric stasis as a result of outlet obstruction. **Right,** Computed tomography shows the hairpin curve of the gastric outlet at the adhesion site (*arrow*).

the cut surface of the liver also occurs more frequently after left-sided hepatectomy than after right lobectomy. Such adhesion causes gastric stasis (Fig. 42–2). Donor candidates should be advised of all possible donor risks.

Even though the recipients are children, they have the right to select the treatment option according to their age and ability. Family members or physicians and coordinators must explain the treatment before the procedure. During puberty or adolescence, LRLT is sometimes difficult for patients to accept. They may be distressed to live with the sacrifice being made by their parent or relative. They may experience considerable anxiety about the operation and the future if not completely informed. Their anxiety should be relieved after a patient, thorough explanation. The goal that all family members can enjoy and participate in the happy healthy life of the patient should be presented as the motivation for LRLT.

Indications

Indications for LRLT are basically no different from those for deceased donor transplantation. However, in LRLT, the organ is donated to a specified recipient and not shared by other candidates. Therefore, the indication is not affected by the problem of organ allocation as it is in deceased donor transplantation. Contraindications to deceased donor transplantation are not necessarily the same for LRLT. For example, livers with malignant disease such as hepatoblastoma, which is large and invasive, may be considered to have low priority in deceased donor transplantation. However, if there is a possibility of total excision, including local invasion without distant metastasis, such a case should be considered for LRLT with the full understanding of the potential donor, recipient, and other relatives about the potential risks of surgery, tumor recurrence, and donor surgery.[16]

Donor Evaluation

Current Status of Donor Evaluation in Pediatric Living Related Liver Transplantation

Donor evaluation in LRLT is necessary for the safety of the donor and recipient (Table 42–3). Suitable donors can be selected on the basis of two perspectives: (1) donors with normal liver function and normal anatomy and (2) donors without any systemic diseases or abnormalities. In Japan, criteria for donor selection are determined in each institution with approval of the institution's review board (Table 42–4). As the initial phase, preliminary conditions such as age, relationship to the recipient, ABO blood matching, and history of any diseases can be identified during basic screening. After full consent has been given, the medical tests start. If multiple candidates are available, conventional studies are performed at the initial screening. Such studies include a blood count, coagulation profile, blood chemistry for hepatic and renal function, serology for hepatitis C and B virus, serological tests for syphilis and human immunodeficiency virus, electrocardiography, chest radiography, and ultrasonography of the liver. If the candidates live far from the hospital, this screening can be performed by a local physician. After preliminary examination, the results are presented as a tool for selecting the final candidate.

The age of the donor should ideally be between 20 and 60 years of age. Younger candidates should be evaluated for their competence in making a voluntary decision. Candidates older than 60 years are judged on an individual basis in terms of cardiopulmonary and neurological function.

Postoperative pulmonary embolism is a genuine threat to the donor. Smoking, routine use of birth control pills, or serious obesity should be considered a possible risk factor for this complication. However, the possibility

Table 42-3. DONOR WORKUP

Confirmation of voluntary willingness to donate after a full explanation of the risks and benefits
Confirmation of cooperative and supportive willingness of the donor candidate's intimate relatives/spouse
Medical history
No major current diseases or drug therapy
No history of malignancies (confirmation of "cure" if positive)
No history of transmittable diseases (confirmation of a nontransmittable state if positive)
Blood tests
Complete blood count; biochemistry, including renal and hepatic function; coagulation profile (prothrombin time, activated partial thromboplastin time, fibrinogen, antithrombin III, bleeding time)
Serology of hepatitis A, B, C; serology for sexually transmitted diseases, human immunodeficiency virus and human T-lymphotrophic virus I, cytomegalovirus, Epstein-Barr virus
Tumor markers (α-fetoprotein, carcinoembryonic antigen, CA 19-9, CA 125)
ABO blood group, preformed irregular antibodies
HLA typing
Electroencephalogram
Chest and abdominal plain radiographs
Spirogram or arterial blood gas analysis
Abdominal ultrasonography of the hepatic parenchyma and vasculature, evaluation of other abdominal organs
Abdominal computed tomography (assessment of hepatic parenchyma, three-dimensional reconstruction of blood vessels, and estimation of graft volume)
Needle biopsy of the liver if steatosis is reasonably suspected

Table 42-4. FACTORS INVOLVED IN DONOR SELECTION FOR LIVING RELATED LIVER TRANSPLANTATION (KYOTO UNIVERSITY)*

Age: 20–60
Relatives: parents, siblings, offspring, spouses, grandparents, uncles, and aunts
ABO matching: compatible or identical (incompatible is not completely excluded)
HLA matching: a homozygous haploidentical donor is not recommended
Health of the donor
History and present condition of any systemic diseases
Longer than 1 month after child delivery
Assessment of the present disease (consult a specialist)
Blood chemistry (liver and kidney), complete blood count, coagulation profile
Electrocardiogram and ultrasonic cardiogram (UCG), chest and abdominal plain radiographs
Arterial blood gas analysis and ventilatory function if older than 50 years
Serious obesity (body mass index > 30)
Neurological evaluation if older than 60 years
Evaluation by the recipient coordinator and psychiatrist
Disease transmission
Infection: positive hepatitis viruses, human immunodeficiency virus, serological test for syphilis
Malignancy
Tumor markers (carcinoembryonic antigen, α-fetoprotein, CA 19-9, CA 125)
Endoscopy of the upper and lower gastrointestinal tract if older than 40 years
No residual tumor after the treatment of any previous malignant disease (consult with a specialist)
Metabolic diseases: loading test, liver biopsy for assessment of target enzyme activity
Graft evaluation
Doppler and conventional ultrasound: fatty liver, space-occupying lesion (SOL)
Three-dimensional computed tomography: fatty liver, architecture of vessels
Three dimensional computed tomographic cholangiography: branching pattern
Needle biopsy (if steatosis or other pathology is suspected on ultrasound, computed tomography, or blood chemistry)
More than 30% of the fatty infiltration should be excluded and treated by diet
Computed tomographic volumetry: expected graft volume > 1%, < 5% of body weight

*Patients with values out of the range in each criterion are evaluated on an individual basis.

of diet and correction of the habit is one of the advantages of living donor transplantation. A body mass index greater than 30 should be corrected, or an alternative donor should be selected out of concern for the donor's safety.

ABO blood typing should be compatible, although incompatible matching is not absolutely excluded in countries in which deceased donor transplantation is not available. The second line of screening is endoscopy of the upper gastrointestinal tract and colon, blood tests to check for tumor markers (α-fetoprotein, carcinoembryonic antigen), respiratory function tests, echocardiography, and an imaging study of the liver. The imaging study of the donor liver is very important to ensure safe surgical procedures in both the donor and recipient. For this purpose, three-dimensional computed tomography (CT) angiography is a suitable modality because it is less invasive and provides considerable information.[17] Conventional catheter angiography is being used less and less frequently because it

is invasive for the donor. Magnetic resonance imaging may present the same information as enhanced CT does, but sometimes the images are not as clear as those obtained with CT.[18] It is very important to assess the potential volume of the graft in adult transplantation. However, in pediatric cases, the graft is usually the whole left lobe or the left lateral segment. Small-for-size problems are rare, but in small infants, large-for-size problems are more important. Specifically, the size of the potential graft estimated on computed tomographic scan should be compared with the diameter of the peritoneal cavity of the recipient. Preoperative three-dimensional cholangiography is also important for both adult and pediatric cases.

Fatty liver is a common contraindication to donation, with fatty infiltration of more than 25% to 35% being a criterion for exclusion.[14] Noninvasive studies such as ultrasonography and CT can identify a severely fatty liver.[19] In our institution, the averaged plain CT value of the liver measured at multiple spots is compared with that of the spleen. If the ratio is lower than 1, which means that the liver has less density than the spleen does, fatty infiltration is more than 30%.[20] However, an exact diagnosis of the degree of fatty infiltration depends on preoperative liver biopsy. Needle biopsy under ultrasound guidance is safe, although it is not routinely recommended in all cases. If any pathology is suspected on imaging studies, needle biopsy is recommended to exclude severe fatty liver or other pathological lesions. Accurate diagnosis of nonalcoholic steatohepatitis, which may be suspected from hepatic profile and imaging studies, depends on the pathological findings by needle biopsy.

Disease Transmission and Donor Selection

In pediatric LRLT, inherited diseases such as metabolic disorders and Alagille syndrome are not as rare as the indication. If a parent is selected as the donor, the potential donor may have a heritable genetic factor or a subclinical manifestation of disease. A metabolic loading test or measurement of the target enzyme in a liver specimen taken by needle biopsy may be helpful as a tool for excluding such a patient from becoming a donor candidate.[21] In the case of Alagille syndrome, the pathological diagnosis of paucity of the intrahepatic bile ducts should be considered and investigated in the potential donor. However, adults with subclinical Alagille syndrome may have only mild elevation of biliary tract–related enzymes without any sign of cholestasis.[22]

Ruling out infectious diseases or malignancy is not specific for determining acceptability for LRLT. Nonetheless, if there is a patient with a disease such as tuberculosis or hepatitis in the family of the patient, the possibility of latent or previous subclinical infection the donor candidates is high. Very careful examinatic of the donor candidates is necessary in such a situ tion. Contraindications to donor selection are summ rized in Table 42–5.

Table 42–5 DONOR CONTRAINDICATIONS

Infectious diseases
Hepatitis B surface antigen, hepatitis C virus antibod human immunodeficiency virus positive
Active infection with any pathogen
Uncured malignancy
Major systemic or organ diseases inappropriate for hepatectomy
Liver abnormality or dysfunction
Steatosis greater than 30%
Rare variant of vascular anatomy that may make harvesting dangerous
Subclinical phenotype of the inheritable diseases of the recipient
Metabolic diseases
Alagille syndrome
One-way mismatch in HLA typing

Significance of HLA Matching in Living Related Liver Transplantation

As in the case of deceased donor transplantation, HLA matching has not been considered a significant tool to date for donor selection in LRLT. In pediatric LRLT, the donor is usually one of the parents, which means that the recipient has haploidentical HLA typing. Sugawara and coauthors reported that zero HLA mismatching was associated with a low incidence of acute rejection in 58 pediatric LRLT cases.[23] Part of this advantage may be related to the better HLA matching in LRLT. However, a study of HLA matching in the largest series of pediatric LRLT by Kasahara and colleagues showed poor correlation of HLA matching and the incidence of rejection.[24] The zero-mismatch group had a tendency toward a lower incidence of steroid-resistant rejection and a lower level of tacrolimus maintenance 5 years after LRLT and a higher rate of withdrawal of immunosuppression, although there was no significant difference. Longer follow-up and further accumulation of experience may be necessary to clarify the role of HLA matching in LRLT. A merit of pre-LRLT HLA matching is the predictability of possible graft-versus-host disease (GVHD). After liver transplantation, GVHD is generally a rare complication. In LRLT from parent to offspring, the donor may have homozygous HLA typing and the

recipient, heterozygous typing. In such a case involving a so-called one-way mismatch, the incidence of GVHD has been reported to be high in organ transplantation, including liver transplantation.[25] Before LRLT, the potential for matching a homozygous donor with a heterozygous recipient in HLA typing should be identified, and in such cases it is better to use an alternative donor.

Size and Anatomy of the Donor Liver

In most pediatric LRLT, graft options consist of the full left lobe, including the middle hepatic vein (segments II, III, and IV); the left lateral segment with a part of segment IV, but without the middle hepatic vein; and the left lateral segment (segments II and III). Selection of the graft is based on graft volume in relation to the recipient's body size. The relative size of the standard liver volume is used as an index.[26] We use the ratio of graft weight to recipient body weight: graft weight (g)/recipient's body weight (g) × 100 (%).[27] If this ratio is within 1% to 3%, the graft size is considered adequate. Generally, the left lobe is used in a recipient with a body weight between 20 and 40 kg, whereas the left lateral segment or the left lateral segment plus a portion of segment IV is used for smaller recipients. When a slightly larger graft than the left lobe is necessary, the left half of the caudate lobe can be added.[28] In preoperative volumetry, the volume of the potential graft is estimated in cubic centimeters. The specific gravity of the hepatic graft is considered to be 1. Therefore, volume is calculated in the same manner as weight. If the potential graft is 200 g and the recipient's body weight is 10 kg, the ratio is 2%. The smallest unit in conventional LRLT is the left lateral segment. If the ratio of graft weight to recipient body weight is more than 5%, poor perfusion of the graft may cause unsatisfactory primary function. In general, the mother may be more suitable than the father in infantile cases because of her possibly smaller liver. Of course, after information is provided about the risks of the large-for-size problem, the final decision is made by the family. If only a large donor liver is available, reduction of the left lateral segment is necessary. Monosegment transplantation using segment III, as discussed later in this chapter, is a solution in such a case. Regarding size matching, the size of the graft should be compared with the size of the recipient's peritoneal cavity on computed tomographic images. If the anteroposterior diameter of the potential graft is 2 cm or longer than the anteroposterior diameter of the recipient's peritoneal cavity, primary closure is expected to be difficult. In such a case, skin closure or prosthesis closure can be used, but this technique may cause more trouble than simple closure.

The anatomy of the left lobe of the donor is an important factor in LRLT in pediatric recipients. The structures that should receive attention are vessels and bile ducts. In left lateral segmentectomy, the hepatic vein from segments II and III may become separated on entry into the inferior vena cava (IVC). In left lobectomy, the left and middle hepatic veins may also separately drain into the IVC. Consideration of such possibilities is necessary when developing a strategy for hepatic vein reconstruction. Regarding the anatomy of the portal vein, P2 and P3 may branch separately from the main portal trunk and form a trifurcation with the right portal trunk (Fig. 42–3). If this branching is located at an extraparenchymal site, it is not difficult to transect these two branches separately. However, if the branching is thought to be intrahepatic, it is very difficult to safely perform a transection. A left-sided gallbladder is frequently associated with this variation of the portal vein.[29] If available, an alternative donor should be chosen. On evaluation of the donor artery, an aberrant left hepatic artery arising from the left gastric artery is not very rare. This artery is in the lesser

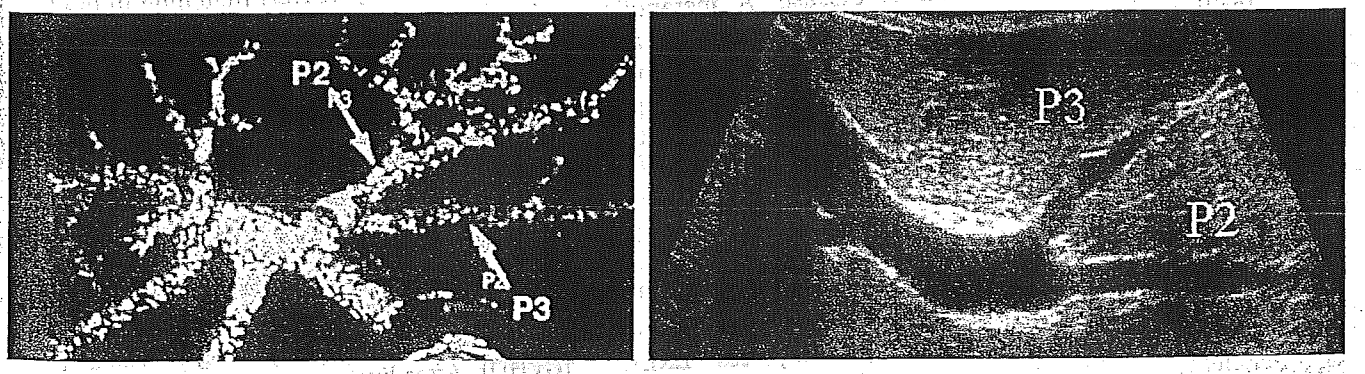

FIGURE 42–3

Variation of the portal vein to the left lateral segment. The portal vein to segment III (P3) and segment II (P2) is branching separately. If this lateral segment is taken as the graft, the graft will have two orifices in the portal stump. Left, Three-dimensional computed tomography. Right, Ultrasonography.

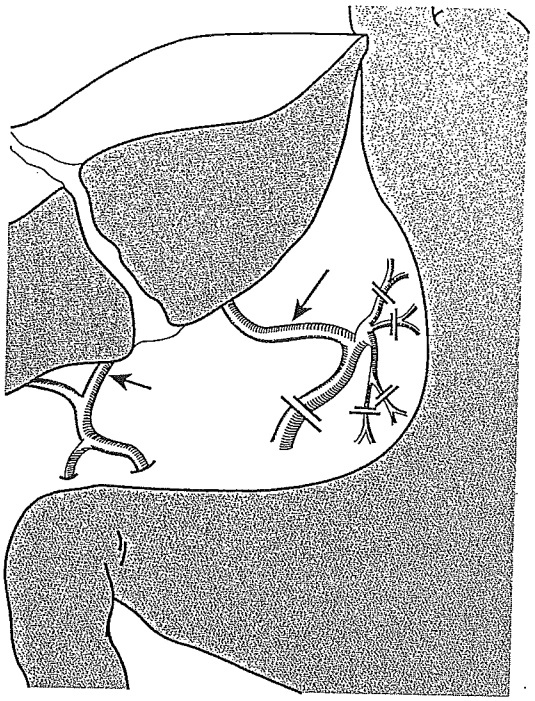

FIGURE 42–4

Aberrant hepatic artery supplying the left lateral segment (*long arrow*) originating from the left gastric artery. If the main left hepatic artery (*small arrow*) is small, this aberrant artery may be large. For reconstruction in the recipient, this artery should be kept long by transecting as indicated by the *double line*.

omentum, and attention should be paid to preserving as long a vessel as possible because a longer vessel can be used as the reconstruction vessel (Fig. 42–4). When considering left lobectomy, the size and distribution of the middle hepatic artery should be assessed. For evaluation of bile duct anatomy, three-dimensional reconstruction CT is very useful. Preoperative assessment by such imaging facilitates better understanding of the intraoperative cholangiogram.

Technical Considerations

Donor Surgery

Left Lateral Segmentectomy and Left Lobectomy

The abdomen is opened through an inverted T incision. The horizontal incision can be very short in left lateral segmentectomy. After transection of the falciform ligament, intraoperative Doppler ultrasound is performed to confirm the anatomy of the hepatic and portal veins. The Arantius duct is transected just at the entrance to the left hepatic vein. The most cranial portion of the caudate lobe is dissected from the left wall of the IVC. After dissection of this area, the hepatic porta is approached. The left hepatic artery is dissected proximally to th point at which it branches from the common hepat artery. If the middle hepatic artery is supplying the le lateral segment, it should also be dissected. The bifu cation of the left hepatic duct is not necessarily ident fied in the left lateral segment. Instead, the wall of th left hepatic duct is identified just on the surface of the le portal vein, usually through the space between th middle and left hepatic arteries (Fig. 42–5). Small hemo clips are applied here as markers for the transection site on the intraoperative cholangiogram. A 24-gauge intravenous catheter is inserted directly into the common bile duct and used for the cholangiogram in left lateral segmentectomy. The common bile duct on the duodenal side and the neck of the gallbladder are clamped with small bulldog clamps. In left lobectomy, cholangiography is performed through the cystic duct because the gallbladder is resected. Since branches may overlap on the film, fluoroscopic images may be more helpful for identification of each duct if the operating table is tilted while the operator is watching the x-ray images. The left portal vein is identified but can be encircled later after transection of the left duct.

In our institution, parenchymal transection is performed without clamping the hepatic pedicle. Makuuchi recommends a Pringle procedure for donor hepatectomy.[30] The line of transection is 0.5 to 1 cm to the right along the falciform ligament in left lateral segmentectomy and along the right side of the traced route of the middle hepatic vein in left lobectomy. The parenchymal transection is performed with the Cavitron ultrasonic aspirator (CUSA) held by the surgeon and a bipolar electrocautery with a water-dripping system held by the first assistant.[31] The bile duct is sharply transected at the marked site under the guidance of intraoperative cholangiography. The stump on the donor side is closed with 6–0 running suture, whereas the graft side is left open. After transection, the

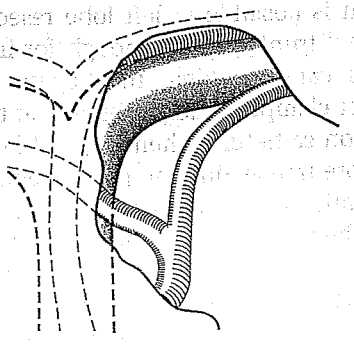

FIGURE 42–5

Identification of the left hepatic duct in left lateral segmentectomy. Between the left and middle hepatic arteries on the ventral surface of the left portal vein, a wall of the left hepatic duct can be identified. Tracing the hepatic duct from the bifurcation of the hepatic ducts is not necessary.

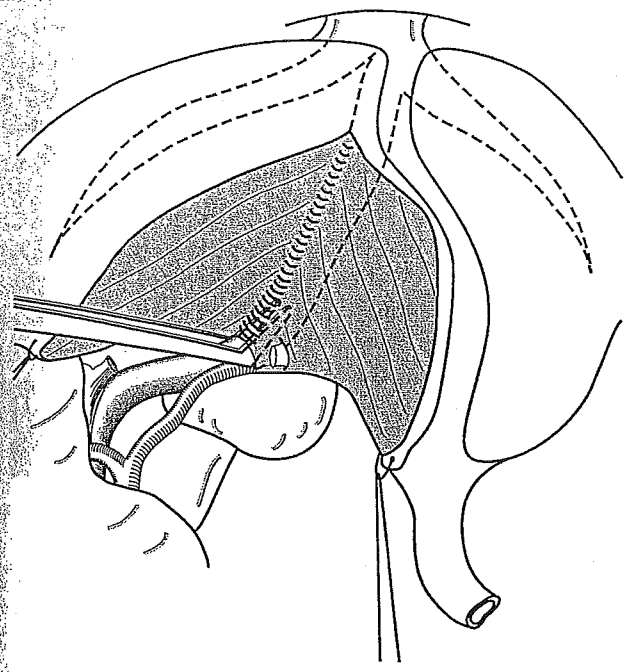

FIGURE 42–6
Parenchymal transection in left lateral segmentectomy. After transection of the left hepatic duct, the left portal vein is encircled. If curved DeBakey forceps are inserted between the lateral segment and the caudate lobe and pulled up ventrally, a crest of parenchyma is fashioned. With this procedure, the direction of transection is clearly shown, and the operating field is made shallow. The operator holds the forceps in the left hand and uses the right hand to manipulate the Cavitron ultrasonic aspirator (CUSA).

left portal vein can easily be encircled. Once the portal vein is encircled, curved DeBakey forceps are inserted under the left lateral segment along the fissure between the segment and the caudate lobe. After the segment is pulled up with the forceps, the transection line is easily identified and resembles a crest in a valley (Fig. 42–6).

Once the parenchymal transection is completed, heparin sodium (1000 units) is injected intravenously just before harvesting. Usually, in situ perfusion of the graft is possible in left lobe resection because the left portal trunk is long enough for insertion of the perfusion catheter. First, the hepatic artery is transected. After clamping the portal vein at the bifurcation, a perfusion catheter is then inserted into the left portal vein before transecting the portal vein. Clamping of the left hepatic vein or the common trunk of the middle and left hepatic veins is followed by transection of the vein or veins, and portal perfusion of the graft is started immediately. To facilitate reconstruction in the recipient, there should be only one orifice in the hepatic vein. To make a single orifice, transection of the Arantius duct and the left phrenic vein is helpful for deeper clamping of the common trunk of the left and middle hepatic veins in left lobectomy.[32] After confirming that the color of the perfusate from the hepatic venous stump has lightened, the graft is removed from the peritoneal cavity and transferred to a basin filled with preservation solution. The weight of the graft is measured. In situations in which the cold preservation time should be kept as short as possible, as in a donor with hepatic steatosis, the graft should remain vascularized in the body of the donor after parenchymal transection until the recipient side is ready.

Recently, laparoscopic left lateral segmentectomy has been reported in pediatric LRLT.[33] This technique requires a combination of special skills in both transplant surgery and endoscopic surgery. Developing a specialized team for the operation is the best way to perform such an advanced technique.

When a vein graft is expected to be necessary during the recipient procedure, the ovarian or inferior mesenteric vein is harvested from the donor.

Monosegment Transplantation

In small babies, it is difficult to keep the graft-recipient body weight ratio less than 5%. If the recipient has a large peritoneal cavity, which is common when ascites is massive, a large graft can be accommodated easily. However, from the perspective of graft perfusion, it is better to keep the ratio less than 5%. When the ratio is larger than 5%, monosegmental transplantation can be performed. The left lateral segment is cut down in situ before the hepatic pedicle is transected in the body of the donor. Segment II or III is used with reduction of the other tissue.[34] If the graft is still large, the caudal portion of the reduced graft can be further resected (Fig. 42–7).

Recipient Procedure

Recipient surgery consists of total hepatectomy and reconstruction. In patients with biliary atresia, which is the most common indication for pediatric LRLT, one or more techniques such as the Kasai procedure have usually been performed previously. The bowel is firmly attached to the anterior margin and lower surface of the liver. Numerous collaterals are passing through these adhesions. Meticulous adhesiolysis by electrocautery is useful to shorten the duration of surgery and decrease blood loss. Possible burn of the bowel can be prevented by the assistant intermittently flushing cold water over the bowel. The Roux-en-Y limb fashioned at the Kasai operation should be kept as long and intact as possible. Hepatic arteries are transected as distal as possible to facilitate selection of a vessel of appropriate diameter for reconstruction. Usually, the wall of the hepatic artery is very fragile in small babies with biliary atresia. To prevent intimal dissection of the artery, holding, ligating, and cutting should be done gently. After transection of the hepatic arteries, the portal vein is

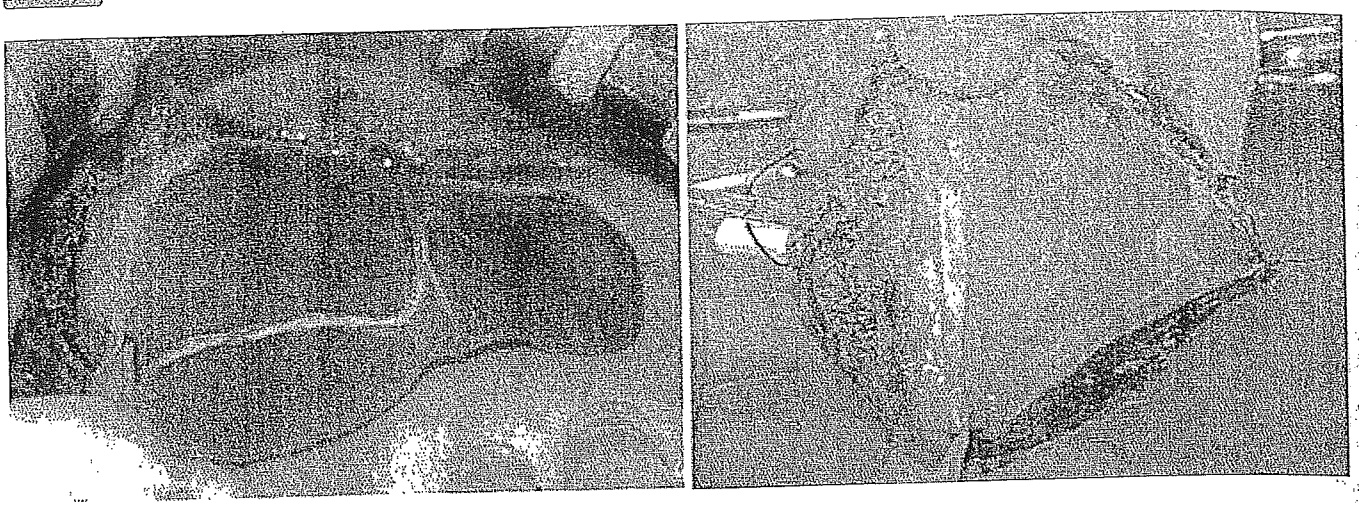

FIGURE 42–7
Reduced left lateral segment transplanted from the mother to her 3.5-kg 1-month-old boy. In this case, the left lateral segment was 200 g, and the transplanted graft was 140 g. **Left,** Marking the reduction on the surface of the left lateral segment. **Right,** After reduction, the graft weighs 140 g.

dissected and preserved untransected until the last phase of the hepatectomy. In LRLT, hepatectomy is performed with the IVC left intact. In patients without cirrhotic changes in the livers, as in those with metabolic diseases or fulminant hepatic failure, it is not difficult to dissect the retrohepatic space while preserving the IVC, even if the hepatic pedicle is not transected. This technique can reduce the clamping time of the portal vein as much as possible. However, in the case of cirrhosis, as in biliary atresia, transection of the hepatic hilum before dissection of the retrohepatic space makes hepatectomy very easy. In such a case, cutting the portal vein in the early phase of the hepatectomy does not usually cause severe congestion of the bowel because of the presence of so many preformed collateral vessels. In general, venovenous bypass or a temporary portosystemic shunt is not necessary in pediatric LRLT, regardless of the indication. After transection of the short hepatic veins, a blunt dissector can easily be passed through the avascular space just to the left of the right hepatic vein to encircle the root of the right hepatic vein (Fig. 42–8). Transection of the right hepatic vein followed by transection of the middle and left hepatic veins completes the hepatectomy.

Vascular Reconstruction

The two basic principles of vascular reconstruction are a "larger anastomosis and abundant flow."

Hepatic Vein

In LRLT, the retrohepatic IVC of the recipient is always preserved, and the graft's hepatic vein is anastomosed to the IVC in an end-to-side fashion. Typically, the left hepatic vein or the common trunk of the left or middle hepatic vein is anastomosed to the recipient side in left lateral segment or left lobe LRLT, respectively. When the hepatic vein has two orifices on the graft side, either reconstruction to make one hole or creation of two separate anastomoses between the two orifices is selected.[34] Anastomosis of a single hepatic vein is simple and safe. If two separate anastomoses are necessary, stumps of the middle hepatic vein and left hepatic vein or stumps of the right hepatic vein and trunk of the middle/left hepatic vein can be used on the recipient side.

When the trunk of the middle and left hepatic vein on the recipient side is used for anastomosis, the orifice is enlarged to a dimension adjusted for the size of the graft's hepatic vein by incising the IVC wall on the right side of the common trunk (Fig. 42–9). This procedure

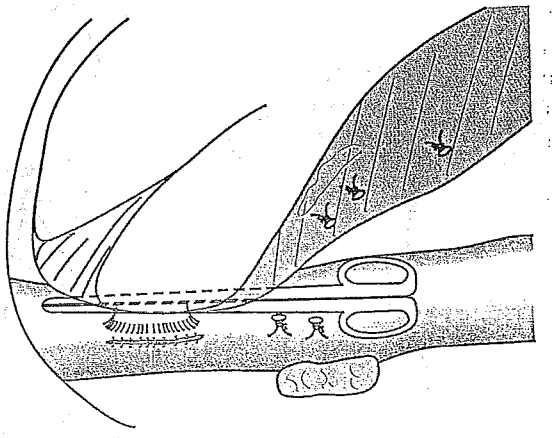

FIGURE 42–8
The final phase of dissection of the retrohepatic space in a recipient. A blunt dissector can be passed through the avascular space just to the left of the right hepatic vein to ensure safe encircling of the root of this vein.

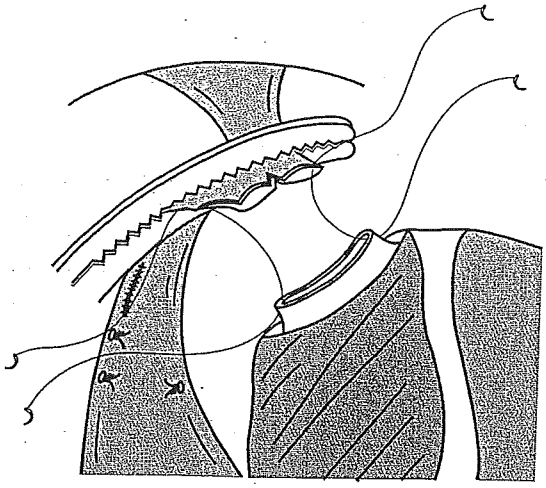

FIGURE 42-9

Hepatic venous anastomosis using the stump of the middle and left hepatic veins. The right edge of the middle hepatic vein is incised to enlarge the orifice to a dimension in keeping with the size of the graft hepatic vein. This technique fixes the graft to the wall of the inferior vena cava itself and is helpful in preventing rotation of the graft.

fits the graft directly to the wall of the IVC and is helpful in preventing rotation of the graft around the axis made by the hepatic vein pedicle.[35] Triangular anastomosis is recommended by Emond and coworkers for creation of a large anastomosis with good fixation of the graft to the IVC wall.[36] End-to-end anastomosis after reconstruction of the recipient's hepatic venous stump is reported to be an easy and safe method by Makuuchi and Sugawara.[37] To prevent restriction of outflow secondary to torsion on the graft, the vascular pedicle should be short. In patients with biliary atresia, the retrohepatic IVC may be incorporated into the severely hypertropic hepatic parenchyma. In patients with situs inversus or polysplenia syndrome, the retrohepatic IVC may be completely absent. In such cases, the hepatic vein of the graft is anastomosed in an end-to-end fashion with complete clamping of the suprahepatic IVC (Fig. 42–10). Venovenous bypass is also not usually necessary in these cases because of good collaterals.

Portal Vein

In pediatric LRLT, portal vein reconstruction is one of the crucial elements for success. In cases of biliary atresia, the portal vein of the recipient is commonly sclerotic and hypoplastic. In such cases, some augmentation of the portal vein is necessary to secure abundant flow.[38] The presence of hepatofugal flow in the portal vein before transplantation indicates a greater possibility that augmentation will be needed. Many methods have been used for such procedures, including donor autologous or homologous grafts. Usually, the segment of portal vein distal to the confluence of the superior mesenteric and splenic veins is replaced by an interposition graft or augmented with a patch graft. Another important point in reconstruction of the portal vein is alignment of the axis of anastomosis. For this purpose, we use curved forceps inserted into the graft's portal vein to determine the direction (Fig. 42–11). The axis of the recipient's side is oriented by placement of the clamp. The anastomosis is usually created with a two-stay suture technique. If the calibers are very different, a four-stay suture technique is

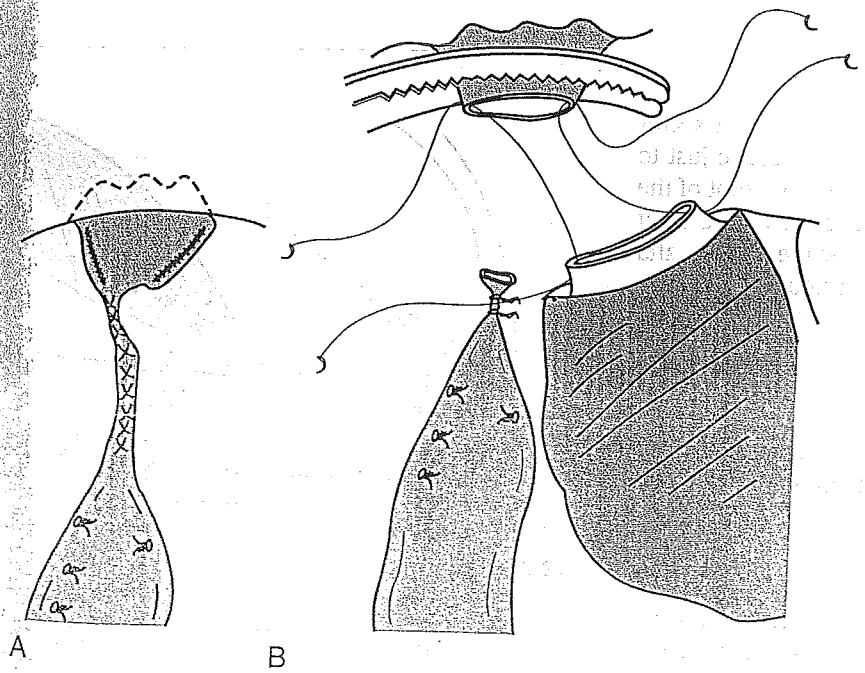

FIGURE 42-10

End-to-end anastomosis of the hepatic vein in a patient with a hypoplastic retrohepatic inferior vena cava (IVC). A, Before transection of the IVC. B, End-to-end anastomosis.

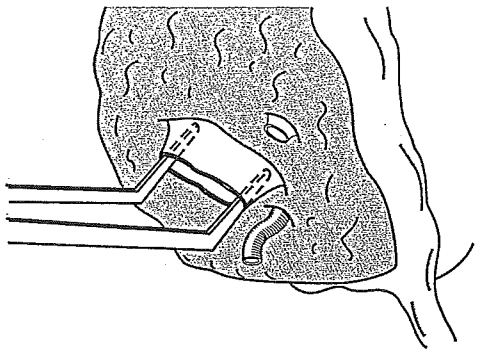

FIGURE 42–11

To clarify the direction of the graft-side portal vein, curved forceps are inserted while closed and then opened while pulling out a little. This technique can be used to determine the horizontal direction of the graft portal vein, even if it is quite short.

recommended. When the diameter is larger than 10 mm, creation of an anastomosis with running 6–0 monofilament suture is easy and fast. If the diameter is smaller, partly or completely interrupted suture is recommended.

Hepatic Artery

Microsurgical technique is recommended for reconstruction of the hepatic artery in pediatric LRLT. Such technique could reduce the incidence of hepatic arterial thrombosis.[39] In pediatric LRLT, establishing an adequate surgical field for reconstruction of the hepatic artery is difficult when the graft is relatively large because the graft covers the surgical field. Holding the graft with a malleable blade fixed to the head arch is very useful for ensuring adequate exposure of the surgical field (Fig. 42–12). Generally, the diameter of the hepatic artery in a cirrhotic recipient is large enough, and its size is compatible with the arterial size of a graft from an adult donor. However, in noncirrhotic cases, the size discrepancy is usually large. The branch patch technique and tapering can be used to adjust the size. End-to-side anastomosis should be avoided because of the high incidence of hepatic arterial thrombosis as a result of turbulence. If the artery on the graft side bifurcates near the anastomosis, it may also cause turbulence after anastomosis. In such cases, the branching artery is transected, and the dominant artery is anastomosed first (Fig. 42–13). If two or more arteries are present, the most dominant one is anastomosed first. Then backflow from the others is checked. If backflow is good and pulsatile, the other artery or arteries can be safely ligated. If backflow is not sufficient, additional anastomosis is necessary. When multiple anastomoses are expected from the findings during the donor operation, at least two orifices should be prepared during hepatectomy of the recipient. The suture material is 8–0 or 9–0 nonabsorbable monofilament, and as little tension as possible is placed on the anastomosis. If the recipient side has some tension, the gastroduodenal artery can be divided to elongate the stump on the recipient side. As an alternative to the proper or common hepatic artery, the stump of the splenic or gastroduodenal artery can be used. In cases requiring an interposition graft, a segment

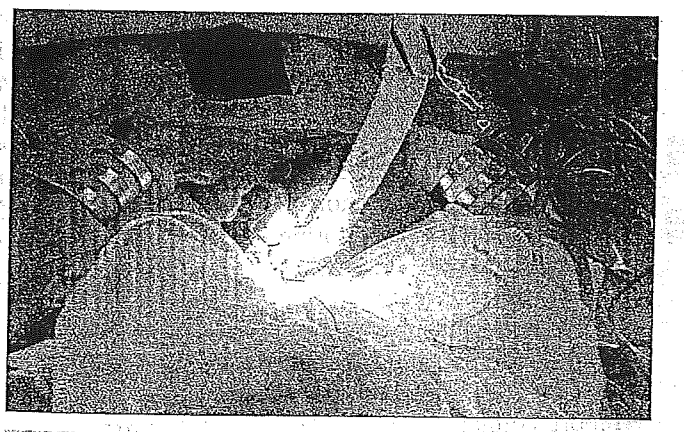

FIGURE 42–12

Establishing an operative field for microsurgical reconstruction of a hepatic artery in a small child undergoing living related liver transplantation. Gentle, but secure, fixation of the graft after reperfusion through the portal vein is necessary for good field exposure.

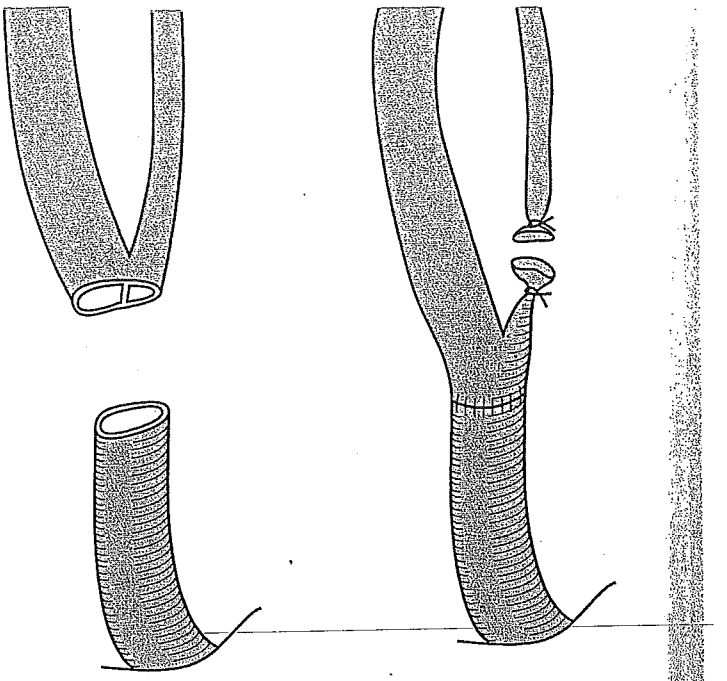

FIGURE 42–13

Anastomosis of the artery in the case of bifurcation just distal to the stump on the graft side. The branch is transected, and the dominant artery is first anastomosed to the recipient side. Usually, good backflow is obtained from the other stump, which indicates that a second anastomosis is not necessary.

of autologous inferior mesentery artery or radial artery can be harvested and used.

Bile Duct Reconstruction

In biliary atresia, the bile duct of the graft is anastomosed to the previously existing or newly made Roux-en-Y limb. Regarding bile duct reconstruction, there are still many controversial issues, such as the suture material, use of an inside or outside knot, continuous or interrupted sutures, and so on. If the bile duct of the recipient can be used in those with metabolic diseases or fulminant hepatic failure, duct-to-duct anastomosis is possible in pediatric as well as adult cases. In infants, the bile duct on the recipient side is very fragile and thin. The blood supply to the distal tip of the recipient's bile duct should be carefully preserved without dissecting the connective tissue around the common bile duct.

Surgical Complications and Treatment of Recipients

Early Complications

Early surgical complications specific for pediatric LRLT are problems related to large-for-size grafts, small vessels for reconstruction, and gastrointestinal tract injury, especially after a failed Kasai procedure for biliary atresia (Table 42–6). Primary nonfunction is quite rare in LRLT.

Table 42–6. RECIPIENT COMPLICATIONS IN PEDIATRIC LIVING RELATED LIVER TRANSPLANTATION

Early
Hemorrhage (intra-abdominal and intestinal)
Vascular complications
Hepatic arterial thrombosis
Hepatic vein stenosis or torsion
Portal vein stenosis
Gastrointestinal complications
Bowel perforation
Anastomotic leakage
Poor perfusion of the graft ("large-for-size" problem)
Late
Vascular complications
Portal vein stenosis
Hepatic vein stenosis
Biliary complications
Biliary stricture at the anastomotic site

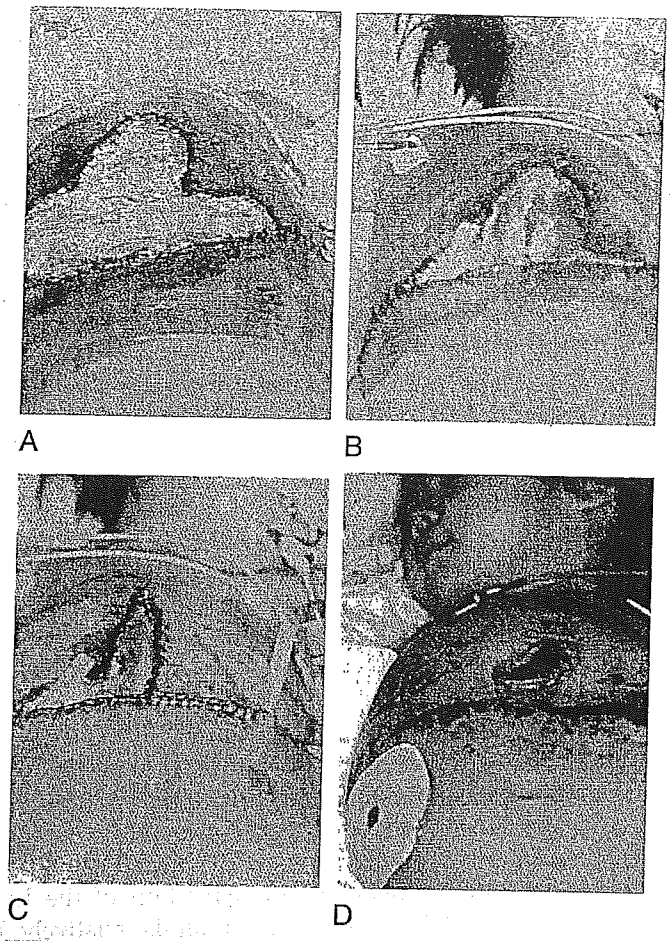

FIGURE 42–14

Closure of the abdominal cavity after transplantation of a large graft. The abdomen could be closed without a prosthesis by performing serial operations over the period of a month. **A**, Just after surgery; **B**, after 7 days; **C**, after 14 days; **D**, after 1 month.

When the graft is relatively large, portal vein inflow may be partly or completely interrupted as a result of the high pressure on the graft after closure of the abdominal wall. Skin closure is performed or artificial mesh is applied in these cases (Fig. 42–14). Artificial mesh or a prosthesis is not strongly recommended because it may add a source of postoperative infection. Skin closure may be safer. Trial closure and monitoring of flow by Doppler ultrasound may be helpful in choosing between primary and secondary abdominal closure.

After the routine use of microsurgical techniques was introduced, the incidence of hepatic arterial thrombosis was 2.4% (8/332) in a large series of LRLT.[40] In a recent report comparing pediatric and adult LRLT, the incidence of hepatic arterial thrombosis in pediatric patients was 0% as opposed to 4% in adults.[41] The most dangerous arterial injury is intimal dissection on the graft or the recipient side (or on both). If intimal dehiscence occurs on the recipient side, the artery must be

traced proximally to obtain an intact wall and good forward flow for safe construction of an anastomosis.

The basic principle in treating hepatic arterial thrombosis in LRLT is reanastomosis to salvage the original graft. Early detection of hepatic arterial thrombosis is essential for successful re-reconstruction. Doppler ultrasonography is performed at least three times a day during the first 7 days and two times daily during the subsequent 7 days. If the signal is detectable but shows poor flow, anticoagulant therapy is increased, and administration of systemic urokinase (60,000 IU/6 hr as a continuous intravenous infusion) is mandatory. Emergency angiography and arterial infusion of a thrombolytic agent such as urokinase may be implemented. Complete disappearance of the arterial signal within the first 10 days necessitates urgent reanastomosis, even though there are no signs of hepatic necrosis on imaging studies or biochemical analysis. Angiography before repeat surgery is skipped to save time. At repeat surgery, quick disruption of the anastomosis should be performed to stop progression of the thrombosis. Good backflow from the graft-side artery after irrigation with a fine soft catheter (24 or 28 gauge) is an encouraging sign for possible success of the reanastomosis. When no arterial signal is detected on Doppler 10 days after LRLT and no signs of hepatic necrosis are apparent, close observation without any intervention can be performed. In such cases—and even in cases in which the reanastomosis was not successful—the graft may survive by portal perfusion and later rearterialization by spontaneously formed collaterals.[42] This route is through the diaphragmatic artery or the mesenteric artery of the Roux-en-Y limb. Even in these "spontaneously recovered" cases, intrahepatic or extrahepatic biliary stricture may subsequently occur several months later.

Biliary complications are more common after LRLT than after whole-liver transplantation. Such complications are not specific for pediatric LRLT. Bile leakage from the hepaticojejunostomy in the immediate early postoperative period may be fatal as a result of peritonitis and sepsis. Early diversion of the limb to prevent reflux of amylase-rich bowel contents is recommended (Fig. 42–15). Bowel injury during vigorous adhesiolysis is also a common complication of pediatric LRLT after a failed Kasai procedure for biliary atresia. Fasting and drainage are not usually sufficient to control infection. Exteriorization of the perforation site may be necessary.

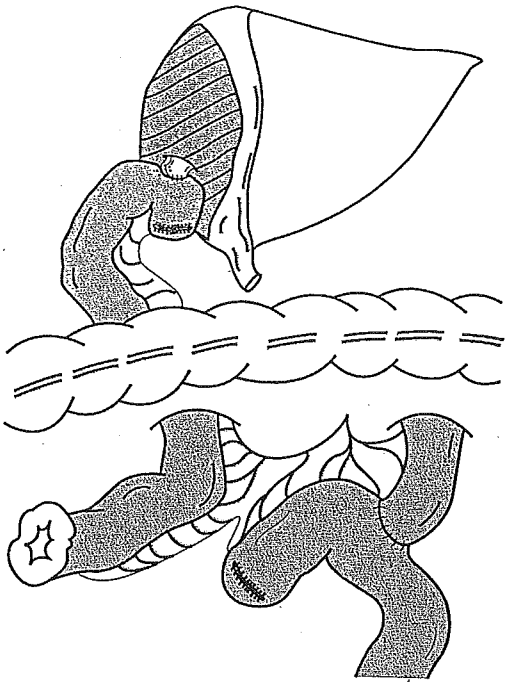

FIGURE 42–15

Diversion of the Roux-en-Y limb in the event of anastomotic dehiscence of the hepaticojejunostomy. The stoma can be taken down after healing of the leakage.

Late Complications

Late complications after pediatric LRLT include hepatic vein stenosis, portal vein stenosis, and biliary stricture (see Table 42–6). These complications are not specific for pediatric LRLT and are relatively common, as in deceased donor partial-liver transplantation.

Torsion or compression of the hepatic venous cuff by the enlarging liver may cause hepatic vein stenosis after several months or a few years. A long cuff may be associated with a higher incidence of such complications. The symptoms of hepatic vein stenosis are ascites, a low albumin level, and a decreased platelet count. Doppler ultrasound shows a dilated hepatic vein with low flow velocity inside the liver and jet flow at the confluence to the IVC. In catheter angiography, imaging with contrast dye enhancement and pressure study through the anastomotic site can confirm the diagnosis. The catheter is inserted via the transhepatic route (normograde) or the IVC route (retrograde). Balloon dilatation has been highly successful. Repeated dilatation may be necessary, and placement of an expandable metallic stent is required in these cases. For possible retransplantation in patients with hepatic fibrosis secondary to graft congestion despite conservative procedures, the location of the stent should be chosen cautiously and in a manner that does not interfere with any reoperation if such becomes necessary.[43,44]

On occasion, portal stenosis is a late complication after pediatric LRLT. Portal vein thrombosis is usually associated with stenosis. Reconstruction using the venous conduit is reported to be associated with a higher incidence of stenosis, although there is no definite evidence.[43]

The symptoms are those of portal hypertension—ascites and thrombocytopenia. Doppler ultrasonography can be used to diagnose stenosis by detection of narrowing of the lumen, poststenotic dilatation, and a jet flow with damping of the flow velocity. If the thrombus is already formed, the lumen cannot be detected by B-mode ultrasonography. If portal flow in the liver is detectable by ultrasound, percutaneous transhepatic portography is the first choice for diagnosis and treatment. A catheter inserted transhepatically is passed through the stenosis or thrombus to the proximal side, and contrast dye flushed from the catheter can show the lesion. Balloon dilatation is the first line of treatment of the hepatic vein.[43] If it successful, surgical thrombectomy plus re-reconstruction is clinically feasible, although it is not easy. Even though portal flow is not detected in the liver, initially the patient may not have any symptoms. However, symptoms of a portosystemic shunt or portal hypertension become prominent later. In such cases with difficult re-reconstruction, retransplantation is indicated.

Late-onset biliary stenosis does not present any specific problems in pediatric LRLT. Because the original anastomosis is mainly a hepaticojejunostomy, intervention through endoscopic retrograde cholangiopancreatography is not possible. Usually, percutaneous transhepatic cholangiodrainage (PTCD) under ultrasound guidance is first selected. Balloon dilatation through this route is commonly used. If not effective after repeated trials, stenting is also possible. Revision after long-term follow-up is not very difficult. If balloon dilatation is not easy or not very effective, it is better to proceed to reanastomosis than to risk any incidental complications caused by interventional procedures.

Repeat Living Related Liver Transplantation in Pediatric Recipients

In the initial experience with LRLT, there was hesitancy about performing repeat LRLT (re-LRLT) after failure of LRLT. It is generally difficult to find another proper donor because the selection range is limited within the closed family. Of course, if a deceased donor is available, it is reasonable to list the patient as an urgent case. Discussing the possibility of re-LRLT when the availability of a deceased donor is not expected may place great pressure on the family. However, if they are not told all of the options, the recipient may progress along the worst course before the family recognizes the necessity for retransplantation. The possibility of re-LRLT should be included as one of the general issues in the informed consent in the initial LRLT. If the recipient is a child, the range of selection of a second donor is wider than for adults. Parents, grandparents younger than 65 years, and uncles or aunts can be included as candidates.

The most common indication for re-LRLT is chronic rejection (Table 42–7). Recurrence of the original disease is rare after pediatric LRLT. However, in the Kyoto experience, young children undergoing LRLT for fulminant hepatic failure have a higher incidence of further massive hepatic necrosis requiring re-LRLT, although it is difficult to differentiate from severe rejection.[45] Naturally, re-LRLT presents greater technical difficulty than the initial procedure does. The overall survival rate after re-LRLT in Kyoto is less than 40%. Early retransplantation is performed if the recipient's condition is poor, and the result is worse than when it is done after a long period (see Table 42–7).

Immunosuppression

Tolerance

After liver transplantation, complete weaning of immunosuppression has been reported to be possible in select cases. In pediatric LRLT, immunosuppression could initially be reduced or the patient weaned because of complications or noncompliance. After confirmation of the possibility of complete withdrawal in such incidental cases, protocols for weaning were developed.[46] During the protocol trial, 25% of the post-LRLT pediatric recipients enrolled in the study could be completely weaned off immunosuppressants for a median of more than 21.9 months.[47] The tentative protocol for weaning is shown in Figure 42–16, and criteria for use of the protocol are listed in Table 42–8. Predicting the possibility of acquiring tolerance is not yet possible.

ABO Incompatibility in Pediatric Living Related Liver Transplantation

ABO-incompatible matching cannot be avoided in countries in which LRLT is the main method of liver transplantation. The outcome after LRLT depends on the age of the recipient. In the pediatric group younger than 1 year, the posttransplant survival rate is comparable to that of the equivalent ABO-matched group of adults.[40] In the experience at Kyoto University, the outcome of ABO-incompatible LRLT in infantile patients is almost the same as that of ABO-compatible LRLT in the same age group (unpublished data). Therefore, in recipients younger than 1 year, the immunosuppression regimen after ABO-incompatible matching is similar to that after compatible matching, except for a procedure to decrease the anti-AB antibody titer before transplantation, such as blood or plasma exchange. In pediatric recipients older than 7 years, innovations in immunosuppression, including intraportal infusion, may be effective, as in adult cases.[48]

Table 42–7. REPEAT LIVING RELATED LIVER TRANSPLANTATION IN PEDIATRIC RECIPIENTS (KYOTO UNIVERSITY 1990–2003)

Age at re-LRLT	Original Indication	Indication for re-LRLT	1st Donor	2nd Donor	Time after 1st LRLT (yr.mo.day)	Outcome
11	BA	SFS	Mother	Father	0.0.2	Dead
9 mo	FHF	Massive necrosis	Grandfather	Grandmother	0.0.24	Alive
8	BA	Massive necrosis	Father	Mother*	0.1.0	Dead
1	FHF	Massive necrosis	Mother	Father	0.1.0	Dead
1	FHF	Massive necrosis	Mother	Father*	0.1.0	Dead
2	BA	CR	Father	Mother	0.1.0	Alive
12	BA	Massive necrosis	Mother	Father	0.2.0	Dead
2	BA	CR	Father	Mother	0.3.0	Dead
1	BA		Mother	Grandmother	0.3.0	Dead
1	BA	CR	Mother	Father*	0.4.0	Dead
5	Alagille syndrome	Cholestasis	Mother	Grandfather	0.6.0	Dead
4	Glycogen storage disease	CR	Mother	Father*	0.6.0	Dead
3	BA	CR	Mother	Father*	1.0.0	Alive
2	BA	HV stenosis	Father	Mother	1.0.0	Dead
4	BA	CR	Mother	Father	1.4.0	Alive
3	BA	CR	Father	Grandmother	2.6.0	re-re-LRLT
9	LC	CR	Father	Mother	3.0.0	Alive
15	BA	CR	Father	Mother	3.1.0	Dead
17	BA	CR	Mother	Domino	4.0.0	Dead
6	BA	Cholangitis	Mother	Father	4.7.0	Alive
16	BA	Massive necrosis	Mother	Aunt	5.8.0	Alive
15	BA	CR	Father	Mother*	5.8.0	Dead
7	BA	HV stenosis	Mother	Father*	6.0.0	Alive
9	BA	FHF	Father	Mother	8.7.0	Dead
11	BA	CR	Mother	Father	11.5.0	Alive

*ABO-incompatible donor.
BA, biliary atresia; CR, chronic rejection; FHF, fulminant hepatic failure; HV, hepatic vein; LC, liver cirrhosis; SFS, small for size.

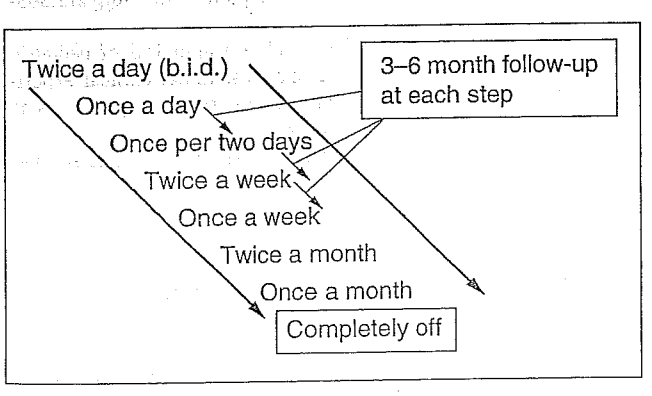

FIGURE 42–16
Protocol for weaning from tacrolimus immunosuppression.

Table 42–8. CRITERIA FOR PROTOCOL WEANING

Longer than 2 years after liver transplantation
Normal liver function
No episode of rejection during the previous year
Evidence of medical compliance
Cooperative local physician for follow-up

Pearls and Pitfalls

Pearls

- Obtain informed consent detailing the risk to the donor, including mortality, before performance of LDLT.
- Minimal handling of the vascular pedicle and the graft itself is necessary in both the donor and recipient operations.
- A flat and straight line should be used for transection of hepatic parenchyma in the donor operation.
- The Arantius duct should be completely transected at its confluence with the left hepatic vein when harvesting the left lobe from the donor.
- The bowel should be cooled by flushing of water during enterolysis by electrocautery.
- Good flow through the portal vein should be confirmed before the graft is inserted.
- In any vascular reconstruction, a stoma as large as possible with flow as abundant as possible is strongly recommended.
- Interrupted suture is recommended in patients with a small portal vein.
- A microsurgical technique of hepatic arterial reconstruction should be used.
- Reconstruction of the dominant artery may be sufficient without reconstructing other arteries in patients with multiple arterial supply to the graft.
- If possible, a duct-to-duct anastomosis is safe and also useful in pediatric LDLT.
- Blood flow should be confirmed by Doppler ultrasonography just after closure of the abdomen and before exiting the operation room.
- A regular (bimonthly) checkup of the grafted liver by Doppler ultrasonography should be performed in the posttransplant outpatient clinic for early detection of vascular and biliary anastomotic stenosis.
- Lifelong follow-up is necessary, especially for pediatric LDLT.

Pitfalls

- Ignorance of the subclinical phenotype in a donor candidate with inheritable diseases such metabolic disorders, Alagille syndrome, or Caroli's disease.
- In HLA matching, a graft from a homozygous donor to a heterozygous recipient.

Pearls and Pitfalls—cont'd

- Unrepaired physical injury in the bowel of the recipient.
- Graft larger than 5% of the recipient's body weight.
- Hesitation regarding portal vein augmentation before insertion of the graft in recipients with sclerotic or thrombotic changes in the portal vein.
- End-to-side anastomosis of the artery may result in a higher incidence of hepatic artery thrombosis.
- In patients in whom hepatic artery thrombosis occurs within 10 days of the operation, waiting until an increase in transaminases occurs will make saving the graft hopeless.
- Bilioenteric dehiscence or intestinal perforation after transplantation requires a more aggressive surgical intervention than simple drainage and fasting.

Acknowledgment

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Magnet Compression Anastomosis for Bile Duct Stenosis After Duct-to-Duct Biliary Reconstruction in Living Donor Liver Transplantation

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A 44-year-old woman who had undergone living donor liver transplantation for fulminant hepatic failure presented obstructive jaundice 1 year after transplantation. A right lobe from her husband had been used for the original graft. Intraoperative cholangiography of the donor showed the bile duct of posterior inferior segment (B6) branching from the bile duct of anterior segment (Fig. 1). The bile duct of the donor was transected in the very short segment of the common trunk of the posterior and anterior branches of the right lobe. The orifice of the bile duct of the graft was single, but the shape of it was like the nose of a pig. This single orifice was anastomosed to the stump of the recipient's common hepatic duct. A biliary stent tube (4-French-sized) was inserted into only the bile duct of the posterior segment. Cold- and warm-ischemia time was 42 and 45 minutes, respectively. She initially recovered uneventfully in the early period after liver transplantation. The external stent tube was removed 3 months after the transplantation.

Laboratory data at 11 months after the transplantation showed slight elevation of transaminases (aspartate aminotransferase: 80 IU/L, alanine aminotransferase: 100 IU/L) and total bilirubin (1.4 mg/dL). One month later, ultrasonography showed the dilated intrahepatic duct. Endoscopic retrograde cholangiography and percutaneous transhepatic cholangiography disclosed the complete obstruction of the anterior branch (Fig. 2). The dilated duct was drained by the percutaneous transhepatic cholangiography drainage tube. Balloon dilatation was attempted though the percutaneous transhepatic cholangiography drainage tube, but it was

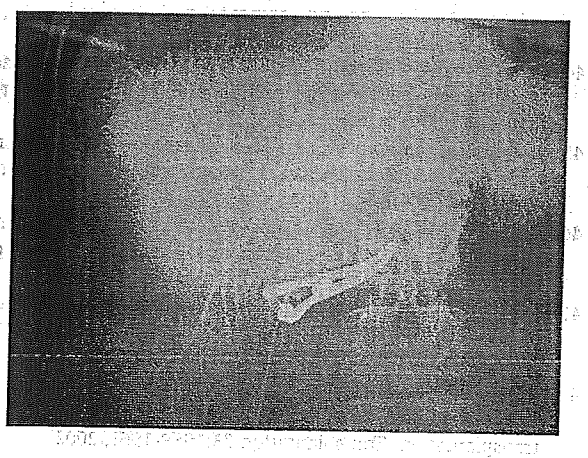

Figure 1. Intraoperative cholangiogram of the donor in the initial living donor liver transplantation. Bile duct of posterior inferior segment (B6) branching from the bile duct of the anterior segment

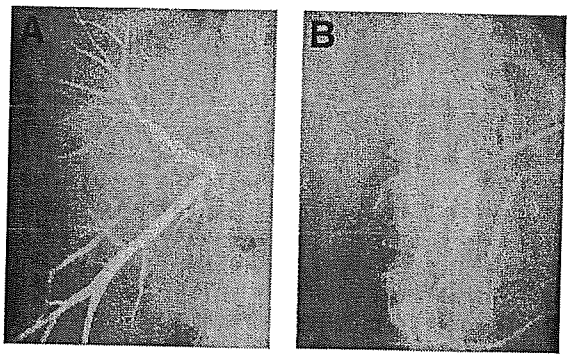

Figure 2. (A) Percutaneous transhepatic cholangiography showed complete biliary obstruction of the anterior branch. (B) Endoscopic retrograde cholangiography could not show the anterior branch.

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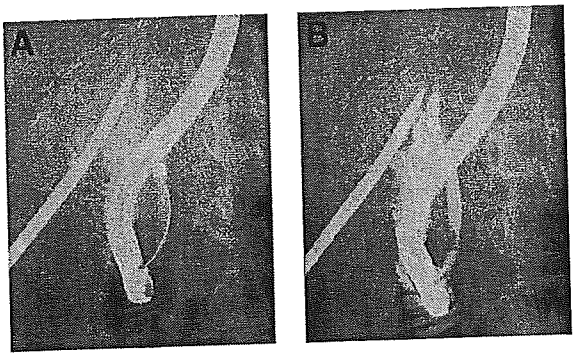

Figure 3. Placing of the parent magnet. (A) A parent magnet (diameter 4 mm) attached to a guide with covered tube was placed endoscopically through the papilla Vateri that was enlarged enough with endoscopic sphincterectomy at supine position. (B) The parent magnet was placed at the stricture point.

not possible because the guidewire could not pass the stenosis. Relaparotomy with choledochojejunostomy was considered, but the patient strongly preferred the nonsurgical procedure. That is why the magnet compression anastomosis was applied.

Magnet Compression Anastomosis

As preparation for the procedure, the percutaneous transhepatic cholangiography drainage tube had been gradually dilated by 2-French-size every week from 8 French to 18 French. The papilla Vateri had been also enlarged by the endoscopic sphincterectomy, A minor tranquilizer (diazepam 10 mg) was given to the patient prior to the procedure. The parent magnet (diameter 4 mm) attached to a guide with a covered tube was inserted into the common bile duct and placed at the common bile duct side of the stricture (Fig. 3). A 16-French-sized sheath tube was inserted through the dilated percutaneous transhepatic cholangiography drainage fistula, and the daughter magnet attached to a guide wire was inserted to the intrahepatic duct (Fig. 4A-B). The 2 magnets were immediately attracted toward each other, sandwiching the stricture (Fig. 4C) (Yamauchi

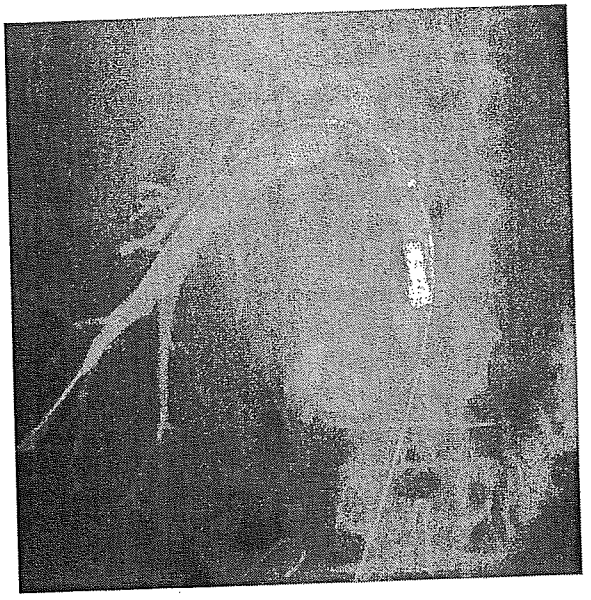

Figure 5. Reanastomosis was established by day 42 after magnets were inserted.

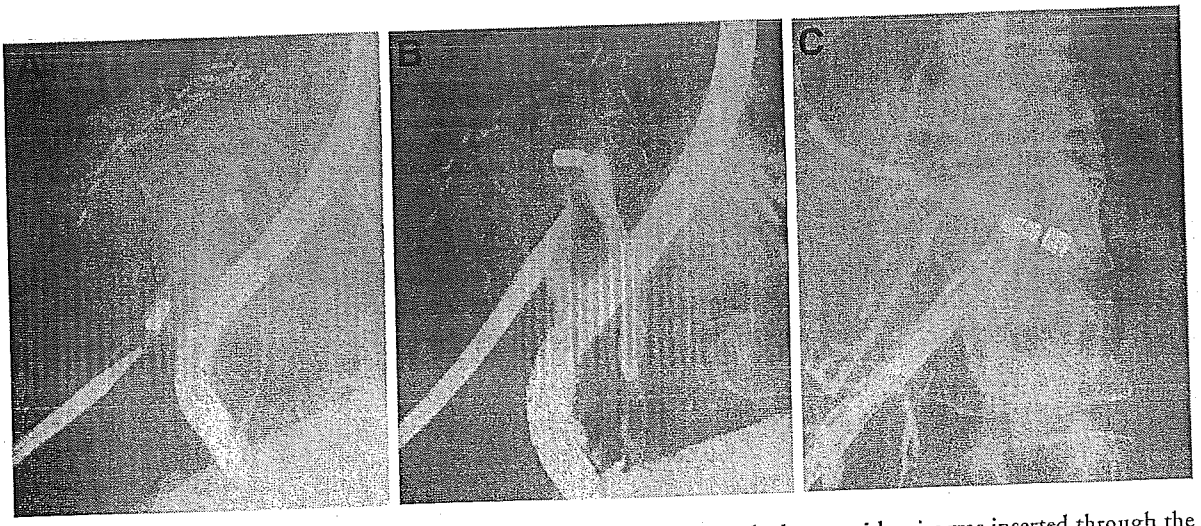

Figure 4. Placing of the daughter magnet. (A) The daughter magnet attached to a guide wire was inserted through the sheath tube. (B) The daughter magnet was placed into the obstructed intrahepatic duct. (C) The 2 magnets were immediately attracted toward each other.

procedure[1,2]). The sheath tube was removed and changed to the indwelling porous percutaneous transhepatic cholangiography drainage tube. Establishment of the reanastomosis was assured by day 42 with radiological examinations (Fig. 5). The indwelling drainage tube was pushed and was inserted down to the common bile duct through the anastomosed stoma, as the internal stent tube maintained the patency. The stent tube was removed 3 months later. There has been no recurrence of the stricture in the 15 months of follow-up after the creation of the new stoma.

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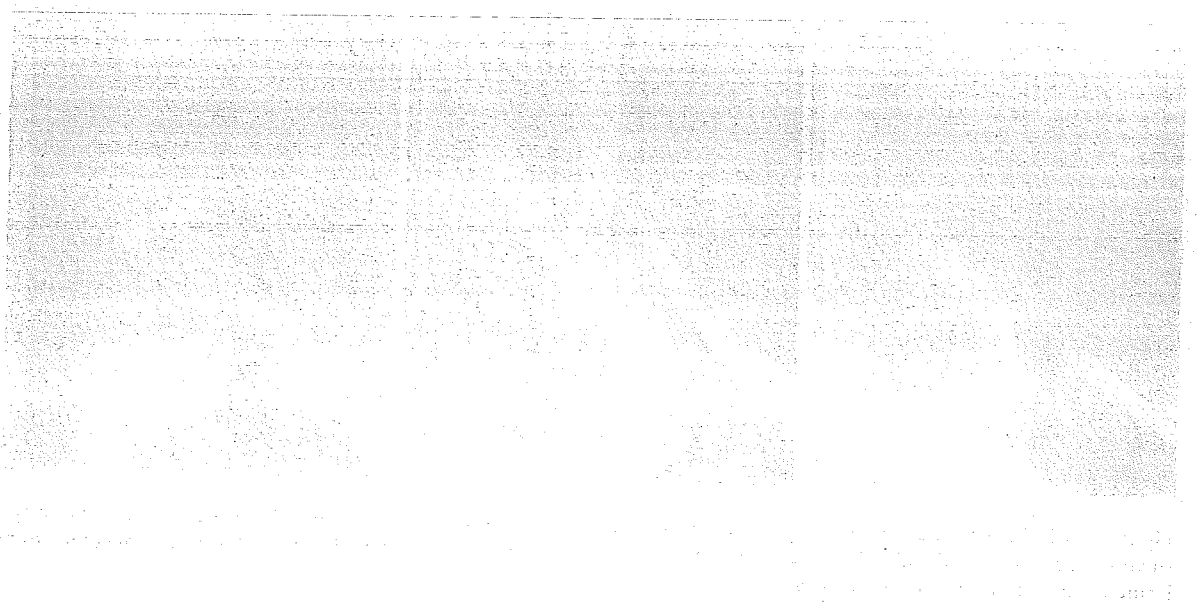

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Hepatitis B virus infection in lymphatic tissues in inactive hepatitis B carriers

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***Background/Aims*: Hepatitis B virus (HBV) infection in extrahepatic tissues is controversial. To clarify whether episomal HBV can infect nonhepatic tissues, we investigated the molecular forms of HBV in the lymphatic cells of inactive HBV carriers who lacked viremia, thus avoiding contamination with HBV genomes originating from the viral particles present in the serum.**

***Methods*: We assessed HBV genome, replicative forms, and viral integrants in the liver, serum, peripheral blood mononuclear cells (PBMC), and lymph nodes of 21 inactive HBV carriers who tested positive for antibodies against the HBV core antigen (anti-HBc).**

***Results*: Of the 21 anti-HBc positive individuals, HBV-DNA was detected in liver samples of 15 (71.4%), in the lymph nodes of 11 (52.4%), and in PBMC of three (14.3%). However, none of the detected HBV genomes from lymphatic tissues included the replicative forms of HBV. In one case, integrated HBV was present in the lymphatic tissues and the host–viral junction was present in the intronic sequences of chromosome 17.**

***Conclusions*: These data suggest that human lymphatic tissues cannot support viral replication in anti-HBc positive inactive HBV carriers, while retaining the viral genome as an integrated form.**

Keywords: **HBV; Latent infection; Occult HBV; PBMC; cccDNA; Lymph node**

1. Introduction

Hepatitis B virus (HBV) is a partially double-stranded DNA virus belonging to the Hepadnaviridae family [1,2]. Hepadnaviruses are characterized by their hepatotropic features and have a strong preference for infecting hepatocytes, although small amounts of hepadnaviral DNA is found in extrahepatic organs [2]. The existence of extrahepatic replication of HBV is controversial [3–15]. Several previous studies have suggested the presence of replicative intermediate forms of HBV in extrahepatic organs [4–6,14]. For example, viral mRNA and covalently closed circular DNA (cccDNA) were detected in peripheral blood mononuclear cells (PBMC) of highly viremic patients by PCR-based methods [14]. In contrast, others have demonstrated that human PBMC cannot be infected with HBV in vitro and in vivo [15]. Most of those studies tested the PBMC of HBV carriers who were positive for hepatitis B surface antigen (HBsAg) and/or HBV-DNA in the serum. However, in HBV carriers with circulating viral particles, the possibility that the detected viral genomes were attributed to viruses that had only adsorbed to the cells could not be completely excluded [15].

We recently demonstrated that occult HBV maintains persistent infection in the livers of individuals who have

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antibody to hepatitis B core antigen (anti-HBc), but not HBsAg without causing any clinical liver dysfunction [16]. Because HBV is frequently transmitted to liver transplant recipients from anti-HBc positive and HBsAg-negative donors, there is growing recognition that most anti-HBc positive healthy individuals have latent HBV infection in their liver tissues [16–21]. Moreover, we and other researchers have shown the reactivation of latent HBV infection in some leukemia patients under newly introduced immunosuppressive therapy or after bone marrow transplantation [22–26]. These findings suggest that most healthy individuals who are positive for anti-HBc have latent infections as the episomal form of HBV. Importantly, active HBV replication was found in the liver tissue of latent HBV carriers without any detectable HBV-DNA in their serum [16].

The aim of this study was to clarify whether episomal HBV infection can occur in extrahepatic tissues. We nvestigated the molecular forms of HBV in the lymph iodes and PBMC of latent HBV carriers who lacked 'iremia. We chose these subjects to exclude the possibility of contamination by HBV genomes originating from the 'iral particles present in the serum. Our findings showed iat the HBV genome could be present in the lymph nodes nd PBMC of latent HBV carriers, although these human ymphatic tissues lack the ability to support viral replication.

. Patients and methods

1. Patients

Between April 5, 1996 and August 22, 2003, 724 patients underwent ing-donor liver transplantation (LDLT) at Kyoto University. Before rgery, the liver function of all donors was examined by blood chemistry d serological analyses of HBV markers including HBsAg, antibodies to 3sAg, anti-HBc, hepatitis B e antigen(HBeAg), and antibodies to HBeAg ing commercial enzyme immunoassay kits as described previously [27]. the original 724 patients, 103 donors (14.2%) were positive for anti-HBc d negative for HBsAg. From these 103 patients, the liver tissues, lymph des, PBMC and serum of 21 donors were available for further analyses. ese 21 anti-HBc positive individuals included 10 men and 11 women, ed 24 to 63 years (mean age, 43.4 years). None had a history of liver sfunction, blood transfusion, drug abuse, or family history of HBV ection. From the remaining 621 donors without any HBV markers, 10 re randomly selected as the negative control group (six men and four men). None of the donors enrolled in this study was positive for HBV-IA in their sera at the time of operation. All subjects provided written ormed consent and the study was conducted in accordance with the nciples of the Declaration of Helsinki.

2. Tissue samples

Liver tissue samples were obtained at the time of transplantation, frozen nediately, and stored at −80 °C until use. Blood samples were obtained ore surgery, and samples from the lymph node in the hepatoduodenal ment were taken by biopsy during the operation. DNA was extracted n the liver tissue, lymph node, and serum using procedures as described viously [28]. DNA extraction from the PBMC was performed using the e Trapping by Liquid Extraction kit (Takara, Tokyo, Japan) according ne manufacturer's protocol.

2.3. PCR amplification of HBV-DNA

HBV-DNA was amplified by nested or semi-nested polymerase chain reaction (PCR) using AmpliTaq Gold (Perkin–Elmer Cetus, Norwalk, CT) [16]. Primer sets for amplification of the S, pre-S, Core(C) /pre-C, and X regions have been described previously [28]. We defined a sample as HBV-DNA positive when amplification products were detected in two or more of four regions in the same sample in three or more independent experiments. As a positive control, DNA samples were prepared from liver tissues of patients with hepatocellular carcinoma (HCC) who were positive for HBsAg. As negative controls, PCR was performed using DNA samples extracted from liver tissues of healthy donors without any HBV markers, PCR buffer without DNA, or water only.

2.4. Selective detection of cccDNA and pregenomic RNA of HBV

To detect the cccDNA forms of HBV-DNA, PCR amplification was performed using DNA samples treated with mung bean nuclease and primer sets specific for the X region spanning DR1 and DR2 across the gap of the relaxed circular DNA (rcDNA). Mung bean nuclease cleaves a part of the single stranded gap and triple stranded region selectively. Thus, the sequences around the DR region in HBV rcDNA are expected to be digested by this nuclease [29]. In contrast, the digestion with mung bean nuclease prior to PCR amplification does not affect the same region of cccDNA [16]. In addition, to enhance the efficiency of cccDNA amplification, cellular DNA samples were digested with EcoRI (5 U) at 37 °C for 2 h before the PCR analysis [30]. Isolation of total RNA from lymphatic and liver tissues, RT-PCR, and southern blotting analyses were performed as described previously [16].

2.5. Detection of the integrated form of HBV-DNA

To discriminate the integrated viral DNA from the episomal HBV-DNA forms, the host genomic DNA (high molecular weight fraction; HMW) was separated from the low molecular weight fraction by applying the modified alkali-lysis procedure used to isolate plasmid DNA, as previously described [16]. Inverse-PCR is based on the digestion of DNA with certain restriction enzymes and circularization of cleavage products before amplification using primers synthesized in the opposite orientation to those normally employed for PCR [31–34]. As amplification of the S region of HBV-DNA was found to be the most sensitive among the four sets of primers for the HBV genome, selective digestion of the HBV-S region was performed using the restriction enzyme DdeI or RsaI followed by the amplification of this fragment using inversely designed primer sets specific for the S region. Accordingly, 4 μg of extracted DNA was digested with DdeI or RsaI in a total volume of 50 μL at 37 °C for 4 h. After confirmation of complete digestion by agarose gel electrophoresis, the enzyme was heat inactivated at 70 °C for 15 min. After the purification of the digested DNA using a PCR clean-up system (Promega, Madison, WI), samples were incubated with T4 DNA ligase (New England BioLabs, Beverly, MA) at 16 °C for 6 h. Finally, circularized DNA was used as the template for PCR amplification. The primer sets used for inverse-PCR amplification were as follows: R-HBS1.5′-GGGTCCTAGGAATCCTGAT-3′: R-HBR1.5′-GTATGT-TGCCCGTTTGTCCT-3′: R-HBS2.5′-GTCAACAAGAAAAACCC-CGC-3′: R-HBR2.5′-GCCTCATCTTCTTGTTGGTTC-3′: Equal amounts of restriction enzyme-digested but noncircularized DNA were used as a negative control.

3. Results

3.1. The presence of HBV-DNA in lymph nodes and PBMC of anti-HBc positive latent HBV carriers

We first examined whether HBV-DNA was present in the serum, liver, lymph node, and PBMC samples of individuals who were positive for anti-HBc but negative for HBsAg