

REGRESSION OF LIVER FIBROSIS AFTER BILIARY DRAINAGE IN PATIENTS WITH CHRONIC PANCREATITIS AND STENOSIS OF THE COMMON BILE DUCT

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ABSTRACT

Background Chronic obstruction of the common bile duct may cause hepatic fibrosis and secondary biliary cirrhosis.

Methods We studied liver-biopsy specimens from 11 patients with chronic stenosis of the common bile duct due to chronic pancreatitis; all the patients had undergone liver biopsy before or at the time of surgical biliary decompression and underwent a subsequent liver biopsy for various clinical reasons. The patients were followed as part of a prospective study of 501 patients who had been treated for chronic pancreatitis. Two pathologists, who were unaware of the sequence of specimens, graded fibrosis on a scale of 0 (none) to 3 (cirrhosis).

Results The 11 patients were all men. Chronic pancreatitis was due to alcohol abuse in 10 of the men; 1 had idiopathic disease. The median age at diagnosis was 38 years. The median interval between the first and second liver biopsies was 2.5 years (range, 0.3 to 9.0). The two patients who had restenosis of the biliary anastomosis were excluded from the analysis of fibrosis. In the group of nine patients without restenosis, the second specimen showed significant improvement in fibrosis ($P=0.01$). The fibrosis improved by two grades in two patients and by one grade in four patients; in three patients, the grade did not change. The pathologists agreed on the grading of specimens from 10 of the 11 patients.

Conclusions In patients with chronic pancreatitis and stenosis of the common bile duct, liver fibrosis may regress after biliary drainage. (N Engl J Med 2001;344:418-23.)

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CHRONIC obstruction of the common bile duct may cause hepatic fibrosis and secondary biliary cirrhosis.^{1,2} Hepatic fibrosis is usually considered an irreversible process, even when the underlying cause is treated or removed.³ However, the fibrosis can be ameliorated — for example, in patients with primary biliary cirrhosis treated with ursodiol⁴ or methotrexate.⁵ Regression of hepatic fibrosis has been observed after treatment with interferon alfa in patients with chronic hepatitis C.⁶ Studies in rats suggest that liver fibrosis due to chronic obstruction of the common bile duct may regress after the obstruction has been corrected.⁷ According to a 1963 report describing an infant with cirrhosis due to atresia of the common bile duct, regeneration of the liver occurred after bypass surgery for the biliary atresia.⁸

Stenosis of the common bile duct is a common complication of chronic pancreatitis, occurring in 8 to 30 percent of patients.^{1,2,9} It can be treated by surgical biliary drainage^{1,2,9} or by endoscopic drainage.^{10,11} We studied liver-biopsy specimens from 11 patients with chronic stenosis of the common bile duct due to chronic pancreatitis; all 11 had undergone an initial biopsy before or at the time of biliary drainage and had undergone a second liver biopsy at a later date.

METHODS

Patients

Data from a series of 501 patients with chronic pancreatitis who were followed at Beaujon Hospital, Clichy, France, were collected prospectively from 1975 to 1999. The median follow-up period was 7 years (range, 0 to 35), for a total of 4086 patient-years. Of the 501 patients, 101 (20.2 percent) had stenosis of the common bile duct and cholestasis. Histopathological findings in liver specimens from 48 patients were reported in 1993.¹ Seventy-nine of the 101 patients (78.2 percent) underwent surgical biliary drainage. The other 22 patients did not undergo surgery because the associated risks were considered to be too high. A preoperative or perioperative liver biopsy was performed in all 79 patients who underwent surgery, including 11 who underwent a subsequent liver biopsy for various reasons. These 11 patients constituted our study sample. None of them had received concomitant drug therapy known to induce cholestasis, and none had hepatitis B viral markers (hepatitis B surface antigen or antibodies against hepatitis B surface antigen) or were known to be positive for hepatitis C virus antibodies.

The diagnosis of chronic pancreatitis was established on the basis of one or more of the following criteria: the presence of pancreatic calcifications on abdominal plain films, ultrasonograms, computed tomographic (CT) scans, or endosonograms; moderate-to-marked ductal lesions according to the Cambridge classification¹²; or characteristic histologic findings in an adequate surgical specimen. The duration of follow-up was defined as the interval between the first sign clearly attributable to chronic pancreatitis and the last contact with the patient. Alcohol consumption was considered the cause of chronic pancreatitis if the patient's intake of pure alcohol had exceeded 60 g per day for at least two years in the absence of other causes.¹³

Stenosis of the common bile duct was suspected on the basis of ultrasonographic, endosonographic, or CT findings. Stenosis was confirmed if endoscopic retrograde or operative cholangiography showed that the diameter of the common bile duct was reduced by 50 percent or more with proximal dilatation. Serum alkaline phosphatase, γ -glutamyltransferase, and aminotransferase levels were recorded in all patients. Cholestasis was defined by an alkaline phosphatase value that was above the upper limit of the normal range.

At the time of liver biopsy, a wedge resection was performed,

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with a specimen approximately 15 mm deep and 7 mm in diameter obtained from the third segment of the left lobe (rather than from the apex of the left lobe, which might have contained a thickened capsule). Percutaneous core-biopsy specimens were obtained from the right lobe of the liver through an intercostal route.

Histologic Analysis

All liver-biopsy specimens were evaluated by two pathologists who were unaware of the clinical data and of the sequence of the liver-biopsy specimens. The specimens were fixed in 10 percent formalin solution or in Bouin's fluid and were then embedded in paraffin. The histologic features of sections stained with hematoxylin and eosin, Masson's trichrome, picosirius, chromotrope aniline blue, and Perls were scored with the use of a scale previously validated in a study of the treatment of primary biliary cirrhosis.¹⁴ Fibrosis was scored on a scale from 0 to 3, with 0 denoting no fibrosis, 1 portal and periportal fibrosis, 2 the presence of numerous septa, and 3 cirrhosis. Portal and periportal inflammation was scored on a scale from 0 to 3; 0 denoted no inflammation, 1 mild inflammation (cells in less than one third of portal tracts), 2 moderate inflammation (cells in one third to two thirds of portal tracts), and 3 severe inflammation (dense packing of cells in more than two thirds of portal tracts). Ductular proliferation was scored on a scale from 0 (absent or mild) to 2 (severe). Histologic features of cholestasis were scored on a scale from 0 to 3, with 0 denoting none, 1 bile accumulation in centrilobular hepatocytes, 2 bile accumulation in centrilobular and periportal hepatocytes or in portal tracts, and 3 bile infarcts (bile accumulation and hepatocellular necrosis surrounded by foamy histiocytes). The specimens were carefully examined for histologic features that are consistent with the presence of alcoholic liver disease, including Mallory's bodies, acidophilic necrosis, sinusoidal fibrosis, and polymorphonuclear infiltrates.

Statistical Analysis

Data are reported as medians and ranges. Histologic findings in the first liver-biopsy specimen (obtained at the time of or immediately before biliary drainage) and those in the specimen obtained at a later date were compared with the use of Wilcoxon's

signed-rank test for matched pairs.¹⁵ A P value of less than 0.05 was considered to indicate statistical significance. The findings in the two patients who had restenosis of the biliary anastomosis (Patients 10 and 11) were excluded from the statistical analysis.

RESULTS

Characteristics of the Patients

The characteristics of the 11 patients, all of whom were men, are shown in Table 1. Chronic pancreatitis was due to alcohol abuse in all but one man (Patient 4), who had idiopathic chronic pancreatitis. The median duration of follow-up was 11 years (range, 4 to 27). The median age at the time of the clinical onset of chronic pancreatitis was 36 years (range, 14 to 50), and the median age at diagnosis was 38 years (range, 33 to 54). Among the nine patients without restenosis of the biliary anastomosis, data on alcohol consumption before the first biopsy were available for all but one (Patient 8). These eight patients had all been abstinent for a median of 4 months (range, 1 to 48) before the first liver biopsy. Three of the eight patients had resumed drinking before the second biopsy (Patients 1, 2, and 8).

First Liver Biopsy

The median interval between the clinical onset of chronic pancreatitis and the diagnosis of stenosis of the common bile duct with cholestasis was 3 years (range, 1 to 21) (Table 1). All 11 patients had pancreatic calcifications when the stenosis was diagnosed. The median interval between the diagnosis of bile duct stenosis and the first liver biopsy was 11 weeks (range, 2 to 98). Liver biopsy was performed during surgery

TABLE 1. CHARACTERISTICS OF 11 PATIENTS WITH STENOSIS OF THE COMMON BILE DUCT DUE TO CHRONIC PANCREATITIS.

| PATIENT No. | AGE AT ONSET OF PANCREATITIS | AGE AT DIAGNOSIS OF PANCREATITIS | DURATION OF FOLLOW-UP | INTERVAL BETWEEN ONSET OF PANCREATITIS AND DIAGNOSIS OF BILIARY STENOSIS | INTERVAL BETWEEN DIAGNOSIS OF BILIARY STENOSIS AND FIRST BIOPSY | SURGICAL TREATMENT OF STENOSIS | CLINICAL MANIFESTATIONS OF STENOSIS AT TIME OF FIRST BIOPSY | MAXIMAL DIAMETER OF COMMON BILE DUCT* |
|-------------|------------------------------|----------------------------------|-----------------------|--|---|--------------------------------|---|---------------------------------------|
| | | | | years | wk | | | |
| 1 | 34 | 34 | 4 | 1 | 11 | Choledocoduodenostomy | Jaundice | 11 |
| 2 | 36 | 38 | 14 | 5 | 2 | Choledocoduodenostomy | Ascending cholangitis | 10 |
| 3 | 34 | 34 | 6 | 6 | 47 | Hepaticojejunostomy | Ascending cholangitis, jaundice | 12 |
| 4 | 14 | 35 | 27 | 21 | 98 | Choledocoduodenostomy | Jaundice | 14 |
| 5 | 50 | 54 | 7 | 1 | 13 | Choledocojejunostomy | Jaundice | 9 |
| 6 | 42 | 42 | 12 | 6 | 9 | Choledocojejunostomy | Jaundice | 12 |
| 7 | 32 | 33 | 13 | 2 | 80 | Hepaticojejunostomy | Jaundice | 10 |
| 8 | 41 | 41 | 15 | 2 | 2 | Pancreaticoduodenectomy | Jaundice | 10 |
| 9 | 48 | 48 | 5 | 1 | 2 | Choledocoduodenostomy | Ascending cholangitis, jaundice | 15 |
| 10 | 46 | 50 | 11 | 3 | 58 | Hepaticojejunostomy | Jaundice | 13 |
| 11 | 31 | 35 | 6 | 6 | 2 | Choledocoduodenostomy | Jaundice | 12 |

*The diameter of the common bile duct was measured with the use of ultrasonography, CT, cholangiography, or endoscopic ultrasonography.

for biliary drainage in 10 patients; 1 patient underwent percutaneous biopsy. In all 11 patients, the liver was firm and green at the time of the first biopsy, and no regenerative nodules were observed. Histologic analysis of liver-biopsy specimens from all the patients revealed secondary biliary disease without signs of alcohol-induced liver damage. Six patients had severe fibrosis with numerous septa (grade 2), and one had Child–Pugh class A secondary biliary cirrhosis (grade 3) (Table 2). At the time of the first biopsy, none of the patients had hepatic insufficiency, including the patient with cirrhosis.

Second Liver Biopsy

After biliary drainage, the results of laboratory tests were normal in nine patients. The two patients with biliary anastomotic restenosis (Patients 10 and 11) had persistent cholestasis. The median interval between the first and second liver biopsies was 2.5 years (range, 0.3 to 9.0). In nine patients, the second liver biopsy was performed during surgery for another complication of chronic pancreatitis (pancreaticoduodenectomy was performed in two patients, left-sided pancreatectomy in three, vagotomy in two, and reconstruction of biliary anastomosis in two); a percutaneous biop-

TABLE 2. RESULTS OF BIOCHEMICAL TESTS AND HISTOLOGIC FINDINGS.*

| PATIENT NO. | INTERVAL BETWEEN BIOPSIES | AST | ALT | ALP | GGT | BILIRUBIN | GRADE OF FIBROSIS† | |
|-------------|---------------------------|---------|-----|------|------------|-----------|--------------------|----------------|
| | | | | | | | PATHOL-OGIST 1 | PATHOL-OGIST 2 |
| | mo | U/liter | | | μmol/liter | | | |
| 1 | 30 | | | | | | | |
| Biopsy 1 | | 160 | 83 | 4160 | 795 | 61 | 2 | 2 |
| Biopsy 2 | | 32 | 28 | 92 | 25 | 8 | 1 | 1 |
| 2 | 108 | | | | | | | |
| Biopsy 1 | | 205 | 407 | 258 | 805 | 12 | 1 | 1 |
| Biopsy 2 | | 37 | 25 | 87 | 38 | 12 | 1 | 1 |
| 3 | 65 | | | | | | | |
| Biopsy 1 | | 283 | 81 | 1289 | 2412 | 270 | 3 | 3 |
| Biopsy 2 | | 78 | NA | 19 | 2 | NA | 1 | 1 |
| 4 | 42 | | | | | | | |
| Biopsy 1 | | 128 | 200 | 528 | 1588 | 60 | 1 | 0 |
| Biopsy 2 | | 27 | 32 | 110 | 28 | 11 | 1 | 0 |
| 5 | 32 | | | | | | | |
| Biopsy 1 | | 204 | 285 | 265 | 78 | 42 | 2 | 2 |
| Biopsy 2 | | 32 | 30 | 97 | 35 | 15 | 1 | 1 |
| 6 | 11 | | | | | | | |
| Biopsy 1 | | NA | NA | NA | NA | NA | 2 | 2 |
| Biopsy 2 | | 34 | 38 | 78 | 35 | 13 | 1 | 1 |
| 7 | 73 | | | | | | | |
| Biopsy 1 | | 403 | 405 | 1950 | 1189 | 59 | 2 | 2 |
| Biopsy 2 | | 28 | 26 | 82 | 32 | 10 | 0 | 0 |
| 8 | 13 | | | | | | | |
| Biopsy 1 | | 200 | 207 | 388 | 1120 | 60 | 1 | 1 |
| Biopsy 2 | | NA | NA | NA | NA | NA | 1 | 1 |
| 9 | 4 | | | | | | | |
| Biopsy 1 | | 279 | 239 | 1690 | 1612 | 60 | 2 | 2 |
| Biopsy 2 | | 25 | 27 | 95 | 29 | 12 | 1 | 1 |
| 10‡ | 29 | | | | | | | |
| Biopsy 1 | | 80 | 78 | 785 | NA | 45 | 2 | 2 |
| Biopsy 2 | | 92 | 95 | NA | 7 | 10 | 3 | 3 |
| 11‡ | 5 | | | | | | | |
| Biopsy 1 | | 195 | 155 | 392 | 725 | 48 | 1 | 1 |
| Biopsy 2 | | 118 | 92 | 15 | 8 | 212 | 1 | 1 |

*The normal value for aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltransferase (GGT) is less than 40 U per liter; the normal value for alkaline phosphatase (ALP) is less than 130 U per liter. All biopsies were surgical wedge biopsies except for the first biopsy in Patient 2, the second biopsy in Patient 3, and the second biopsy in Patient 8, which were performed percutaneously. To convert the values for bilirubin to milligrams per deciliter, divide by 17.1. NA denotes not available.

†Fibrosis was graded on a four-point scale, with 0 denoting none, 1 portal and periportal fibrosis, 2 the presence of numerous septa, and 3 cirrhosis. P=0.01 for the difference in the grade of fibrosis between the first and second biopsies (with Patients 10 and 11, who had anastomotic restenosis, excluded from the analysis).

‡The patient had anastomotic restenosis.

sy was performed in two patients because of possible acute alcoholic hepatitis. None of the patients had hepatic insufficiency at the time of the second biopsy.

The quantification of fibrosis by the two pathologists was concordant for both series of biopsies in all the patients except one (Patient 4) (Table 2). The second biopsy showed that the fibrosis had worsened in one of the two patients with anastomotic restenosis and remained the same in the other. In the other nine patients, there was a significant reduction of fibrosis ($P=0.01$) (Fig. 1). On the four-grade scale, fibrosis improved by two grades in two patients and by one grade in four; in three patients, the grade did not change. In the patient with secondary biliary cirrho-

sis at the initial liver biopsy (Patient 3), only mild portal and periportal fibrosis was found at the second biopsy.

The second biopsy also showed significant improvement over the first biopsy with regard to ductular proliferation and portal inflammation ($P=0.01$ for both comparisons, data not shown). In addition, there was a decrease in bile accumulation between the first and second biopsies, but the difference was not significant (data not shown). We detected no signs of alcohol-induced liver damage in any of the specimens from the second liver biopsy. The two patients with suspected acute alcohol hepatitis had steatosis in more than 20 percent of their hepatocytes.

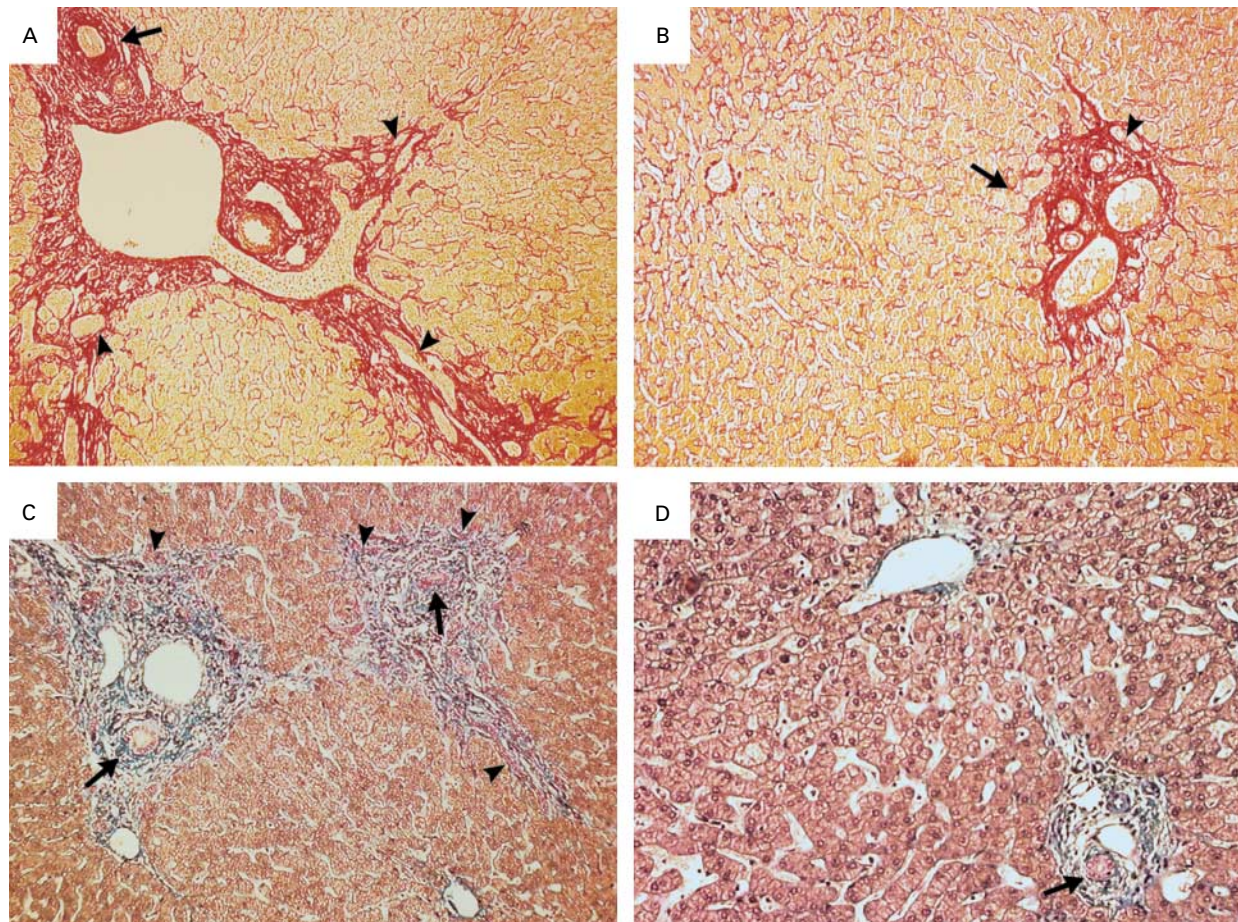


Figure 1. Histologic Features of Liver-Biopsy Specimens Obtained during and after Biliary Decompression in Two Patients with Stenosis of the Common Bile Duct Due to Chronic Pancreatitis.

Panel A shows a specimen obtained from Patient 1 during biliary compression (picrosirius stain, $\times 80$). The portal tract is enlarged by edematous fibrosis, with periportal ductular proliferation (arrowheads). The interlobular bile duct is surrounded by dense fibrosis (arrow). Panel B shows a specimen obtained from the same patient 30 months later (picrosirius stain, $\times 70$). The portal fibrosis is mild, with faint ductular proliferation (arrowhead). The structure of the interlobular bile duct is preserved (arrow). Panel C shows a specimen obtained from Patient 5 during biliary decompression (chromotrope aniline blue, $\times 50$). The portal tracts are enlarged, with edematous fibrosis and pronounced ductular proliferation (arrowheads). The interlobular bile ducts are surrounded by fibrosis (arrows). Panel D shows a specimen obtained from Patient 5 32 months after biliary decompression (chromotrope aniline blue, $\times 120$). The portal fibrosis is mild, and the interlobular bile duct is normal (arrow).

DISCUSSION

Animal models have provided much information about the structure and function of the liver in chronic obstruction of the common bile duct.^{7,16,17} In a study of rats with bile-duct obstruction for four weeks, biliary cirrhosis was found in all surviving animals.¹⁶ Several surgical methods of biliary decompression have been described in such models.^{7,18,19} In one study, relief of obstruction after 14 days led to normalization of portal pressure and hepatic venous wedge pressure.¹⁹ If biliary obstruction persisted for a longer period, relief of the obstruction failed to lower portal pressure, although biochemical signs of cholestasis resolved. In another study, secondary biliary fibrosis was reversed in rats after four weeks of bile-duct obstruction.⁷ Improvements in histologic findings (ductular proliferation, fibrosis, and portal hypertension) were correlated with improvements in liver-enzyme values, and these changes were accompanied by improved hepatic function and the reversal of portal hypertension.

There are few data on the effect of surgery on histologic findings after biliary decompression. In a study reported in 1968, biliary decompression appeared to alleviate portal hypertension.²⁰ When stenosis of the common bile duct is due to chronic pancreatitis, the stenosis is usually incomplete. It is largely due to pancreatic fibrosis rather than pancreatic pseudocysts and may be associated with duodenal stenosis.²¹ In 6 to 29 percent of patients, stenosis of the common bile duct may cause severe liver disease, including cirrhosis.^{1,2,9} In one study, secondary biliary cirrhosis led to portal hypertension with esophageal or gastric varices in 23 percent of patients,²² and patients with biliary cirrhosis may die from hepatocellular failure or sepsis.²³ The condition may develop in a relatively short period (3 to 12 months in one third of the patients studied by Scobie and Summerskill²²).

Stenosis of the common bile duct due to biliary compression in patients with chronic pancreatitis provides a unique opportunity to study the course of liver disease after the obstruction has been relieved. Other causes of chronic stenosis of the common bile duct (e.g., ampullary tumors) are rare or are associated with a poor prognosis (e.g., pancreatic adenocarcinoma), with death occurring shortly after decompression. Our data confirm the potential severity of liver disease in a selected group of patients with severe stenosis of the common bile duct due to chronic pancreatitis. The damage appears to occur rapidly; the median time between the detection of stenosis and the first liver biopsy was 11 weeks.¹

Our study provides evidence of the reversibility of secondary biliary fibrosis after surgical treatment of chronic obstruction of the common bile duct. Since in the absence of clinical reasons it would be unethical to perform a second liver biopsy, in our study the second biopsy was performed for identifiable clinical reasons or during surgery. There was selection bias

in the study, because only 11 patients in a series of 501 met the criterion of a second biopsy. Thus, our patients may not be representative of patients with stenosis of the common bile duct due to chronic pancreatitis.

In our patients the stenosis was severe; 10 of the patients (91 percent) had jaundice at the time of the first liver biopsy, a higher proportion than that in our earlier study (40 percent).¹ However, each patient was his own control, and selection was not based on the severity of the disease. We also cannot exclude the possibility that the variation in histologic findings was due to a sampling error. However, only 3 of the 22 specimens were from core biopsies of the right lobe. The other 19 were wedge-biopsy specimens obtained in the same way from the same hepatic segment in all cases. In addition, there is no documented evidence that biliary changes due to distal obstruction of the common bile duct are not widely distributed in the liver.^{1,2,7} Despite the retrospective design of our study, we minimized bias by ensuring that the two pathologists were unaware of both the clinical data and the sequence of the biopsy specimens and by using a scoring system that has been validated for cholestatic disease.¹² Comparison of our patients with a control group consisting of patients with bile-duct obstruction in whom bypass procedures were not performed would have been valuable. However, it is not possible to perform such a comparison because the detection of an obstruction of the common bile duct is usually followed rapidly by surgical decompression.

None of the patients in our study had both biliary and alcoholic changes on liver biopsy. This finding is probably due to the severity of biliary lesions, which may mask minor changes related to the consumption of alcohol. We cannot rule out a synergistic effect of biliary decompression and abstinence from alcohol. However, the pathological findings in the three patients who continued to abuse alcohol were similar to those in the patients who remained abstinent. Regression of fibrosis due to alcohol consumption has not been clearly demonstrated.²⁴ Thus, the major benefits we observed were probably due to relief of biliary obstruction. With the exception of the two patients with restenosis of the biliary anastomosis, all the patients had significant improvement in liver damage, even those with severe damage initially.

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