ANNALS OF SURGERY
Vol. 224, No. 6, 712–726

Auxiliary Partial Orthotopic Liver Transplantation for Fulminant Hepatitis

The Paul Brousse Experience

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Objective
The authors objective is to report their experience with auxiliary partial orthotopic liver transplantation in fulminant hepatitis (FH) and to discuss the principles that may help in its safe application.

Summary Background Data
Auxiliary partial orthotopic liver transplantation is an attractive therapeutic method in FH because it provides hepatic function, whereas the remaining native liver is given the possibility to recover. Despite early encouraging reports, its place in the treatment of FH remains to be defined.

Methods
Evaluation of 5 cases of FH treated with auxiliary partial orthotopic liver transplantation from a collective of 22 transplantations for 35 cases of FH referred to the authors' center from January 1994 to November 1995. The grafts were one left lobe, two left livers, and two right livers.

Results
The native liver regenerated in three patients: one with Reye's syndrome who died of irreversible neurologic damage, one with FH caused by the hepatitis B virus who is alive 20 months after ABO incompatible graft removal, and one with FH caused by the hepatitis A virus who had her graft removed at 4 months. In two patients, regeneration did not occur: one with drug-induced FH who died of sepsis 3 months after surgery and one with FH of unknown origin who was retransplanted with a standard liver transplantation at 4 months for uncontrollable biliary rejection of an ABO incompatible graft (alive at 10 months). Two of the three patients who survived suffered severe neurologic complications.

Conclusions
Auxiliary partial orthotopic liver transplantation is an attractive treatment for FH, especially in the presence of good prognostic factors for native liver regeneration: a young patient, rapid

onset of the disease, and viral hepatitis. It should be considered cautiously in patients with advanced encephalopathy. By providing a smaller mass of liver tissue than with standard orthotopic liver transplantation, and as a more complex operative procedure, auxiliary partial orthotopic liver transplantation may not be as effective in arresting the progression of neurologic damage.

The outcome of fulminant hepatitis (FH) is dramatically dual: either the patient recovers, generally with normal liver function, or the patient dies.[1,2] In fact, although many failing livers have the potential to regenerate with time, most patients will suffer fatal neurologic damage before this has had the chance to occur.

Orthotopic liver transplantation (OLT) was a revolution in the management of fulminant hepatic failure (FHF),[3] this at the cost of removing the native liver that may have recovered. Ideally, what the patient with FH needs is a reliable temporary support to "tide him over" the period of illness, before regeneration of the native liver has taken place. The concept of auxiliary partial orthotopic liver transplantation (APOLT), placing the graft next to the diseased organ, is therefore appealing: when and if the native liver recovers, the graft either can be abandoned or removed, and the patient can be freed from immunosuppression. The procedure, technically more complex than standard OLT, has been rendered possible by outstanding recent advances in liver surgery and transplantation such as the reduced liver and the split-liver transplantation techniques,[4–7] and initial results are encouraging. The aim of our article is to report our experience with APOLT, to discuss the problems we encountered with it, and to formulate some recommendations that may help in its safe application.

PATIENTS AND METHODS

From January 1994 to November 1995, 35 patients were referred to our center for FH or sub-FH, defined as acute hepatitis complicated by acute liver failure and hepatic encephalopathy occurring less than 2 weeks and between 2 weeks and 12 weeks, respectively, after the onset of jaundice.[8] Encephalopathy was classified into four stages according to the classification of Trey and Davidson.[9] Stages 3 and 4, confusion and coma, respectively, were classified into four grades as described previously (Table 1).[10]

Patients were admitted to the intensive care unit and managed according to a protocol described in detail elsewhere.[10] The criteria for liver transplantation were: the presence of encephalopathy stage 3 or 4 associated either with a factor V level less than 20% of normal in a patient younger than 30 years of age, or with a factor V level less than 30% of normal in a patient older than 30 years of age.[10,11] As soon as the decision to transplant was taken, patients were placed on the "super-emergency" list of the French organ-sharing organization, giving them absolute priority for available donor livers.

Of the 35 patients, 10 did not fulfill the criteria for urgent transplantation: 7 improved spontaneously and 3 died. Twenty-five patients were listed for urgent transplantation. Three were not transplanted: two died of brain edema before a donor could be found and one improved spontaneously. Twenty-two patients were transplanted: they were 8 women and 14 men with a mean age of 38 years (range, 13–68). The causes of FH in these 22 patients were viral hepatitis in 10 (hepatitis A virus in 5, hepatitis B virus in 5), drug toxicity in 6, Reye's syndrome in 1, and indeterminate in 5. Seventeen underwent OLT: 12 with an ABO blood group (ABO) identical or compatible graft and 5 with an ABO incompatible graft. In five patients, APOLT was performed as detailed below.

Case Reports

Case 1

A 20-year-old man became jaundiced on March 14 1994, with serum bilirubin levels of 230 μmol/L, and alanine transaminase levels (ALAT) of 3580 international units/L. The diagnosis of hepatitis B was established. Confusion appeared on March 27, 1994; his condition deteriorated and he was admitted to our center on March 30, 1994. At this time, he was on a mechanical ventilation with encephalopathy stage 4, coma grade 3 (not localizing pain), and had repeated episodes of myoclonia and seizures. Liver function test (LFT) results showed bilirubin 1050 μmol/L, ALAT 1300 international units/L, prothrombin 20% of normal. Twelve hours after arrival, an ABO incompatible liver became available and it was decided to perform an APOLT with a left hepatectomy on the native liver and segments 2, 3, and 4 of a reduced-size liver graft placed in left orthotopic position (Fig. 1, upper left and right). The histologic analysis of the native liver showed hepatocyte necrosis over 90% with no signs of regeneration (Fig. 2A). Post-transplant LFT results are listed on Table 1. The patient awoke on day 5 with signs of a severe frontal syndrome. A cholestatic biochemical profile without jaundice developed with normal prothrombin levels. The sequential assessment of the function of both livers showed the following:

1. On the graft, cholangiographic analysis showed the progressive appearance of diffuse intrahepatic biliary stric-

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Accepted for publication June 20, 1996.

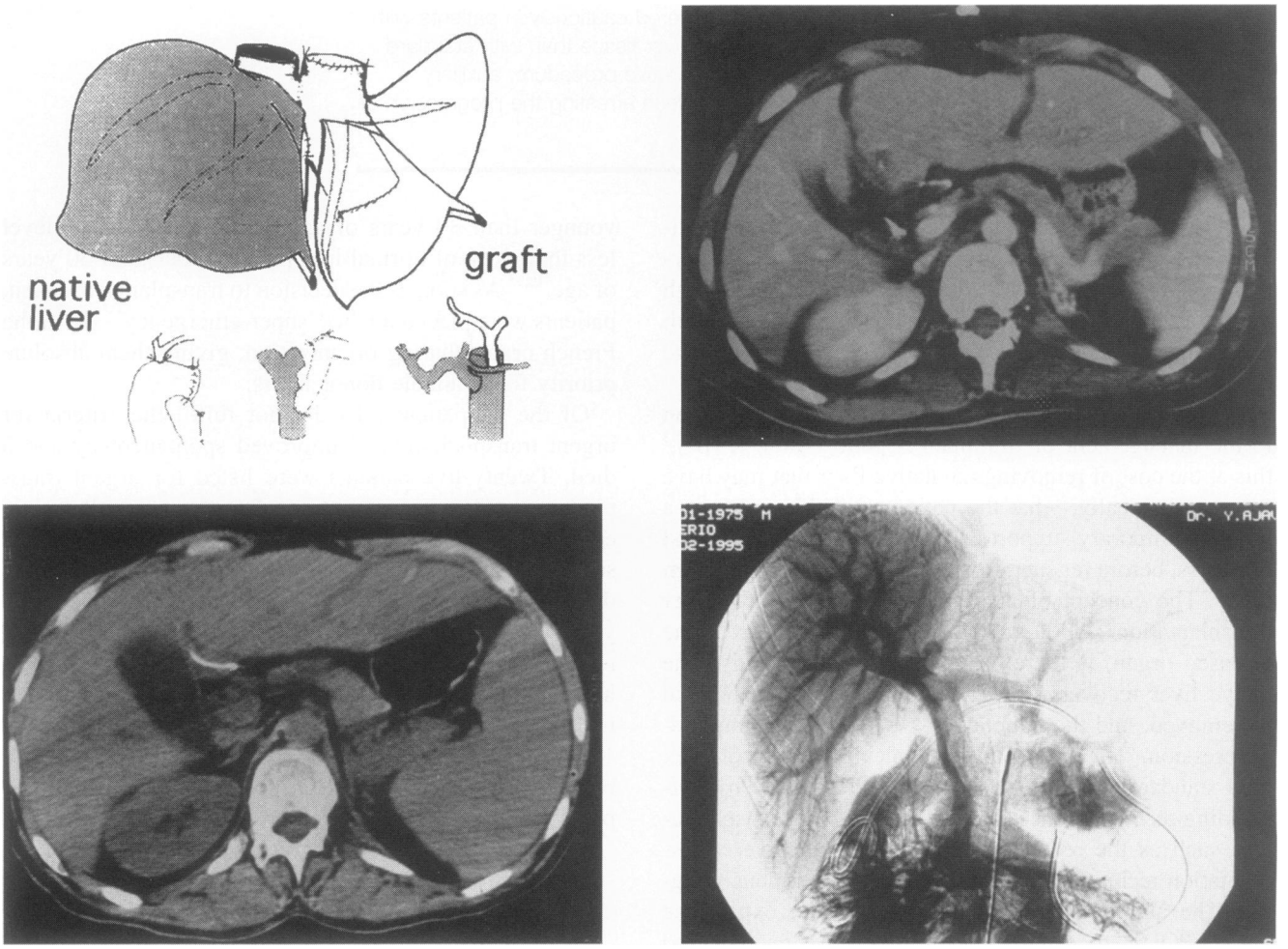

Figure 1. (Patient 1) Auxiliary partial orthotopic liver transplantation of a left liver graft. (Upper left) Schematic representation of the surgical procedure. (Upper right) Computed tomographic scan at day 4 after transplantation showing the two quadrate lobes. (Lower left) Computed tomographic scan at 10 months. The native right liver has increased in size and the left-sided graft has atrophied. (Lower right) Venous phase angiogram at 10 months. Preferential portal flow to the native liver.

tures with a patent hepatic artery (most likely due to rejection of the ABO incompatible graft). Histologic analysis showed a moderate acute rejection with septic features such as ductular proliferation, polymorphonuclear infiltrate in the interlobular ducts, and diffuse cholestasis.

2. On the native liver, histologic analysis showed the progressive disappearance of hepatocyte necrosis, and the development of portal and interportal fibrosis, with cholestasis.

The comparison of both livers on computed tomography (CT) scan showed a decrease in the volume of the graft and a progressive increase in the volume of the native liver at 9 months after transplantation (Fig. 1, lower left). The successive aspects of both livers on radionuclide hepato-iminodiacetic acid (HIDA) scan are shown in Figure 3. At 10 months, results of bilirubin levels, prothrombin time, and tracer uptake and excretion by the native liver on the HIDA scan were normal. Histologic analysis showed normal lobular appearance of the hepatocytes that had regenerated fully and a mild portal and interportal fibrosis (Fig. 2B). It was decided to remove the graft because of recurrent episodes of cholangitis, and the postoperative course was uneventful. Results of histologic examination of the graft showed features of cholestasis, inflammatory infiltration, ulceration of the main biliary ducts, and ductular proliferation. Fourteen months after graft removal, the patient is doing well with substantial improvement of neurologic function, still needing, however, external support for some activities of daily living.

Case 2

A 13-year-old boy became jaundiced on August 15, 1994, with encephalopathy appearing 2 weeks later. The diagnosis of FH of unknown cause was made. His clinical conditions deteriorated, requiring mechanical ventilation, and he was referred to our center on September 3, 1994,

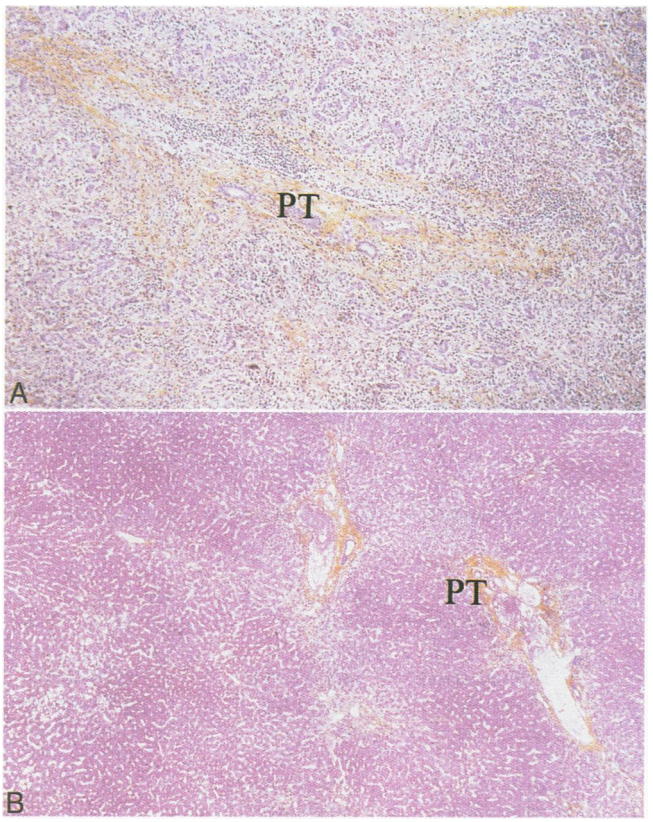

Figure 2. (Patient 1) Histologic analysis of the native liver. (A) At transplantation, massive hepatocyte necrosis around the portal tract (PT). (B) At 10 months (liver biopsy), hepatocyte regeneration, mildly enlarged portal tracts with moderate portal fibrosis (original magnification hematein-eosin-safran × 350).

with encephalopathy stage 4, coma grade 3 (not localizing pain), and a unilateral dilated pupil. Blood test results showed bilirubin 700 μmol/L, prothrombin 9% of normal, and factor V 18% of normal. An intracranial pressure monitor was inserted showing a pressure of 35 mmHg. Because of oliguria and intracranial hypertension, the patient was put on continuous venovenous hemofiltration. Only an ABO incompatible liver graft was available, and it was decided to perform an APOLT. After a right hepatectomy on the native liver, a right reduced-size liver graft was placed in the orthotopic position (Fig. 4). The histologic analysis of the native liver showed massive necrosis affecting more than 90% of the hepatocytes with no signs of regeneration. The postoperative evolution of LFT results is listed in Table 1. The first signs of an improving level of consciousness were observed at day 2; however, complete awakening allowing extubation occurred only at day 15 and signs of a severe frontal syndrome were present (with normal CT scan). Diffuse intrahepatic biliary strictures, secondary to biliary rejection and worsening on sequential cholangiograms, developed on the graft with repeated episodes of cholangitis. Results of histologic examination of the native liver showed no hepatocyte necrosis, the appearance of portal and interportal fibrosis, and cholestasis. At 4 months, LFT results were bilirubin 440 μmol/L, γ-glutamyltransferase 525 international units/L, alkaline phosphatase 750 international units/L, ALAT 150 international units/L, prothrombin 100% of normal. On CT scan, the volume of the native liver increased from 180 to 500 mL, and radiologic features of intrahepatic biliary dilatation and abscesses were present in the graft (Fig. 4, lower right). The first HIDA scan showed no uptake by the native liver, all the function being ensured by the graft. On the HIDA scan at 4 months, the kinetic of the tracer was similar in both livers with a low uptake and no biliary excretion (Fig. 5). Removal of both the graft and the native liver was therefore decided, and a standard OLT was performed on January 15, 1995. The graft showed marked signs of cholestasis with ischemic necrosis of the main biliary ducts and intrahepatic abscesses with a patent hepatic artery, and there was portal and interportal fibrosis on the native liver. The postoperative course was uneventful with LFT results rapidly returning to normal. At 1 year, the patient is doing well with normal liver test results. Neurologic function improved slowly over the 6 first months, and at 1 year, the patient has regained full independence with only some long-term memory loss.

Case 3

A 14-year-old boy was admitted to another hospital for FH of unknown cause on August 20, 1994. Jaundice and confusion had appeared simultaneously the day before, after 1 week of nausea and weakness, which was treated with aspirin. Mechanical ventilation was required because of severe encephalopathy. The ALAT levels were 40 times normal, and factor V 15% of nor-

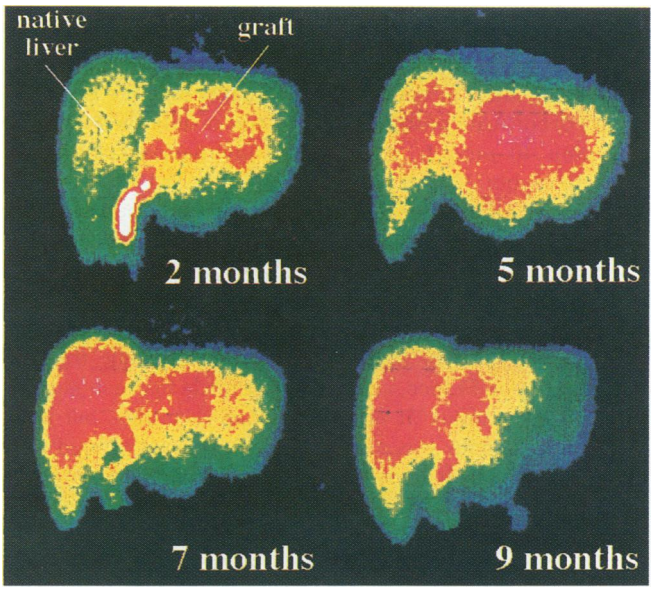

Figure 3. Hepato-iminodiacetic acid scintigrams of patient 1 after transplantation. At 2 months, low uptake and no biliary excretion by the native right liver. At 5 months, the function of the graft remains predominant, but there is an increase of the uptake by the native liver. At 7 and 9 months, there is virtually normal uptake and biliary excretion by the native liver and relative decrease in the function of the graft.

Table 1. SUMMARY OF PATIENT STATUS AT TRANSPLANTATION, OPERATION DATA, AND OUTCOME

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Recipient					
Age (yr)	20	13	14	68	41
Weight (kg)	70	75	52	65	75
Indication	HBV	Unknown	Reye	Drug	HAV
Encephalopathy*/coma†	Stage 4/grade 3	Stage 4/grade 3	Stage 4/grade 3	Stage 4/grade 3	Stage 3/grade 1
Delay jaundice-encephalopathy	13 days	15 days	Simultaneous LRLT	Simultaneous	2 days
Donor					
Age	25	57	40	57	41
ABO matching (donor/recipient)	Incompatible (B/O)	Incompatible (A/O)	Identical (O/O)	Compatible (O/A)	Identical (A/A)
Graft:side/weight (g)	Left/680	Right/1180	Left/300	Left/1120	Right/1080
Transplantation					
CIT/operative time	12 hr 55 min/13 hr	8 hr 38 min/16 hr	1 hr 30 min/6 hr	10 hr 30 min/14 hr	8 hr 30 min/11 hr
Units of red blood cells	13	19	10	7	7
Liver function tests					
ASAT day 5 (IU/L)	182	93	102	48	69
PT day 3/day 5/day 15	52/69/90	71/60/77	58/51/80 (D11)	59/83/83	63/75/69
Outcome	Liver regeneration, graft removed (10 mo) alive, neurologic sequelae	No liver regeneration, severe rejection OLT (4 mo), alive, neurologic sequelae	Liver regeneration, brain-stem death (day 11), no technical complication, deceased	No liver regeneration, myelinolyis, MOF, no technical complication deceased	Liver regeneration, graft removed (4 mo), alive

HBV = hepatitis B virus; Reye = Reye's syndrome; HAV = hepatitis A virus; LRLT = living-related liver transplantation; CIT = cold ischemia time; ASAT = aspartate transaminase; PT = prothrombin; Tx = transplantation; OLT = orthotopic liver transplantation; MOF = multiple-organ failure;
* Encephalopathy stages: 1 = slow mentation; 2 = drowsiness and/or asterixis; 3 = confusion; 4 = coma.[9]
† Coma grades: 1 = inappropriate response to voice; 2 = localizes pain; 3 = does not localize pain; 4 = brain death[10]

mal. The patient was referred to our center with encephalopathy stage 4, coma grade 3, weakly reactive pupils, and decorticate posturing. Blood test results showed bilirubin 40 μmol/L, ALAT 4370 international units/L, prothrombin 22% of normal, and factor V 19% of normal. An intracranial pressure monitor was inserted and showed a pressure between 30 and 40 mmHg, with a cerebral perfusion pressure between 25 and 45 mmHg. He received mannitol intravenously, and continuous venovenous hemofiltration was prepared. The patient immediately was listed for super-emergency transplantation in France, and calls were made to organ-sharing organizations of other European countries, but no cadaveric donor was available. Both parents offered to give part of their liver for transplantation, and after approval by the ethical committee of our University, the donation was accepted. The mother was chosen because of the homologous blood group (O) and because the left lobe (300 mL was bigger than the father's. Organization of the procedure, including approval by the ethical committee, took 5 hours. A left hepatic lobectomy was performed simultaneously in the mother and in the recipient, and living-related auxiliary orthotopic transplantation was performed on August 20, 1994 (Fig. 6). The donor received no transfusion, her postoperative course was uneventful, and she was discharged on day 10. Histologic analysis of the native liver of the recipient showed massive microvesicular steatosis compatible with Reye's syndrome. The child had fixed bilateral pupils immediately in the postoperative period with massive cerebral edema on CT scan. Despite intensive neurologic support, brain function did not recover, and the patient was declared brain dead on day 11 after transplantation. The results of the LFTs are listed in Table 1. Necropsy showed patent vascular anastomoses; results of histologic examination of the native liver showed complete disappearance of the steatosis and full hepatocyte regeneration. On the graft, there were histologic features of mild acute rejection.

Case 4

A 68-year-old woman was admitted for FH due to a drug overdose with many different tablets, including paracetamol, on March 16, 1995. The cause of the suicide attempt was a depressive syndrome secondary to chronic osteoarticular pain. Liver function deteriorated, mechanical ventilation was started, and the patient was transferred

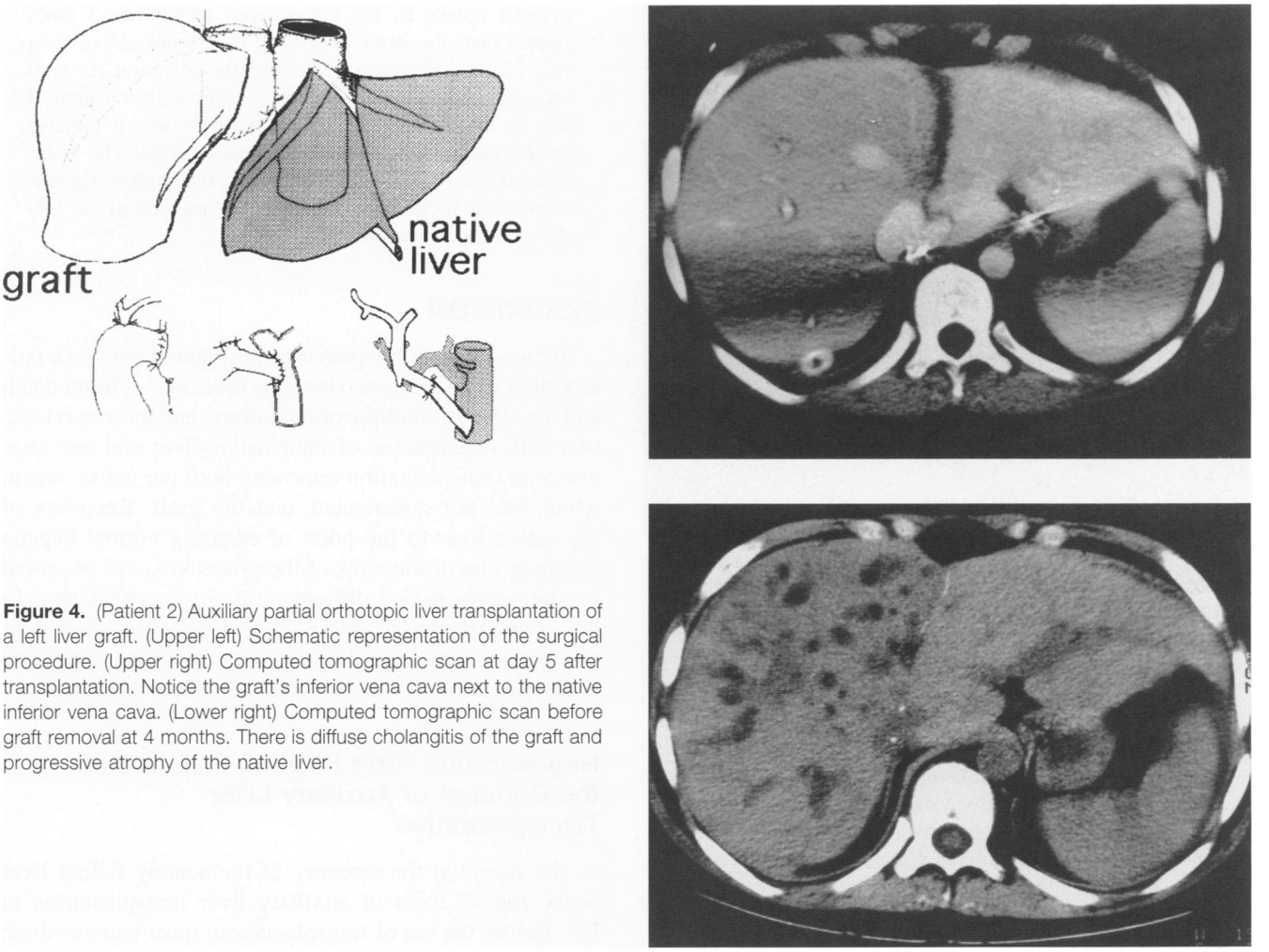

Figure 4. (Patient 2) Auxiliary partial orthotopic liver transplantation of a left liver graft. (Upper left) Schematic representation of the surgical procedure. (Upper right) Computed tomographic scan at day 5 after transplantation. Notice the graft's inferior vena cava next to the native inferior vena cava. (Lower right) Computed tomographic scan before graft removal at 4 months. There is diffuse cholangitis of the graft and progressive atrophy of the native liver.

to our center on March 20, 1995, with encephalopathy stage 4 and coma grade 3 (not localizing pain). Biologic test results showed bilirubin 350 μmol/L, γ-glutamyltransferase 69 international units/L, ALAT 4309 international units/L, prothrombin 11% of normal, and factor V 12% of normal. A CT scan of the brain was considered normal. Her clinical condition deteriorated, and she was listed for emergency liver transplantation. The decision to perform an APOLT was taken because of the good chances of liver function recovery associated with paracetamol overdose, and this was performed using a reduced-size (1120 g) left ABO compatible graft. Postoperative LFT results are listed in Table 1. Despite good liver function, the patient remained unconscious until day 15, then improved progressively to full consciousness with tetraparesis and myoclonic jerks due to myelinolysis. The CT scan at 1 month estimated the volume of the graft at 1261 mL and the native liver at 576 mL. These volumes were unchanged at 3 months. The patient remained conscious but could not be extubated because of the tetraparesis, became septic with multiple organ failure, and died 3 months after the operation. At necropsy, no technical complications were found. The weight of the native liver was 600 g and histologic analysis showed the persistence of massive hepatocyte necrosis with no signs of regeneration. The results of the graft were almost normal on histologic examination with minimal signs of rejection.

Case 5

A 42-year-old woman was admitted to another hospital for severe hepatitis A on November 12, 1995. Jaundice had appeared the previous day with ALAT 1590 international units/L and prothrombin 6% of normal. On November 14, 1995, the patient was confused and was transferred to our center. On admission, she was suffering from encephalopathy stage 3 and coma grade 1 (confusion, inappropriate response to voice). Bilirubin was 150 μmol/L, ALAT 3500 international units/L, prothrombin 6% of normal, and factor V 16% of normal. The decision to perform an APOLT was taken because of the association of favorable prognostic factors (viral hepatitis A, young age, short history, and only mild neurologic involvement), and the same day, the patient underwent an auxiliary liver transplantation using the right part of an ABO identical graft (Fig. 7). Results of histologic analysis of the native liver are shown in

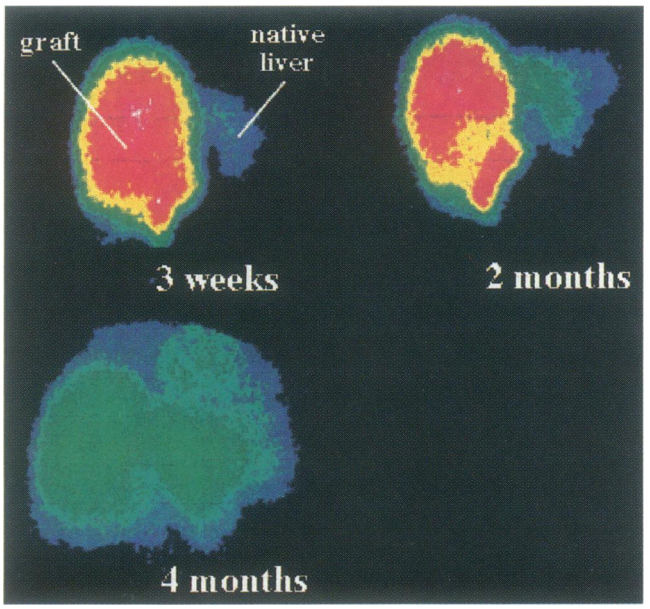

Figure 5. (Patient 2) Hepato-iminodiacetic acid scintigrams after transplantation at 3 weeks and 2 months. The right graft is functioning, and there is no uptake by the native liver. At 4 months, there is equalization of the function of the graft and of the native liver, but the function of each liver remains poor with low uptake (the heart is seen, for comparison) and there is no biliary excretion.

Figure 8. The patient awoke at day 1 and was extubated at day 2. At this time, factor V was 130% of normal (Table 1). There was a gradual improvement of her native liver function with a progressive increase of the volume of the native liver on CT scan (Fig. 7, lower left and lower right), and of the vascular uptake and biliary excretion of the tracer by the native liver on the HIDA scan (Fig. 9). A staphylococcal abscess developed between the raw surfaces of the two livers and was drained percutaneously. At 3 months, LFT results were bilirubin 34 μmol/L, γ-glutamyltransferase 528 international units/L, and ALAT 70 international units/L. The HIDA scan showed normal vascular uptake by the native liver, which was 5 times greater than the graft's, as well as normal native liver biliary excretion. Four months after the operation, the graft was removed surgically. It was atrophic with a weight of 600 g, and at histologic analysis, there was a massive lobular necrosis, probably of ischemic origin. The histologic analysis of the native liver showed complete regeneration of the hepatocytes with normal structure of the lobules and mild portal fibrosis (Fig. 8).

DISCUSSION

In this series of five patients transplanted with an auxiliary orthotopic graft, two patients died, one of brain death and the other of multiple organ failure, and three survived, two with regeneration of their native liver and one after a second transplantation removing both the native organ, which had not regenerated, and the graft. Recovery of the native liver to the point of ensuring normal hepatic function, one of the aims of the procedure, was observed in three patients and did not occur in the other two. In this series, the rate of neurologic complications was high: one patient died from brain edema, a frontal syndrome developed in two, and one patient became tetraparetic.

Regeneration After Hepatic Failure and the Concept of Auxiliary Liver Transplantation

The potential for recovery of the acutely failing liver is the logical basis of auxiliary liver transplantation in FH. Before the era of transplantation, most patients died; a small number (15%–20%), however, recovered and in these patients, the restoration of the hepatic function usually was complete.[12–15] Little is known about the factors that may predict regeneration after acute liver failure. It

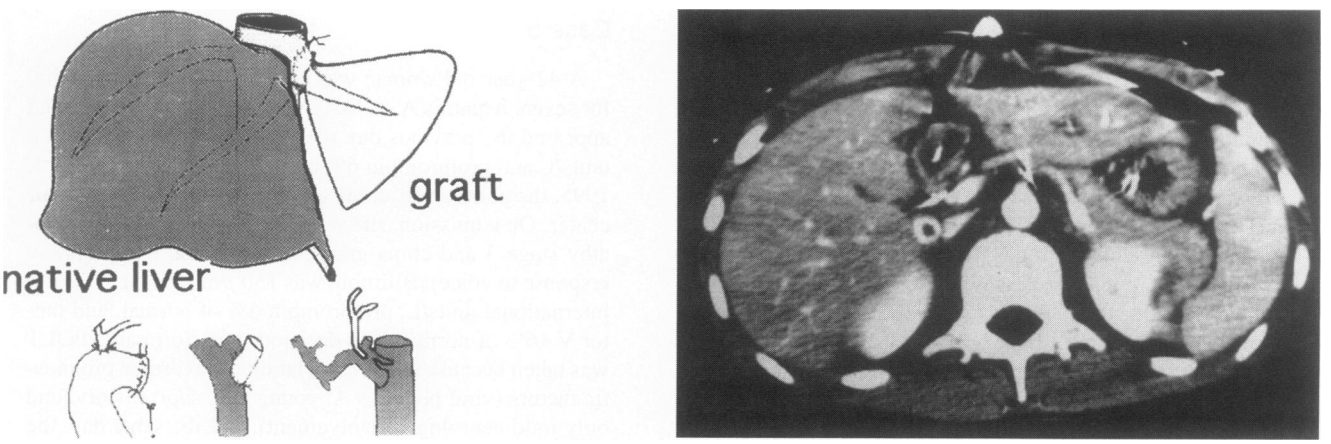

Figure 6. (Patient 3) Auxiliary partial orthotopic liver transplantation of a left lobe graft from a living-related donor. (Left) Schematic representation of the surgical procedure. (Right) Computed tomographic scan at day 3 after transplantation. Note the small volume of the graft (300 mL for a 52-kg recipient).

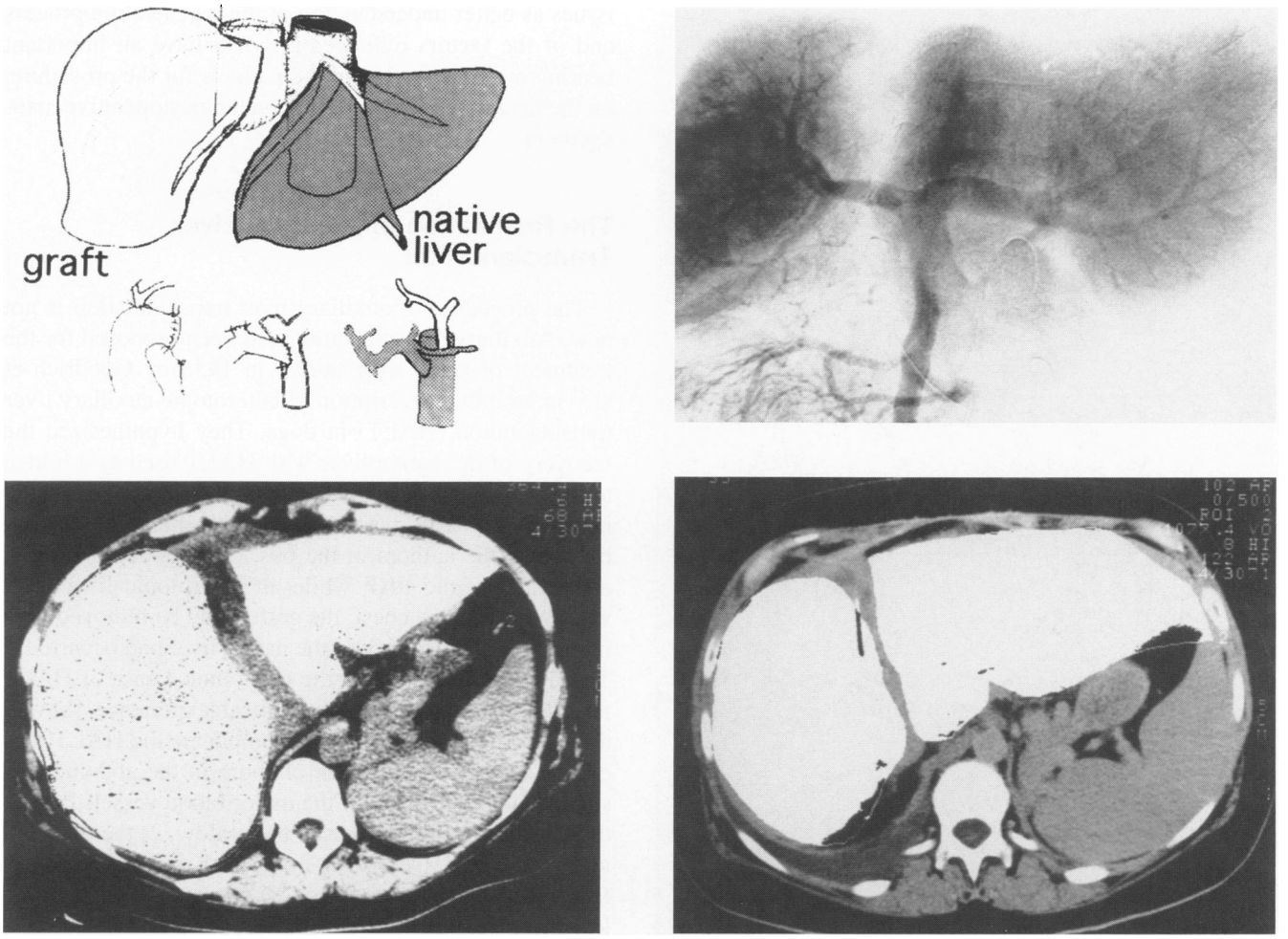

Figure 7. (Patient 5) Auxiliary partial orthotopic liver transplantation of a right liver graft. (Upper left) Schematic representation of the surgical procedure. (Upper right) Venous phase angiogram before graft removal at 4 months. Note the hypertrophy of the native liver and the atrophy of the graft. (Lower left) Computed tomographic scan volumetry early after transplantation (graft: 1900 mL, native liver: 625 mL). (Lower right) Computed tomographic scan volumetry before graft removal at 5 months (graft: 1130 mL, native liver: 1061 mL).

has been shown that the extent of hepatocyte necrosis on the liver biopsy specimen at the time of the acute injury is not helpful.[12,16] The cause of the disease may have an influence: paracetamol-induced liver failure and viral FH, especially hepatitis A, may have a better chance for regeneration than FH of indeterminate cause or due to idiosyncratic drug toxicity. In addition, gradual deterioration of hepatic function seems to be less susceptible to recovery than FH with a more rapid onset, and a study of some patients with a relatively prolonged course of acute liver failure has shown that, although regenerative nodules do develop, these have a low functional capacity.[17] The importance of the above-mentioned factors has been confirmed recently in a multicenter series on auxiliary liver transplantation.[18]

In practice, the first clinical observations after auxiliary liver transplantation have shown that the process of regeneration is inconstant, and when it occurs, it may require a variable amount of time. In our experience, full regeneration took 10 days in patient 3 suffering from Reye's syndrome, 3 months in patient 5 suffering from FH caused by the hepatitis A virus, and 10 months in patient 1 suffering from FH caused by the hepatitis B virus.

Could the procedure of auxiliary liver transplantation affect the chances and the time course of regeneration? Theoretically, the derivation of part of the portal flow toward the graft may have a detrimental effect on the chances of recovery of the native liver. The introduction of immunosuppression too may influence hepatocyte regeneration directly, and it has been suggested that FK506 may have a superior hepatotrophic action to cyclosporine[19,20] and indirectly by modulating the virus–host interactions, as it is known that the immunosuppression affects the process of viral clearance in hepatitis.

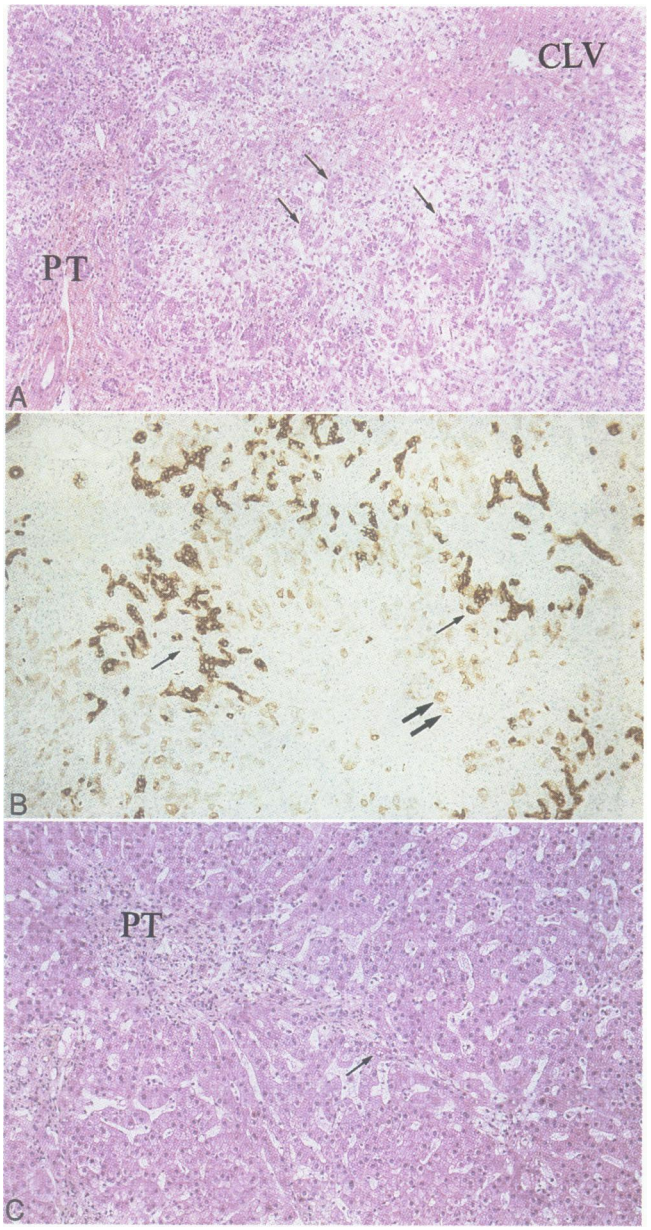

Figure 8. (Patient 5) Histologic analysis of the native liver. (A) At transplantation, massive hepatocyte necrosis with persistence of small foci of intact hepatocytes (arrow). PT = portal tract; CLV = centrilobular vein. (B) At transplantation, immunohistochemical staining of hepatocytes with anticytokeratine antibodies. Ductular proliferation is intensively labeled (thin arrows). Persistence of few hepatocytes with weak cytoplasmic labeling (large arrows). (C) At 4 months, almost complete regeneration of hepatocytes (arrow). Mild interportal fibrosis. (A, C: hematein-eosin-safran; B: immunoperoxidase; original magnification × 350).

Furthermore, it is unlikely that the partial hepatectomy on the native liver in case of APOLT could stimulate the process of regeneration: this occurs on nonfunctional liver tissue, which should have no effect on the distribution of hepatotrophic factors, unlike the case of hepatectomy on a healthy organ. Additional research is needed on these issues as better understanding of the regeneration process and of the factors influencing it will have an important bearing on the selection of the patients for the procedure, on the operative technique, and on the postoperative management.

The Realization of Auxiliary Liver Transplantation

The procedure of auxiliary liver transplantation is not new. Auxiliary transplantation had been proposed for the treatment of acute liver failure in 1956 by Goodrich et al.[21] in an initial description of heterotopic auxiliary liver transplantation (HALT) in dogs. They hypothesized the recovery of the native liver with HALT used as a bridge to "tide the patient over" the period of acute hepatic insufficiency. This was independently put into practice by one of the authors in the 60s, on a model producing a lethal ischemic FHF while an heterotopic liver graft was in place in the chest: the graft could be removed with impunity after recovery of the native liver had occurred.[22] These experiments led to the first clinical case of HALT for FH.[23] However, further clinical experience showed that major technical problems complicate the HALT procedure, namely: 1) the lack of room in the abdomen resulting in compression of the major blood vessels, and of the graft itself with decreased blood flow, 2) the difficulties in directing the portal flow (with its hepatotrophic factors) toward the graft, and 3) the necessity to have a low pressure outflow anastomosis (therefore close to the

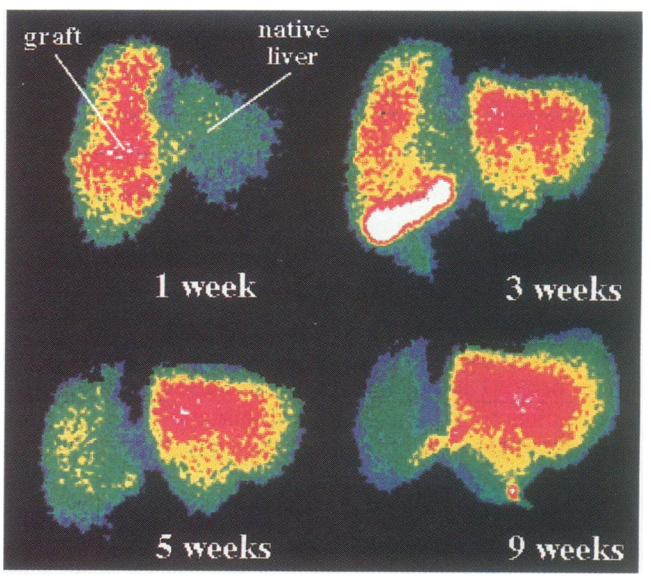

Figure 9. (Patient 5) Hepato-iminodiacetic acid scintigrams after transplantation. At 1 week, low uptake by the native liver. At 3 weeks, note the absence of bile excretion in the drain and preferential elimination in the gut. At 9 weeks, the uptake by the native liver is normal and 5 times higher than the graft that has atrophied.

right atrium) to avoid an increased sinusoidal pressure leading to reduced graft blood flow and even thrombosis.[24] These problems override the main operative advantage of the HALT procedure, of avoiding the dissection of the liver in an unstable patient. Eleven cases of HALT for FHF have been reported in the literature.[23,25–34] Six patients died, all of them within 60 days after the procedure. Five patients survived, one after standard OLT for primary nonfunction of the graft, one with a functional graft, full immunosuppression, and cirrhosis on the native liver. Only in three patients was the procedure a complete success, with regeneration of the native liver and no need for immunosuppression.

Partial native liver resection to make room in the right hypochodrium to transplant an auxiliary partial liver in the orthotopic position (*i.e.*, APOLT) in a patient with cirrhosis was first reported in 1985.[5] More recently, the first successful APOLT for FH was reported by Gubernatis et al.[35] in 1991 for hemolysis, elevated liver enzymes, and low platelet count syndrome in a 33-year-old patient. Three centers have reported a total of 16 patients in whom APOLT has been performed.[35–39] Five patients died (31%), of whom 2 died with a functioning native liver, after complications, following removal of the graft; 11 are alive, of whom 9 have recovered native liver function (56%) and 2 are dependent on the graft with full immunosuppression. One multicenter European study, including 30 cases of auxiliary liver transplantation from 12 centers, was reported lately in an abstract.[18]

Practical Approaches to Auxiliary Partial Orthotopic Liver Transplantation in Our Center

Technical Aspects

The three main drawbacks of HALT concerning the abdominal space, the portal inflow, and the venous drainage are obviated in the APOLT procedure by having the graft in the orthotopic position. Furthermore, this is an advantage, should either 1) the graft be removed if the native liver has recovered or 2) the native liver be removed if regeneration has not occurred.

The main goal of liver transplantation in the setting of acute liver failure is to save the patient with no neurologic sequelae. This can be achieved only if a sufficient mass of functioning hepatic tissue is provided rapidly. As shown by concomitant experience with split-liver transplantation in our unit, there is a limiting ratio of graft–recipient weight of 1%, below which elective transplantation is risky. This should be the lower limit of graft size in FHF and will mean transplantation of a right-sided graft after a right hepatectomy on the native liver in most adult patients.

Competition for portal blood flow has been suggested as a possible mechanism for failure, either of the graft or of the native liver. Portal vein thrombosis has been postulated to occur as a result of a steal syndrome, and a technique of banding the portal vein branch feeding the native liver has been devised, with improved results in an experimental model.[40] In fact, this does not seem to be a problem, and the orthotopic position of the auxiliary graft seems to allow an autoregulatory distribution of the portal flow between the native and the donor liver.

According to the concept that the graft should serve only as temporary support and could be removed later, no essential structures of the native liver should be jeopardized. The artery of the graft should not be anastomosed to the native hepatic artery. Biliary reconstruction can be best accomplished with a standard Roux-en-Y choledochojejunostomy. Compared with a direct duct-to-duct anastomosis, leak and stricture are less likely to occur.[37] In addition, a choledochojejunostomy makes later native or graft hepatectomy, if required, easier and safer for the remaining liver. Both livers should be drained with biliary drains (usually in the cystic ducts) to allow cholangiography in the postoperative period and to monitor bile production.

Appreciation of the Function of the Graft and of the Native Liver

We found that one of the most difficult aspects of the technique was to evaluate degree of recovery and function of the native liver and to differentiate it from the function of the graft. This was done by cumulating the information provided by the different clinical, laboratory, and radiologic indexes of liver function. It was easy in the more straightforward case 5 and much more difficult in cases 1 and 2, for instance, where some elements of the information were conflicting.

Liver function test results only offer an estimate of the global function of both livers and would not allow differentiation of the metabolic activity of each. The external appearance of the bile on sequential examination is a good bedside indicator of function. In most cases, the native liver does not produce bile at the time of graft failure, and the appearance of a dark bile heralds recovery. However, appreciation of the color is subjective, and the absence of bile in the drain simply may reflect that bile is not eliminated through it but directly in the intestine (Fig. 9).

Results of histologic examination of regenerating livers showed the disappearance of hepatocyte necrosis and the replacement by normal hepatocytes. Some degree of portal and interportal fibrosis was observed in all these cases, its significance is difficult to appreciate, and it is variably interpreted in the literature.[37,38] Sequential biopsy specimens of both livers after transplantation were a precious guide in the evaluation of the regeneration process despite the difficulties to correlate the functional activity of the

liver and the histologic aspect. The problem arose particularly in patient 2, in whom there was a discrepancy between the reappearance of normal hepatocytes and, conversely, severe jaundice and low and heterogeneous captation on the HIDA scan. The depressed function of the native liver probably is to be attributed to the influence of the particularly severe portal and interportal fibrosis observed in this case.

An increase in the volume of the native liver associated to a decrease of the volume of the graft on CT scan may be a sign of regeneration. However, size is only a rough indicator and may not reflect the respective function of each liver, especially for the graft. The venous phase of the angiogram showing the respective distribution of the portal flow between the graft and the native liver also may be a reflection of the function of each liver, although this procedure is invasive and can not be used for sequential evaluation. Radionuclide HIDA scans were the most useful test in our experience. By showing the rapidity and the magnitude of the uptake and of the biliary excretion of the tracer, these scans permit a quantitative analysis of the function of the graft relative to that of the native liver, which can be easily repeated for comparison. Progression of recovery most often appeared on HIDA scans as a gradual increase of the uptake and of the biliary excretion by the native organ and as a decrease of the function of the graft as observed in patients 1 and 5 (Figs. 3 and 9). In patient 2, the HIDA scan showed a poor vascular uptake and a low biliary excretion by both livers. This was a more faithful reflection of the actual clinical conditions of the patient, who had severe jaundice, than was the histologic aspect of the liver biopsy specimen.

The Issue of Detransplantation

When the native liver has regenerated, the question arises on the best way to deal with the graft. One option is to taper down the immunosuppression to provoke a controlled rejection of the donor liver, which is left to atrophy. The theoretical disadvantage of this attitude is the risk to cause a severe rejection of the graft, requiring its prompt surgical removal, which may be a difficult procedure on an inflamed organ. The other option is to take out the graft electively without discontinuing the immunosuppression. The latter solution was somehow forced on our two cases: in patient 1, because of chronic biliary sepsis, and in patient 5, because of a persistent abscess between the two livers. In both instances, removal of the graft was done as a formal intraparenchymal hepatectomy, without looking for the vascular anastomoses to avoid any risk of injury to the native liver. The procedure of surgical removal of the graft, however, may be difficult and is not without risks. Three cases of death have been reported after graft removal[37] and Boudjema, personal communication, 1996).

Analysis of Our Results

Auxiliary partial orthotopic liver transplantation is a conceptually attractive therapeutic option in the management of FH. The challenge is to define its precise indications, that is, to be able to predict which patients will survive without transplantation, who may benefit from APOLT, and who may be better served by a traditional OLT. Although reports have shown a 63% survival rate after APOLT,[18] the comparative analysis of the results between OLT and APOLT is difficult because the clinical severity may differ in the patients treated with each method. Indeed we have shown that survival after OLT for FHF may vary from 90% to 53% according to the condition of the patient at the time of transplantation and particularly to the grade of coma.[10] The same can be said for the risks of neurologic complications.[41] With APOLT, the amount of liver tissue may be insufficient when immediate liver function is needed. The other potential disadvantages related to the technique of APOLT are as follows: 1) the longer operative time needed to perform the two hepatectomies, as compared with the standard OLT, which may be deleterious for patients in critical neurologic conditions, and 2) the increased risk of hemorrhagic complications and of biliary leaks due to the raw surfaces of the graft and native liver.

On critical review of our five cases, it appears that the indication of APOLT was, in retrospect, not good in patient 4, because her native liver did not regenerate. The old age in this patient may have been an important element in the lack of recovery of native liver function.

Patient 1, at the beginning of our experience, received a 600 g graft representing less than 1% of his body weight. The recovery of neurologic function in this patient might have been faster with a greater liver mass.[42] An insufficient amount of hepatic tissue also was used, out of necessity, in patient 3, who received the left lobe from a living donor. In retrospect, irreversible neurologic damage probably had occurred already, and any form of transplantation should not have been performed in this case. However, the high rate of neurologic complications in our series, although possibly related to the severity of coma at the time of transplantation, should be taken as a message of caution against the use of APOLT for patients suffering from the most severe stages of encephalopathy. By increasing operative time and providing a smaller liver mass than with OLT, APOLT might increase the risk of neurologic injury in these patients.

Two original points of our experience should be discussed: 1) the use of ABO incompatible grafts and 2) APOLT with a living-related donor. The fact that we could only obtain an ABO incompatible graft for patients 1 and 2 played an important part in the decision to perform APOLT rather than perform OLT. Indeed, we have shown previously that in ABO incompatible liver transplantation,

there is a risk of hyperacute rejection within the first 10 days and of intrahepatic biliary strictures within the first year, leading to graft loss in 50% of the cases.[43,44] In fact, for many patients undergoing OLT with an ABO incompatible graft, this represents only a bridge to an ABO matched liver. We had hoped that in this setting, APOLT, with regeneration of the native liver while the ABO incompatible graft is rejected, was going to offer the chance of a more definitive treatment. This was indeed the case for patient 1, who was reoperated at 10 months for removal of the failing graft. Unfortunately, in patient 2, native liver regeneration did not occur, and both the graft and the native liver had to be removed at 4 months.

Patient 3 is, to our knowledge, the first reported case of living-related auxiliary partial liver transplantation performed as an emergency for fulminant hepatic failure. Living-related APOLT in this case was the only option because of the absence of cadaveric donors and the small size of the graft. The patient was suffering from Reye's syndrome, usually regarded as a controversial indication for liver transplantation, which may in fact be a good indication for APOLT because the potential for regeneration is high. Living-related APOLT, however, as the last resort for FH when no cadaveric organ is found is bound to be penalized by higher chances of a poor outcome because the patient is transplanted too late. In addition, the respect of the necessary steps needed to make the procedure ethically acceptable will require a delay, which could be detrimental in the contest of an emergency.

CONCLUSIONS

Our preliminary experience and the good results in other published series show that APOLT can be performed with little technical complications. Despite this and of its theoretical appeal, many issues still need to be resolved before this procedure definitively can take its place next to OLT in the treatment of FHF. The groups of patients most likely to benefit from APOLT will need to be defined. Possibly of greater importance, it will have to be seen whether, by providing a smaller amount of liver tissue and by its complexity, this procedure exposes some recipients to a higher risk of neurologic complications. At present, we do not recommend APOLT for patients with severe grades of encephalopathy. Even if this problem could be avoided by transplanting patients at an earlier stage, we do not think that traditional criteria for transplantation in FH should change before proper evaluation of APOLT, as compared with OLT, is available. The role of OLT and APOLT will need to be in the context of the development of bioartificial liver, which may serve as a bridge to transplantation or to full recovery.

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Discussion

DR. PAUL MCMASTER (Birmingham, United Kingdom): I compliment you on your presentation. Perhaps I could ask you to discuss a little further the histologic evaluation of the capacity of the liver to regeneration. We know that when you take a liver out that has failed because of fulminant hepatic failure, there is a remarkable variation in the degree of hepatocyte survival within that liver. How are we going to take a clear judgment if we use histology? Are we going to take multiple biopsies? Are we going to be confident, as our pathologists often are not, that we can determine viable hepatocytes? I think this is clearly crucial.

A second important issue that I think Professor Bismuth was eluding to in this situation is the prevention of neurologic damage in FHF, which is so crucial, and the volume of the transplanted liver to ensure that cerebral damage does not occur. Again, we have been anxious about grafting just segments 2 and 3 in this severe acute situation in young patients because of the fear of delay in resolving encephalopathy. Replacing a fulminant hepatic liver by transplantation takes only 2 to 3 hours and is a simple procedure, and done at the right time can achieve nearly a 90% patient survival. Our problem, as always, is the shortage of suitable organs. So the prognosis of the native liver we would see as crucial if APOLT is to be considered and trying to determine the volume of graft. Indeed we wonder if we are going to put in the right lobe to achieve adequate volume whether, with the current morbidity associated with segmental grafting, this is not an argument for putting in the whole liver as well. Having said this, as we split our cadaveric livers more and more, the orthotopic auxiliary graft may be a small but important area of development.

DR. CHRISTOPH BROELSCH (Hamburg, Germany): I would like to congratulate the speaker for this courageous work. This is a difficult task and Dr. Mc Master has already raised most of the issues. I would just like to shed some controversy into the discussion. I think that APOLT is going to become an obsolete procedure in the future. The big advantage of having the native liver regenerated is probably going to be overcome by spontaneous tolerance or by tolerance that we induce with immunosuppression in the very near future. If we look at how many patients already live without immunosuppression for quite some time after transplantation, and as I see in my outpatient clinic, how many patients are maintained under very low doses of immunosuppression 3 or 4 years after transplantation, I do not think that these are "patients" any more, but just normal individuals who are getting back to work. Patients who have one chance in a lifetime to have the right procedure done at the appropriate moment should not receive an APOLT. This is, I think, the crucial point to make the right decision at the crucial moment. I would ask Henri Bismuth what he thinks is the role of the living-related donation because determining the type of transplantation is so crucial, particularly in these acute fulminant liver failures. Another question: Neither of you mentioned the Hannover procedure, that is, total excision of the liver to gain time in acute liver failure, to get the histology done or something. Do you think it has still a place in fulminant liver failure?

DR. JAMES GARDEN (Edinburgh, United Kingdom): I would like to congratulate the speaker for the presentation. We do not have the experience of APOLT as reported in his series. We are glad that he is pioneering the technique and we have lessons to learn from it. A few issues that I would like to raise have been already covered by Paul Mc Master. Clearly, the attempt to salvage the native liver does not appear to have compromised long-term survival with a mortality fairly similar to that we might expect for patients transplanted by conventional means. I am concerned about the morbidity and I would like to ask