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Auxiliary Liver Transplantation: Regeneration of the Native Liver and Outcome in 30 Patients With Fulminant Hepatic Failure—A Multicenter European Study

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Auxiliary liver transplantation (LT) is a special procedure of LT which could be proposed to patients with fulminant hepatic failure (FHF) and has for aim that complete regeneration of the native liver (NL) left in place will allow the graft recipient to resume normal liver function after allograft withdrawal.

We report 30 cases of auxiliary LT performed for FHF in 12 European centers. Twenty-five of 30 patients were younger than 50 years. The cause of FHF was hepatitis A virus (HAV) in 4 patients, hepatitis B virus (HBV) in 7, paracetamol overdose in 5, ecstasy in 2, hepatotoxic drugs in 4, autoimmune hepatitis in 2, liver lesions of preeclampsia in 1 and unknown in 5. A postoperative, both clinical and histological follow-up of more than 3 weeks was obtained in 22 patients, enabling us to look for indicators predictive of NL regeneration and outcome. Histological changes observed in the NL included complete regeneration in 68%, incomplete regeneration with obvious fibrous sequelae in 14% and severe liver fibrosis or cirrhosis in 18%, of the 22 patients studied. The percentage and distribution of necrosis observed in tissue samples of the NL at the time of transplantation was not related to the final outcome. Complete NL regeneration was observed in 15 patients, out of whom 14 were younger than 40 years. Patients with complete regeneration were mainly affected by FHF due to HAV, HBV, or paracetamol overdose. After a follow-up of 18/11 (mean/median) months (range, 3 to 67 months), 19 of the 30 patients (63%) survived and 13 of them (68%), i.e., 43% of the 30 patients, had resumed normal NL function, with interrupted immunosuppression, the ultimate goal of emergency auxiliary LT.

We conclude that, in patients with FHF, auxiliary LT is a procedure feasible in a number of centers and is associated with a complete regeneration capability of the NL in a majority of survivors, especially in those younger than 40 years. Confirmation of these encouraging preliminary results by large-scale prospective studies is required. (HEPATOLOGY 1996;23:1119-1127.)

Fulminant hepatic failure (FHF) is a life-threatening syndrome defined as an acute liver disease complicated by encephalopathy within 3 months after the onset of jaundice.[1,2] The rare cases of a hitherto asymptomatic chronic liver disease, particularly Wilson's disease, are now included in this definition.[1,3] Orthotopic total liver transplantation (LT) is currently considered to be an acceptable life-saving therapy in patients with FHF, but implies the counterpart of long-term immunosuppression. The aim of auxiliary LT, a procedure in which part of the native liver (NL) is left *in situ*, is to provide a temporary support until the NL has recovered.

Whether auxiliary LT is a valid therapeutic option for patients with FHF depends primarily on the incidence of complete regeneration of the NL, but also on the technical difficulties of the procedure and its postoperative mortality. A number of reports of successful auxiliary LT in patients with FHF have been published in recent years,[4-9] but the rarity of FHF and the dispersal of the cases make it difficult to evaluate this new procedure. The aim of this study was to present the evaluation of

Abbreviations: FHF, fulminant hepatic failure; LT, liver transplantation; NL, native liver; AG, auxiliary graft; NSAID, nonsteroidal anti-inflammatory drugs; HBV, hepatitis B virus; HAV, hepatitis A virus.

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TABLE 1. Case Distribution According to the Geographic Origin and Cause of FHF in 30 Patients Treated by Auxiliary LT

Geographic Origin	Patients (n = 30)	HAV (n = 4)	HBV (n = 7)	Toxic Substances (n = 7)	Drugs (n = 4)	AIH (n = 2)	Others (n = 6)
Clichy, France	5		2	Ecstasy	NSAID Multiple drugs		
Créteil, France	1						Unknown
Essen, Germany	3	1	1				Unknown
Geneva, Switzerland	1			Ecstasy			
Ghent, Belgium	1		1				
Hamburg, Germany	1			PO			
Hannover, Germany	3			PO			Unknown Preeclampsia
Leiden, The Netherlands	1		1				
London, England	3			PO (2)			Unknown
Montpellier, France	1			PO			
Rotterdam, The Netherlands	1					1	
Strasbourg, France	9	3	2		NSAID Halothane	1	Unknown

Abbreviations: AIH, autoimmune hepatitis; PO, paracetamol overdose.

the NL regeneration and the outcome in a series of 30 patients with FHF treated by auxiliary LT.

PATIENTS AND METHODS

A preliminary evaluation of auxiliary LT was attempted by inviting European groups that already performed the procedure in patients with FHF to join a workshop meeting held in Strasbourg, France, in October 1994. The aim of this workshop was primarily to identify criteria, especially morphological criteria, predictive of complete NL regeneration and patients' recovery.

All 12 European LT groups, listed in the European auxiliary LT register (Leiden, the Netherlands), provided their data on 30 patients who underwent auxiliary LT for FHF. Twenty-five patients were adults (age range, 15-65 years; mean ± SD, 34 ± 14.3; median, 33) and 5 children (age range, 3-14 years; mean ± SD, 7.6 ± 4,5; median, 5). All surgical procedures were performed between January 1989 and May 1994. The cases of 15 of these 30 patients were reported previously.[4-6,8-10] Table 1 shows the geographic origin of the patients and the cause of FHF. In 24 patients, the auxiliary graft (AG) was implanted orthotopically beside the reduced NL, using either a whole liver (n = 4), or a left (n = 16) or a right (n = 4) reduced graft, as described by Gubernatis et al.[5] and Boudjema et al.,[8] respectively. In 6 cases, the AG was implanted heterotopically below the NL, as described by Terpstra et al.,[11] using either an entire (n = 1) or a reduced (n = 5) liver. Except for 3 patients who initially received antilymphocyte antibodies, immunosuppression was based on a triple-therapy regime of steroids, azathioprine, and cyclosporin A. Features characterizing the clinical condition of the patients at the time of transplantation are shown in Table 2. Encephalopathy was graded into four stages according to Trey and Davidson.[12] Emergency LT was decided according to the Clichy criteria[13] and the King's College criteria[14] in 17 and 13 patients, respectively. The decision for auxiliary LT was based on two features. First, at the onset of the 1990s, two successful reported cases[4,5] showed that it was a reachable goal to obviate life-long immunosuppression in patients requiring emergency LT for FHF. Second, age, which is known to be an important parameter for normal liver regeneration, was a key factor in deciding auxiliary LT. Accordingly, in 25 of 30 patients, an age <50 was chosen as a reasonnable limit to try to offer the patient a chance to avoid long-term immunosuppression.

Histological Assessment. Sections of the NL on the day of transplantation (day 0) were available for the 30 patients. Tissue samples were taken from the excised NL segments in 27 cases and through peroperative needle biopsy in the 3 remaining cases. Only 22 patients underwent 2 to 9 follow-up NL biopsies (either percutaneously with ultrasonographic control or by the transjugular route) from day 6 to 3 years after auxiliary LT and were included in the morphological analysis. Eight patients were excluded from this analysis because no follow-up liver biopsy was available.

The slides were stained with hematoxylin and eosin, and with Masson's trichrome and/or silver stain for reticulin. Three pathologists (J. P. B., M. P. C., C. D.) defined the morphological features to be sought during the workshop. All slides were then analyzed by seven pathologists (M. P. C., V. C., F. T. K., H. M., M. P., L. R., E. S. Z.) on a multihead microscope with concomitant video projection in the presence of surgeons and hepatologists aware of the patients' clinical course. The following features were assessed: 1) location of liver cell necrosis (acinar zones 2 and 3, panacinar, multiacinar), its type (confluent necrosis or loss of hepatocytes), and its percentage of the entire specimen (fraction of the total surface area of the section which is occupied by parenchymal necrosis), as estimated semiquantitatively by consensus among the seven pathologists; 2) type of the inflammatory cell infiltrate (lymphocytes, macrophages, plasma cells, polymorphonuclear leukocytes), its main distribution (portal, acinar, or both), and its intensity (mild, moderate, or severe); 3) fibrosis and, if present, density and location; and 4) regenerative activity (either presence of mitotic liver cells, multinucleated hepatocytes, enlarged hepatocytes with cytoplasmic clarification, thickened plates, or cholangiolar proliferation).[15,16]

RESULTS

Clinical Outcome

In October 1994, 19 of the 30 patients (63%) were alive after a 3- to 67-month follow-up (mean ± SD, 18 ± 17.3 months; median, 11 months). Patient 18 underwent a

TABLE 2. Cause of FHF and Features Characterizing the Clinical Condition of 30 Patients at the Time of Auxiliary LT

Case No.	Cause	Age	J/E (d)	EN (grade)	PR† (%) or (s)	T Bil (μmol/L)	MV	PH	SC (μmol/L)
1	HAV	4	45	4	<10%	650	+	+	277
2	HAV	12	48	4	17%	350	–	–	63
3	HAV	15	50	4	12%	430	+	+	78
4*	HAV	49	6	4	32s	412	+	–	106
5	HBV	23	2	4	10%	208	–	–	58
6	HBV	24	5	3	78s	321	+	–	27
7	HBV	26	1	4	38s	299	+	–	65
8	HBV	46	6	2	<10%	575	–	–	26
9	HBV	51	4	4	18%	572	+	+	509
10	HBV	65	20	4	<10%	150	+	+	249
11*	HBV	21	1	3	<10%	211	–	–	50
12	Paracetamol	18	1	4	19%	81	–	–	112
13	Paracetamol	20	2	4	12%	60	+	+	145
14*	Paracetamol	36	4	2	22%	53	–	–	42
15*	Paracetamol	36	1	3	38s	142	+	+	381
16*	Paracetamol	31	2	3	140s	311	+	+	354
17	Ecstasy	33	11	4	10%	642	–	–	89
18	Ecstasy	19	15	4	18%	500	+	–	74
19	NSAID	23	30	4	10%	320	+	–	68
20*	NSAID	54	14	4	23%	715	–	–	124
21*	Multiple drugs	57	27	2	<10%	364	–	–	59
22	Halothane	54	21	1	15%	330	–	–	187
23	Autoimmune	35	49	4	33s	291	–	–	61
24	Autoimmune	30	14	4	<10%	320	+	+	100
25	Preeclampsia	33	5	4	29%	219	+	–	130
26	Unknown	16	9	4	<10%	600	+	–	60
27	Unknown	3	14	3	57s	405	–	–	53
28	Unknown	5	14	4	12%	550	–	–	72
29	Unknown	14	13	3	45s	550	+	+	340
30*	Unknown	35	14	4	10%	524	+	+	67

* No histological follow-up.

† Expressed as either a percentage of normal or in seconds (with a control of 13 seconds).

Abbreviations: J/E, interval between the onset of jaundice and encephalopathy; EN, encephalopathy; PR, prothrombin; T Bil, total bilirubinemia; MV, mechanical ventilation; PH, preoperative hemofiltration; SC, serum creatinine.

second auxiliary LT as an early retransplantation for primary nonfunction of the first graft. Thirteen of these 19 survivors regained normal NL function, allowing immunosuppression to be stopped permanently (68%). The AG was removed in 9 patients and left to atrophy in 4 others, with no deleterious effect on NL function. Immunosuppression was tapered in patient 27. Five patients were still on immunosuppression 5, 6, 9, 10, and 18 months after auxiliary LT (26%) (Table 3).

The other 11 patients died between 6 days and 8 months after auxiliary LT (37%). The AG was inserted heterotopically in 3 patients and orthotopically in 8. Because of poor initial function of the graft, 2 patients were retransplanted within 2 weeks (auxiliary LT in patient 3 and total LT in patient 30), but died from multiorgan failure within 2 months of the first graft. In the other 9 patients, death was due to surgical complications or sepsis. According to age, death occurred in 4 of 5 patients >50 years (80%) and in 7 of 25 patients <50 years (28%).

Histological Findings in NL Samples

Liver specimens from the NL, both at the time of LT and on follow-up biopsies, were available in 22 patients, including 18 survivors and 4 patients who died at least 1 month after transplantation. Histological evaluation was not available for 8 patients, including 1 survivor of FHF due to paracetamol overdose in whom the AG was permanently removed on day 9 (patient 14.) and 7 patients who died within 3 weeks after auxiliary LT (patients 4, 11, 15, 16, 20, 21, and 30) (Table 2).

Histological Lesions at Day 0. Liver cell necrosis at the time of transplantation ranged from 50 to 95% (≥90% in 10 patients) (Table 3). Even when liver cell necrosis was found to be extensive, a few hepatocytes were spared, scattered throughout the acini or grouped in small clusters in the periportal areas. In 11 cases, liver cell necrosis was confluent mainly in acinar zones 3 and 2 (50%), whereas in 6 others, the loss of hepatocytes occurred as random foci throughout the acini (27%). In 4 other cases, distribution of liver cell necrosis was found to be heterogeneous, with large areas of panacinar necrosis coexisting with well-preserved zones (18%). In a case of FHF due to autoimmune hepatitis (patient 24), multiacinar necrosis coexisted with large hyperplastic regenerative nodules, but there was no fibrosis.

TABLE 3. Histological Features of NL at the Time of Transplantation (Day 0) and Outcome in 22 Patients With Histological Follow-up

		Day-0 Biopsy		Outcome				
Case No.*	Cause	% of Necrosis	Inflammation	NL	AG	Patient Status	IS	Follow-up (mo)
1	HAV	90	++ (l, m)	cr	Removed	Alive	Stopped	>23
2	HAV	90	++ (l, m)	cr	Removed	Alive	Stopped	>17
3	HAV	60	+ (l, m)	cr	Functional	Died	Tapered	1.5
5	HBV	90	++ (l, m)	cr	Removed	Alive	Stopped	>8.5
6	HBV	95	+++ (l, m)	cr	Removed	Alive	Stopped	>5
7	HBV	50	+ (l, m)	cr	Removed	Alive	Stopped	>17
8	HBV	90	+ (l, m)	c	Functional	Alive	Full	>10
9	HBV	70	+ (l, m, pmn)	cr	Removed	Died	Stopped	4
10	HBV	60	+ (l, m)	c	Functional	Died	Full	1
12	Paracetamol	60	++ (l, m)	cr	Removed	Alive	Stopped	>20
13	Paracetamol	95	–	cr	Removed	Alive	Stopped	>10
17	Ecstasy	80	++ (l, m)	r + f	Functional	Alive	Full	>18
18	Ecstasy	50	++ (l, m)	r + f	Functional	Alive	Full	>5
19	NSAID	90	++ (l, m, pl)	cr	Atrophy	Alive	Stopped	>17
22	Halothane	80	+ (l, m)	f	Functional	Alive	Full	>9
23	Autoimmune	50	++ (l, m, pl)	cr	Atrophy	Alive	Stopped	>67
24	Autoimmune	70	++ (l, m)	c	Functional	Alive	Full	>6
25	Preeclampsia	80	++ (l, m)	cr	Atrophy	Alive	Stopped	>59
26	Unknown	90	++ (l, m)	r + f	Removed	Died	Stopped	8
27	Unknown	95	+++ (l, m, pmn)	cr	Functional	Alive	Tapered	>11
28	Unknown	90	++ (l, m, pl)	cr	Removed	Alive	Stopped	>3
29	Unknown	70	++ (l, m)	cr	Atrophy	Alive	Stopped	>7

Abbreviations: IS, immunosuppression; +, mild; ++, moderate; +++, severe; l, lymphocytes; m, macrophages; pc, plasma cells; pmn, polymorphonuclear leukocytes; c, cirrhosis; f, fibrosis; cr, complete regeneration; r + f, regeneration + fibrosis.

* Case numbers correspond to patient numbers as defined in Table 2.

Mild to severe inflammation was always present in NL tissue, except for one case of paracetamol overdose. In 13 of the 22 NL samples studied, inflammation was moderate, predominantly acinar, and located in necrotic areas (59%). Inflammatory cells were mainly lymphocytes and macrophages. Numerous plasma cells were present in 3 cases (FHF due to autoimmune hepatitis, nonsteroidal anti-inflammatory drug (NSAID)–induced hepatitis, and of unknown cause), and polymorphonuclear leukocytes were present in 2 cases (hepatitis B virus [HBV], unknown cause).

Fibrosis was difficult to evaluate on hematoxylin-eosin–stained sections of NL samples; however, it was never found on trichrome-stained sections.

Regarding regenerative activity in NL specimens, mitoses were rarely seen in liver cells. Hepatocyte enlargement with cytoplasmic clarification, a common feature of liver cell regeneration, was difficult to distinguish from ballooning degenerating hepatocytes. Cholangiolar proliferation, considered as a type of proliferative and reparative reaction following necrosis,[16] was present in all but four cases. Multinucleated hepatocytes were obvious in only one case of FHF due to ecstasy (patient 17).

Follow-up Histological Evaluation. Three types of morphological changes were seen in the NL tissue samples (Table 4). Complete regeneration of the NL (Fig. 1) was observed in 15 patients (68%); in these patients, the cause of FHF was viral hepatitis in 7, (hepatitis A virus [HAV] in 3 and HBV in 4), paracetamol overdose in 2, autoimmune hepatitis in 1, NSAIDs in 1, liver lesions of preeclampsia in 1, and unknown in 3 patients. Complete regeneration apparently developed in two steps: First, hepatocytes proliferated and repopulated the lobules, the centrilobular zones being replaced last. In the 5 cases in which serial biopsies were performed (patients 1, 2, 3, 13, and 28), repopulation was already complete by the third or fourth week after auxiliary LT. The trabecular architecture was restored during the second or third month after auxiliary LT. Inflammation generally vanished when the necrosis disappeared completely. Some very thin, nonbridging, periportal or centrilobular minor fibrotic sequelae persisted in 5 cases (patients 2, 3, 9, 19, and 23).

Incomplete regeneration with areas of obvious fibrosis (Fig. 2) developed in 3 of the 22 patients studied (14%). In patients 17 and 18, in whom FHF was due to ecstasy, fibrous scars were present in the NL tissue. Tapering of immunosuppression was not achieved in these patients who remained graft-dependent 18 and 5 months after LT, respectively. In patient 26, in whom the cause of FHF was unknown, thin, noninflammatory, bridging, fibrous septa were present, but NL function was normal, and the graft was removed 5 months after LT. This patient (patient 5 in reference 8) died 8 months after auxiliary LT from an extrahepatic complication.

Extensive fibrosis that developed in place of col-

TABLE 4. NL Outcome According to Patient Age, Cause of FHF, and the Duration of Jaundice Before the Onset of Encephalopathy in 22 Patients With Histological Follow-up

	Complete Regeneration	Regeneration + Fibrosis	Fibrosis or Cirrhosis
<40 years (n = 18)	14 (78%)	3 (17%)	1 (5%)
Cause*	HAV (3) HBV (3) Paracetamol (2) Others (6)*	Ecstasy (2) Unknown	AIH
J/E: 0-7 days	6	0	0
J/E: 8-28 days	3	3	1
J/E: 29-84 days	5	0	0
>40 years (n = 4)	1 (25%)	0	3 (75%)
Cause*	HBV		HBV (2) Halothane
J/E: 0-7 days	1		1
J/E: 8-28 days	0		2
J/E: 29-84 days	0		0
Total	15 (68%)	3 (14%)	4 (18%)

Abbreviations: J/E, interval between the onset of jaundice and encephalopathy; AIH, autoimmune hepatitis.

* Including autoimmune hepatitis, 1 case; liver lesions of preeclampsia, 1 case; NSAID, 1 case; and unknown cause, 3 cases.

lapsed areas (Fig. 3) was observed on serial biopsies in 4 of the 22 patients studied (18%). In patients 8 and 10, whose liver failure was due to HBV, cirrhosis was diagnosed on day 21 and day 70 after auxiliary LT, respectively. In patient 22, whose liver failure was related to halothane, fibrosis progressed very slowly from thickening of the reticulinic framework to mature collagen that replaced the collapsed areas after 4 months. In this patient, computed tomography showed atrophic NL. In patient 24, whose liver failure was due to autoimmune hepatitis, fibrosis was already present on day 42, and micronodular cirrhosis with moderate inflammatory activity was present 5 months, after auxiliary LT.

The Outcome of NL According to Pre-LT Clinical Features

In the 22 patients with histological follow-up, the outcome of NL was studied in relation to the patients' age, the cause of the FHF, and the interval between the onset of jaundice and encephalopathy (Table 4).

Regarding the patients' age, complete regeneration of the NL occurred in 14 of 18 patients <40 years (78%). Complete regeneration also occurred in 1 of 4 patients >40 years (25%) (χ^2 test with Yates' correction, not significant). This patient (patient 9 in Table 3) died from pulmonary embolism shortly after removal of the graft. In the 3 other patients >40 years, extensive fibrosis or cirrhosis developed in the NL.

Regarding the cause of FHF, complete regeneration of the NL occurred in 9 of 11 patients in whom the cause was HAV, HBV, (7 of 9, combined) or paracetamol overdose (2 of 2). Complete regeneration was also seen in the patient with liver lesions of preeclampsia, in 1 of the 2 patients whose liver disease was due to hepatotoxic drugs, in 1 of the 2 patients with autoimmune hepatitis, and in 3 of the 4 patients in whom FHF was of unknown origin.

According to a recent terminology proposed by O'Grady et al.,[3] the clinical course of FHF may be divided into three subgroups, depending on the interval between the onset of jaundice and encephalopathy: hyperacute (interval, 0-7 days), acute (interval, 8-28 days), and subacute (interval, 5-12 weeks [29-84 days]). In the 22 patients in our histological study, complete regeneration occurred in 7 of 8 patients with hyperacute (87%), 3 of 9 patients with acute (33%), and 5 of 5 with subacute liver failure (100%).

DISCUSSION

The overall survival rate of the 30 patients treated with auxiliary LT for FHF was 63% after a 3- to 67-month follow-up. This result compares favorably with the 1-year survival rate, ranging from 54% to 70%, obtained in 11 series of patients transplanted for fulminant hepatitis between 1987 and 1995.[17] Most importantly, 13 of the 19 survivors (i.e., 43% of the 30 patients) have permanently stopped immunosuppressive therapy and recovered full NL function—the ultimate goal of emergency auxiliary LT. Moreover, since 12 centers were involved in this study, it appears that auxiliary LT is a procedure feasible in most centers with a previous experience in total LT.

A key issue regarding auxiliary LT in patients with FHF is the characterization of criteria for the accurate prediction of complete NL regeneration. Among the 22 patients with histological follow-up, complete regeneration was the most frequent outcome of the NL. Its incidence was 78% in patients <40 years, 82% in those whom the cause of FHF was viral hepatitis or paracetamol overdose, and 87% of those whom FHF followed a hyperacute course. These three factors (an age <40, viral hepatitis or paracetamol overdose, and a delay between the onset of jaundice and encephalopathy <7 days) are all recognized indicators of relatively favorable outcome in patients with FHF.[1,3,14] Since liver regeneration is the cornerstone of recovery in these patients, it is not surprising to find these factors associated with complete regeneration of the NL after emergency auxiliary LT.

Our findings in the 22 patients with a histological follow-up (Table 4) suggest that patient age <40 is a more effective predictor of complete NL regeneration after auxiliary LT than the cause of FHF and the interval between jaundice and encephalopathy. Indeed, among the 14 patients <40 years with complete regeneration of the NL, some were affected by FHF because of causes other than viral hepatitis or paracetamol overdose; others, affected by HAV, suffered subacute liver failure, a clinical course associated with a 14% survival rate according to O'Grady et al.[3] Larger cohorts of patients are required to obtain a more accurate

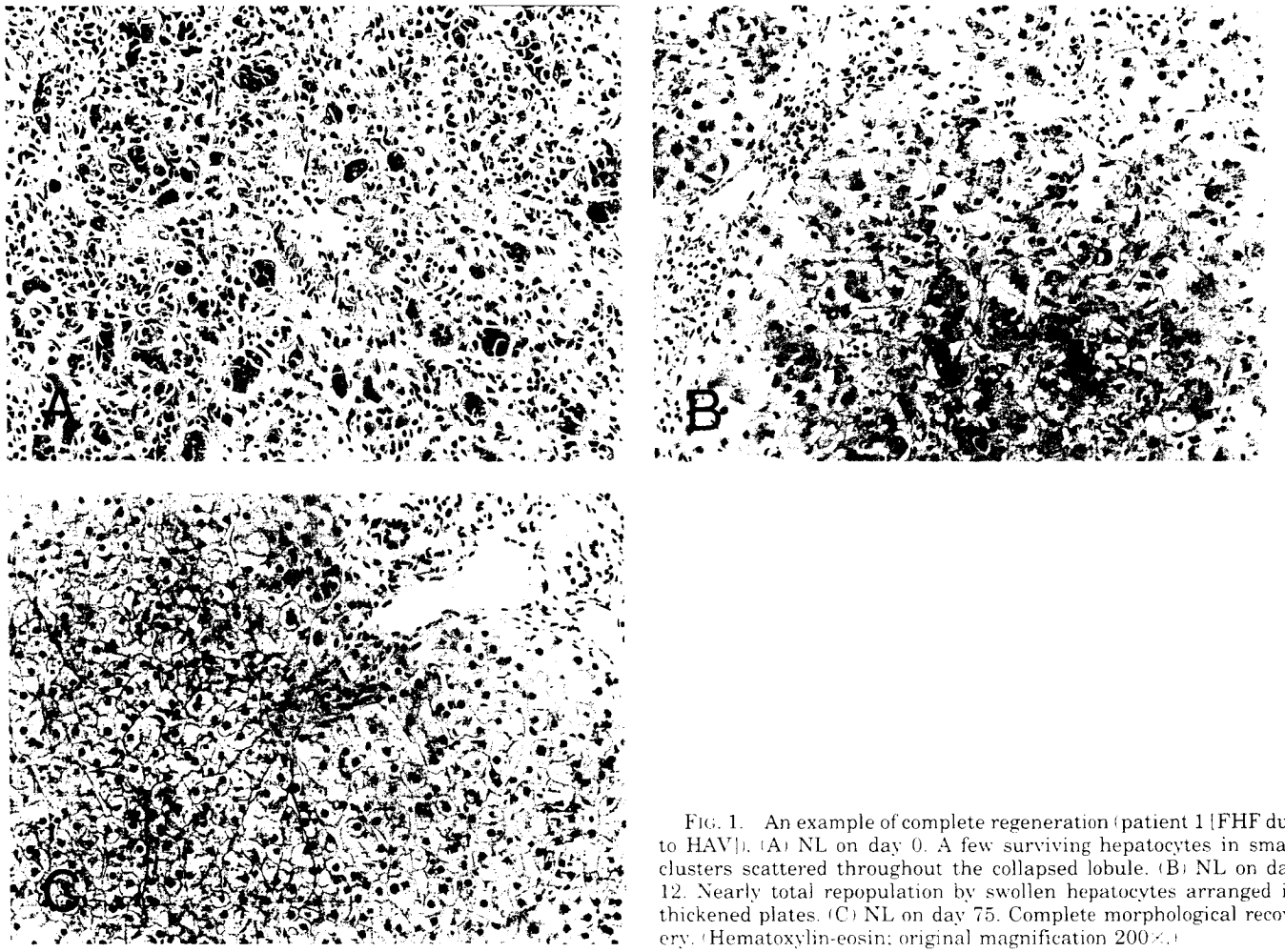

FIG. 1. An example of complete regeneration (patient 1 [FHF due to HAV]). (A) NL on day 0. A few surviving hepatocytes in small clusters scattered throughout the collapsed lobule. (B) NL on day 12. Nearly total repopulation by swollen hepatocytes arranged in thickened plates. (C) NL on day 75. Complete morphological recovery. (Hematoxylin-eosin; original magnification 200×.)

evaluation of factors predictive of complete NL regeneration.

Withdrawal of the AG, the ultimate goal of emergency auxiliary LT, was achieved in 15 patients with normal NL function (14 patients in Table 3, and patient 14 who was excluded from the histological study). It is noteworthy that NL function was normal despite persistent morphological abnormalities of the NL tissue in 4 patients. In 3 of them, liver cell repopulation was complete, but the acinar architecture was still abnormal when the AG was removed within the first month because of surgical complications. In the fourth patient (patient 26), the AG was removed despite significant fibrosis in the NL. Thus, complete regeneration of the NL is not an absolute requirement for withdrawal of the AG.

Withdrawal of the AG was not achieved in the four patients, three of them >age 40, in whom the NL became fibrotic or cirrhotic. Although patients who survive fulminant HBV hepatitis do not spontaneously develop chronic liver disease,[15] two of our patients (>40 years) with HBV-related FHF developed cirrhosis in their NL. These two patients had a left reduced graft implanted orthotopically, and both postoperative arteriography and portal vein ultrasonography yielded normal results. Two hypotheses could, at least in part, explain the exceptional development of cirrhosis after fulminant HBV. The first is that cirrhosis resulted from a very unusual course of the acute liver disease, which was observed because of the patients' survival after auxiliary LT. The second one is that cirrhosis was due to some unexpected deleterious influence of auxiliary LT on normal regeneration of the NL. In the 30-year-old patient 24, who was affected by FHF due to autoimmune hepatitis, hyperplastic regenerative nodules without fibrosis were present in the NL at the time of transplantation. These observations suggest that an age >40 and the presence of regenerative nodules in the NL at the time of transplantation predict a high risk of both abnormal regeneration of the NL and failure to achieve postoperative withdrawal of the AG.

Although rather encouraging, our results raise the question of whether they were influenced by the indication of emergency LT. Emergency LT was decided according to the two sets of criteria described by the Clichy group[13] and the King's group,[14] and used extensively in Europe. Conceivably, one cannot exclude that both criteria may have led to an overindication of emer-

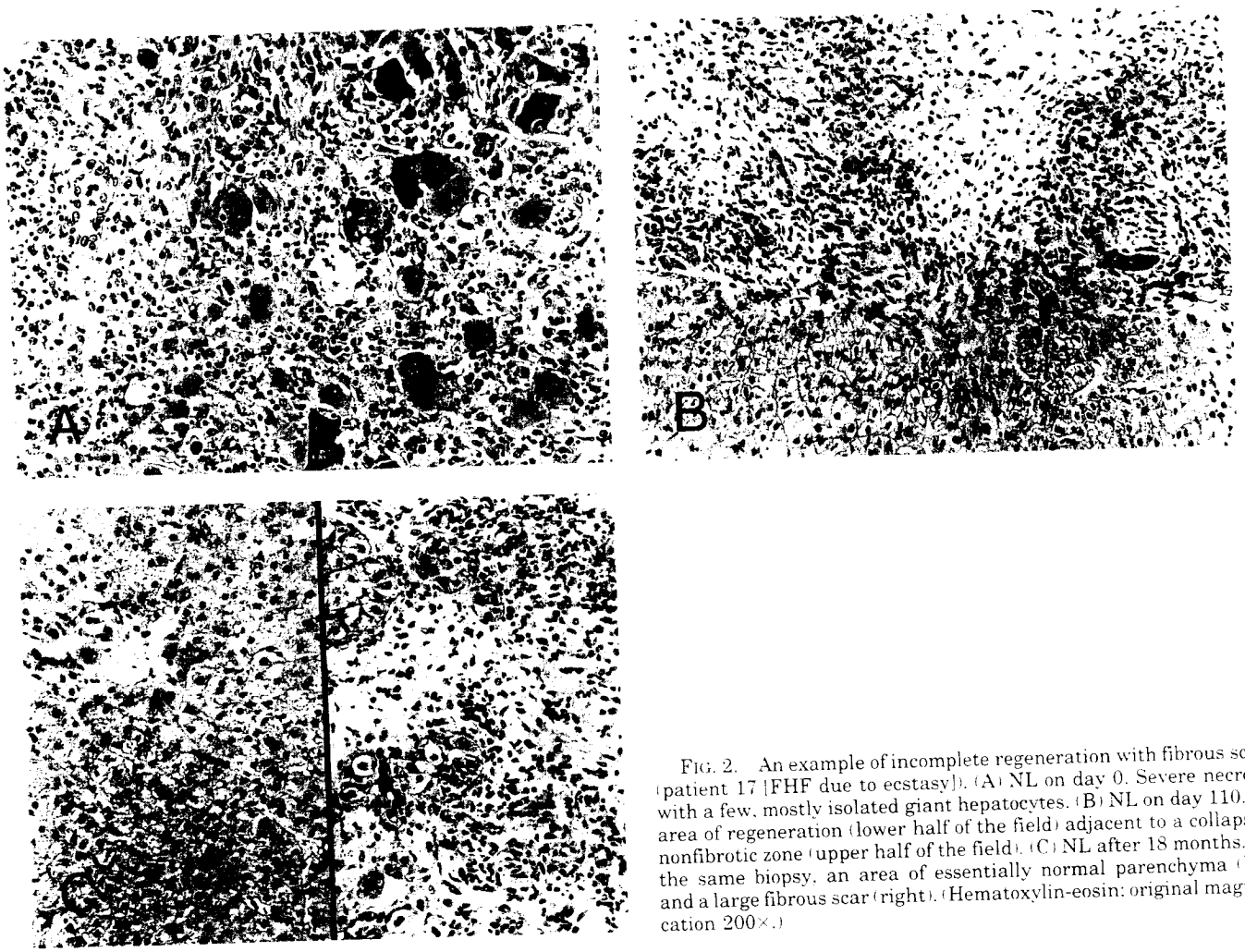

FIG. 2. An example of incomplete regeneration with fibrous scars (patient 17 [FHF due to ecstasy]). (A) NL on day 0. Severe necrosis with a few, mostly isolated giant hepatocytes. (B) NL on day 110. An area of regeneration (lower half of the field) adjacent to a collapsed, nonfibrotic zone (upper half of the field). (C) NL after 18 months. On the same biopsy, an area of essentially normal parenchyma (left) and a large fibrous scar (right). (Hematoxylin-eosin; original magnification 200×.)

gency LT[18] in some patients in whom effective liver regeneration was already initiated at the time of surgery. This hypothesis could be particularly relevant in patients with FHF due to HAV or paracetamol overdose—two causes associated with a relatively high spontaneous survival rate.[1,3,14] Thus, if one accepts the hypothesis of a possible overindication in some of our patients, the outcome of auxiliary LT in these few patients could have been more favorable than in other patients in whom NL regeneration was either not or poorly initiated before auxiliary LT. On the other hand, it can be argued that the results presented in our study have made auxiliary LT an acceptable option in patients in whom the indication of emergency LT might have been uncertain.[18]

In all centers participating in this study, auxiliary LT was considered to be contra-indicated if there was preexisting extensive fibrosis or cirrhosis of the NL, because both lesions were associated with altered capacity of the liver to regenerate normally. Accordingly, since FHF may be due to a chronic liver disease associated with extensive fibrosis or cirrhosis,[1,3] per-operative analysis of frozen NL sections may be crucial for the diagnosis of an unrecognized preexisting fibrosis and, thus, for a secure decision against auxiliary LT.

In this study, peroperative analysis of frozen NL sections did not show other prognostic factors of NL regeneration, such as early fibrosis or the percentage of surviving hepatocytes within the necrotic parenchyma. Presence of early fibrosis, which could indicate a propensity for NL to develop cirrhosis, was difficult to assess on hematoxylin-eosin–stained sections. Furthermore, it was not found retrospectively after applying Masson's trichrome and silver stains (which are generally not used on frozen sections in the emergency setting) to paraffin sections of the four NL that later became fibrotic or cirrhotic. In addition, the percentage of surviving hepatocytes within the necrotic parenchyma observed in NL samples at the time of transplantation (even when determined on large samples taken from the resected NL segments) was not related to the NL outcome. Indeed, in our experience, 9 of the 10 patients with only 5% to 10% of remaining hepatocytes recovered normal NL function, and the distribution of liver cell necrosis varied greatly from case to case and sometimes from one area to another in a given liver. Thus, our results are in accordance with those reported by Hanau et al.[19] who stated that the extent of liver cell necrosis in biopsy specimens is of no value in accurately predicting the survival of patients with FHF.

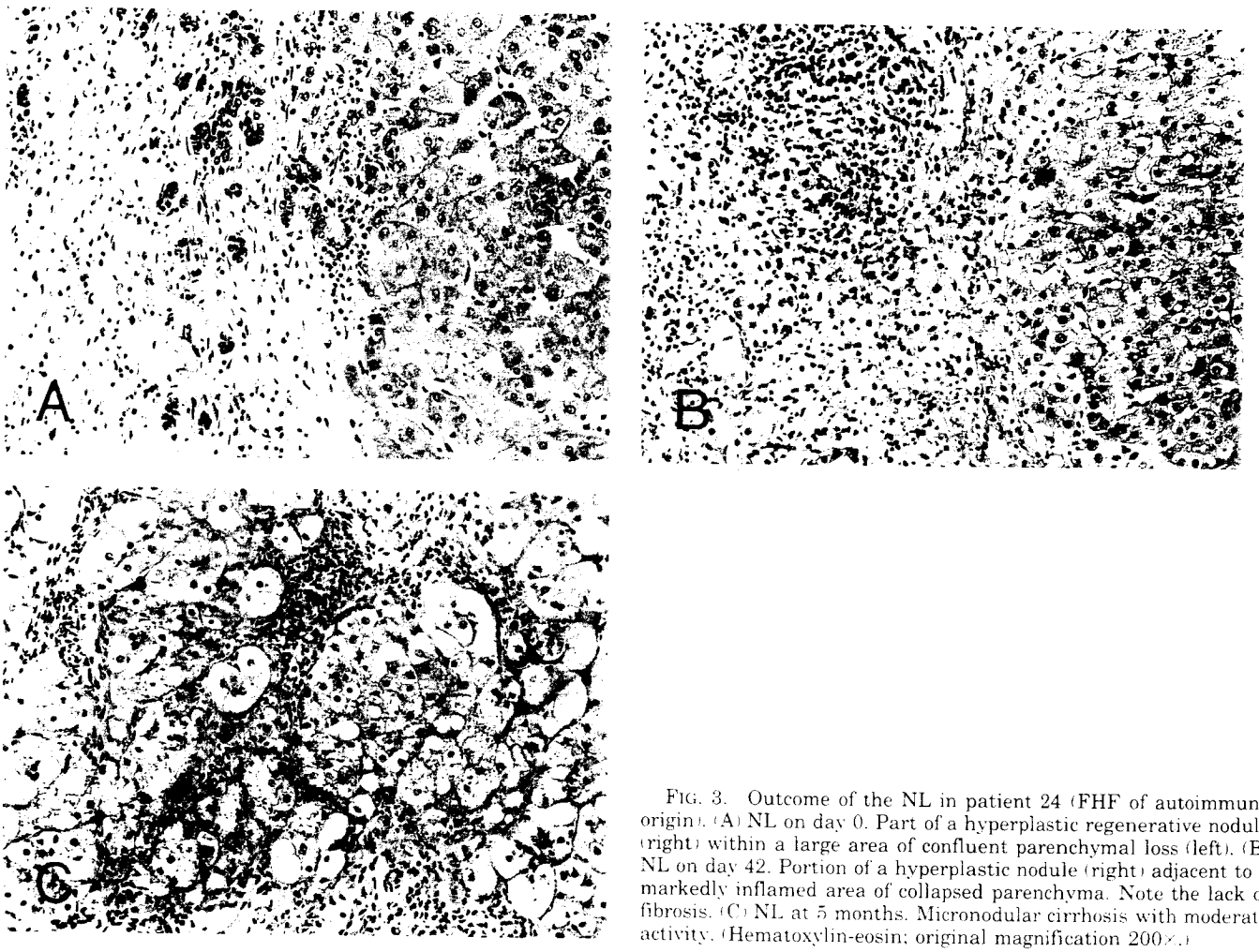

FIG. 3. Outcome of the NL in patient 24 (FHF of autoimmune origin). (A) NL on day 0. Part of a hyperplastic regenerative nodule (right) within a large area of confluent parenchymal loss (left). (B) NL on day 42. Portion of a hyperplastic nodule (right) adjacent to a markedly inflamed area of collapsed parenchyma. Note the lack of fibrosis. (C) NL at 5 months. Micronodular cirrhosis with moderate activity. (Hematoxylin-eosin; original magnification 200×.)

We conclude that, in patients with FHF treated by auxiliary LT, complete regeneration capability of the NL is preserved in a majority of survivors, especially in those <40 years. Although a 43% survival rate associated with cessation of immunosuppression was achieved in this multicenter study, therapeutic utility of auxiliary LT in patients with FHF is not yet fully demonstrated. A large number of patients enrolled in prospective studies are required in order to determine whether auxiliary LT will become a valid treatment of FHF in the future.

Addendum: In March 1996, the total number of patients with normal NL function and without immunosuppression is 16 of the 19 survivors, i.e., 53% of the 30 initial patients.

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