

Regeneration of Human Liver After Hepatic Lobectomy Studied by Repeated Liver Scanning and Repeated Needle Biopsy

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Regeneration of the residual lobe of the liver after hepatic lobectomy in humans was studied by repeated liver scanning in seven noncirrhotic and three cirrhotic patients. Each patient was studied for several months during the study which lasted from 1–12 years. Regeneration was apparent in noncirrhotic liver remnants following hepatic lobectomy. In the case of a long standing, space occupying lesions such as benign giant cysts, the liver remnant would complete its regeneration process rather early, usually within a few months of hepatic lobectomy. In hepatoma cases, however, regeneration of the residual lobe after hepatic resection usually took five or six months for completion. On the contrary, no definite increase in the size of the liver remnant was seen on repeated liver scanning in cirrhotic patients. Histologic study of the residual lobe was repeated on needle biopsy specimens in two noncirrhotic and four cirrhotic patients. Regenerative hyperplasia of liver cells with large hyperchromatic, or double nuclei never seen in the preresection liver appeared in the liver remnant five, 11, and 27 days after hepatic lobectomy in noncirrhotic patients. In cirrhotics, however, there were no histologic changes between the preresection liver and the postresection remnant studied three, five, 15, 40 days or even two years and 8 months after hepatic lobectomy.

ALTHOUGH REGENERATION of the liver after extensive hepatic resection does not occur as rapidly in humans as in small animals, Pack et al.⁵ proved marked regenerative hyperplasia of the liver remnant while performing a second-look exploration or required secondary operation in four patients who underwent extensive right hepatic lobectomy for cancer. They found that the lateral segment of the left lobe of the liver was enlarged to twice its normal size two and a half months after the operation. In the other case explored five months after initial resection, the lateral segment extended across the entire cupola of the diaphragm and occupied the right upper abdomen.

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Another two cases re-explored 21 and 24 months respectively after extensive right hepatic lobectomy demonstrated that the lateral segment of the left lobe was normal in color and consistency and had increased its size to that of an intact whole liver. Histologic examination of the liver in the latter two cases (21 and 24 months after operation) showed normal liver tissue with evidence of marked bile duct proliferation.

Bengmark² also reported a case showing regeneration of the liver remnant to normal size at the time of second-look exploration one year after an extensive right hepatic lobectomy. McDermott et al.⁴ studied the regeneration by repeated liver scanning with rose bengal tagged with I¹³¹ in two cases after an extended right hepatic lobectomy and concluded that restoration of normal liver mass had occurred within 6 months. Starzl et al.⁶ also treated their patients with extensive right hepatectomy (85–90% resection). Repeated liver scanning with ^{99m}technetium disclosed that only a tiny fragment of the liver was visualized two days after operation. Regeneration began one month later and was still evident at the sixth postoperatively, but no further evidence of regeneration was seen on liver scanning taken 13 months after operation. Arousen, Bengmark et al.¹, however, followed regeneration after hepatic lobectomy in two cases of blunt liver injury with repeated liver scanning and found that the liver did not seem to be completely restored to normal size 6 months after operation.

Lin et al.³ studied the regeneration of human liver in six noncirrhotic and five cirrhotic hepatoma patients by applying metal clips around the margins of the liver remnant at the time of hepatic lobectomy. The size of liver remnant was recorded weekly by x-ray and occasionally by liver scanning. These procedures showed

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the liver remnant enlarged in periodic way definitely from the third week after hepatic lobectomy in non-cirrhotic group, whereas increase in the size of the liver remnant was not noted in cirrhotic group.

The purpose of this paper is to study the regeneration of noncirrhotic and cirrhotic human liver remnants after hepatic lobectomy by repeated liver scanning in collaboration with repeated needle biopsy of the liver.

Materials and Methods

Seven noncirrhotic patients were studied by repeated liver scanning with ^{99m}Tc after hepatic lobectomy for a period of 8 months to 12 years. Two were repeatedly needle biopsied after operation for histologic study of the liver remnant. Of the seven noncirrhotics, three were lobectomized on the right lobe for benign giant cyst of the liver, four were lobectomized, three on the right and one on the left lobe, for primary carcinoma of the liver.

Another six patients who underwent hepatic lobectomy for primary carcinoma of the liver were associated with liver cirrhosis. Three were studied over a one and a half year period for regeneration of the liver remnant by repeated liver scanning. Four of the six cases were studied histologically by repeated needle biopsy of the liver remnant at 3, 5, 15, 40 days and 2 years and 8 months after left hepatic lobectomy.

Study of the metabolic function of cirrhotic and non-cirrhotic human livers after hepatic lobectomy was not included in this paper, as they had been reported previously by Lin et al.³

Results

Regeneration of the Liver Remnant in Noncirrhotics and Cirrhotics Studied by Repeated Liver Scanning

Three cases of benign giant liver cyst in noncirrhotic group were repeatedly aspirated and infected before coming to surgery. At operation the cysts contained 3000–4000 cc of chocolate colored fluid and had almost entirely replaced the right lobe which remained merely as a thin layer of liver tissue around the cyst. The left lobe was larger than usual (Fig. 1). Repeated liver scanning after right hepatic lobectomy in these three cases showed that the remaining left lobe had restored to maximum size within three months. No further enlargement of the liver remnant was seen in later scanning (Fig. 1).

Four patients with hepatoma in the noncirrhotic group were seen for two or three months after manifestation of their initial symptoms. At laparotomy three patients showed massive type hepatoma in the right lobe, of which part of the normal liver tissue was still preserved. The left lobe looked normal in size and in appearance. Repeated scanning after hepatic lobec-

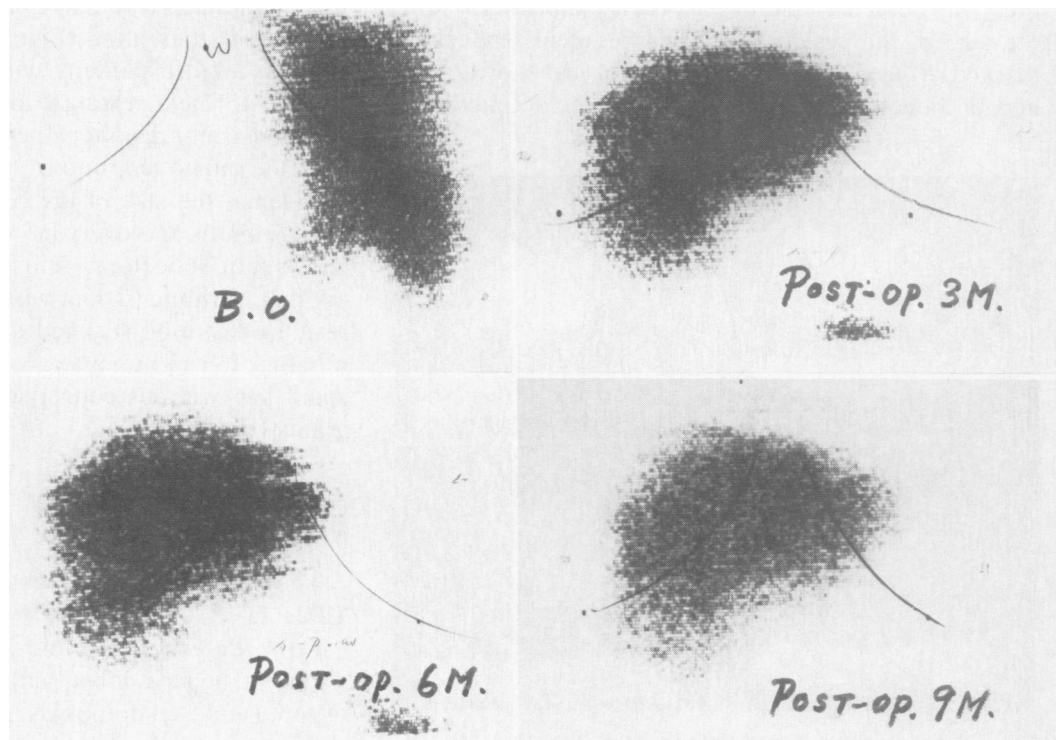


FIG. 1. The remaining left lobe returned to maximum size by the third postoperative month in a case of noncirrhotic benign giant cyst. The liver remnant scanned at six and nine months after right hepatic lobectomy showed no further enlargement.

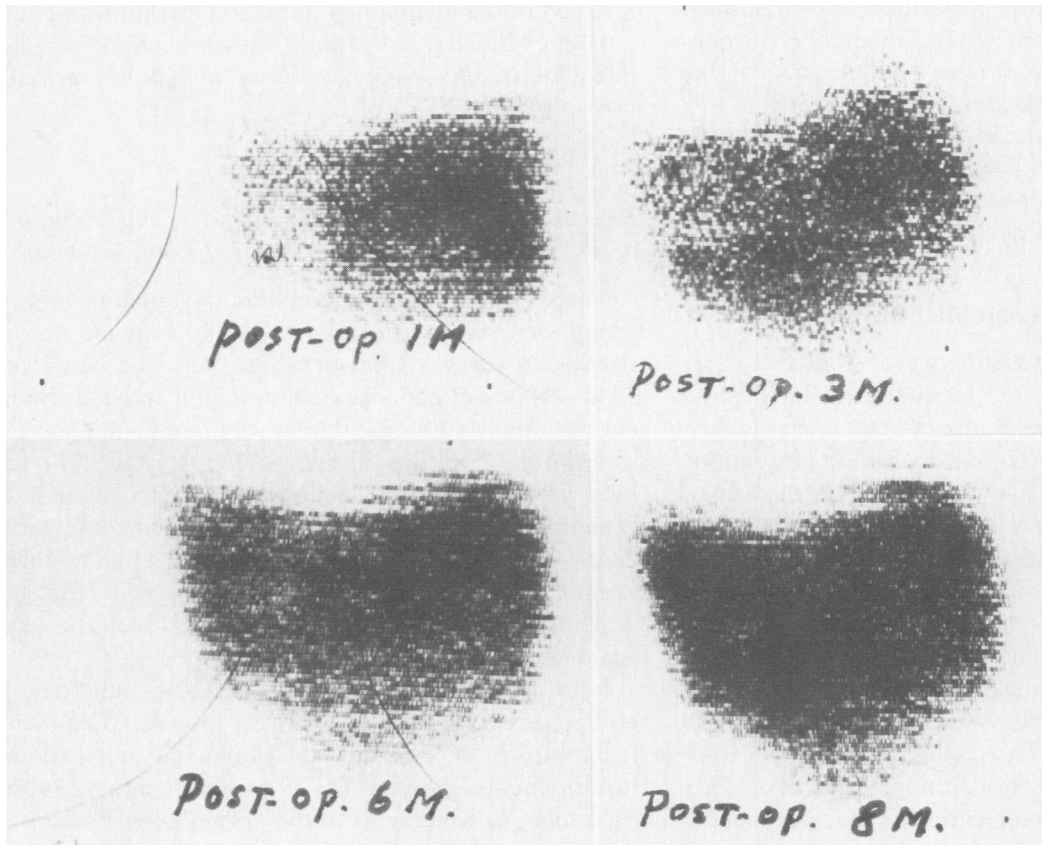


FIG. 2. The change in the size of residual left lobe after right hepatic lobectomy for a noncirrhotic hepatoma. The liver remnant reached maximum size at six months postoperatively. The liver scan taken eight months after operation shows no further increase in the size of the liver remnant.

tomy in these four patients revealed that increase in the size of the residual lobe was evident (especially marked in the right hepatectomized cases) shortly after hepatic lobectomy. The liver remnant reached maximum

size on the scan within five or six months and remained unchanged thereafter (Fig. 2). In other words, the residual lobe in patients with noncirrhotic hepatoma seemed to have restored to a completed size within five or six months after operation.

In the cirrhotic group of two patients with left lobe hepatoma, the size of the residual right lobe scanned at six months and even one year and two months after left hepatic lobectomy remained stationary in size. In another cirrhotic patient with right lobe hepatoma, the residual left lobe scanned at one, two, three and six months after right hepatic lobectomy was consistently small and without conceivable change on the scano-grams (Fig. 3).

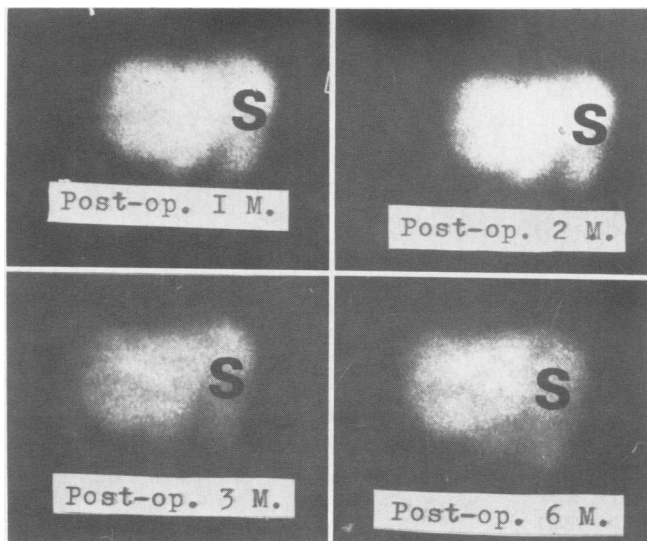


FIG. 3. Liver scan in a case of cirrhotic hepatoma in which a right hepatic lobectomy was performed. The remaining cirrhotic left lobe showed no remarkable increase in size either at one, two, three and six months after operation. The spleen (S) is enlarged.

Histology of the Residual Liver Tissue Studied by Repeated Needle Biopsy

The main pathological changes were summarized in Table 1.

Cirrhotic group. All four cases showed marked cirrhosis at hepatic lobectomy. There were formations of septa and pseudolobules, regeneration nodules (Fig. 4a) an increased number of bile ducts in portal areas and newly formed septa in all sections. The regenerating liver cells were larger than usual with an abundant,

TABLE 1. *Histological Finding of the Liver and the Liver Remnants*

Pathological changes Cases	Pseudo-lobule	Increased Bile Ducts	Regeneration Nodules	Enlarged Liver Cells	Hyperchromatic of Double Nuclei	Basophilic Cytoplasm	Fatty Metamorphosis	Remarks
Cirrhotic Group								
Case 1								
Preresection	+	+	+	+	+	+		Fig. 4a
3 days Postoperation	+	+		+	+	+	+	Fig. 4b
Case 2								
Preresection	+	+	+	+	+			
5 days Postoperation	+	+		+	+	+		
15 days Postoperation	+	+	+	+	+			
Case 3								
Preresection	+	+	+	+	+			
40 days Postoperation	+	+	+	+				
Case 4								
Preresection	+	+	+	+	+			Fig. 5a
2 yrs & 8 m. Postoperation	+	-	-	+	+			Fig. 5b
Noncirrhotic Group								
Case 5								
Preresection	-	-	-	-	±			Fig. 6a
5 days Postoperation		+	+	+	+		+	Fig. 6b
Case 6								
Preresection	-	-	-	-	-	-	-	
11 days Postoperation		+		+	+	+		
27 days Postoperation				+	+			

clear or slightly granular cytoplasm with large, hyperchromatic nuclei. Double nuclei were common. The nearby normal liver tissue was often atrophic due to compression by these nodules (Fig. 5a).

In all needle biopsy specimens following hepatic lobectomy (regardless of the length of the interval from the time of lobectomy) the liver was cirrhotic and similar to the previous examination. Formation of septa and pseudolobules was again evident (Figs. 4b and 5b). In addition, they revealed groups of enlarged liver cells with abundant cytoplasm and common double nuclei.

In the second (Case 2) and the third cases (Case 3), there was evidence of cirrhosis with regeneration nodules in both the preresection and postbiopsy specimens.

In conclusion evidence of cirrhosis continues to exist in needle biopsy specimens regardless of the interval length (ranging from three days, five days, 15 days, 40 days or even to 2 years and 8 months) after hepatic lobectomy in the cirrhotic group.

Noncirrhotic group. Two cases were included in the noncirrhotic group. The first patient (Case 5) underwent needle biopsy five days after a right hepatic lobectomy and the second patient (Case 6) had two needle biopsies 11 and 27 days after the left hepatic lobectomy respectively.

The nontumorous livers at hepatic lobectomy in both patients were found to be normal in lobular structure and in appearance of liver cells (except for a few double

nuclei in case 5, Fig. 6a). The regeneration nodule examined by needle biopsy was remarkable in Case 5 (Fig. 6b), while in Case 6 regenerative changes were evidenced by groups of enlarged liver cells with basophilic cytoplasm and hyperchromatic or double nuclei.

Hepatic regenerative activity in the noncirrhotic group was evident in the needle biopsy specimens after hepatic lobectomy (especially in Case 5 which was thought to be due to a right hepatic lobectomy yet regeneration took place in the remained small left lobe).

Discussion

The study of human hepatic regeneration is not as easy as in animal experiments. In humans regeneration of the residual lobe may be in evidence second or third re-exploration after major hepatic resection. Pack, et al.⁵ reports an instance similar to this during a second look exploration or at required secondary operation. In order to study the rate of regeneration, Lin et al.³ applied metal clips around the margin of the liver remnant at the time of hepatic lobectomy and followed the size of the liver remnant with weekly x-rays. McDermott, et al.,⁴ Aronsen, Bengmark, et al.¹ and Starzl et al.⁶ studied the regeneration of a liver remnant by repeated liver scanning. In this series the rate of regeneration was also studied by repeated liver scanning at one, three, four, five, six, seven, ten months and 1 year or even up to 12 years after major hepatic resection.

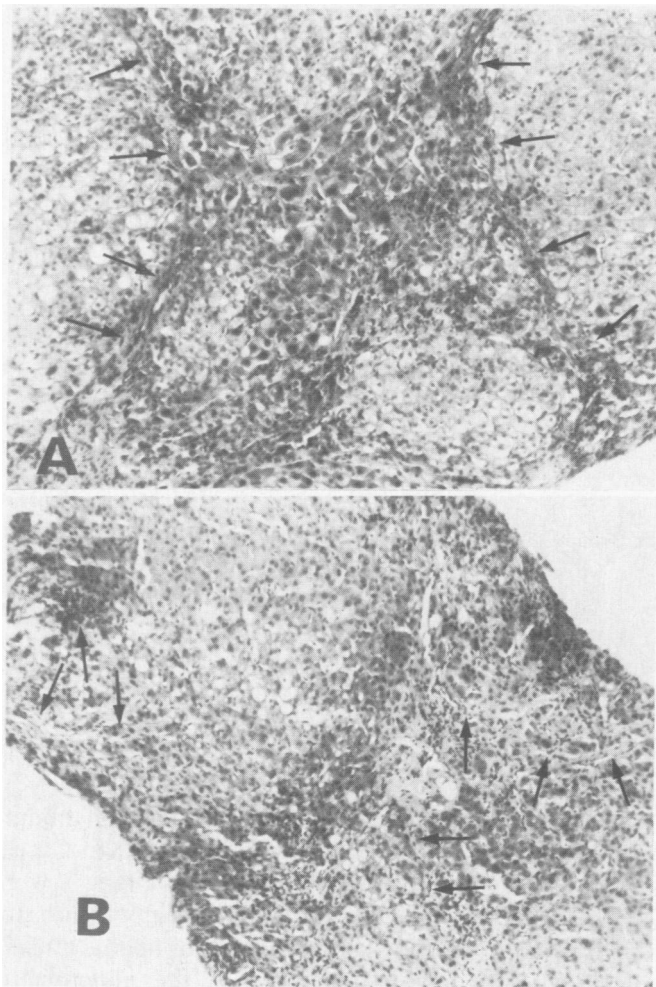


FIG. 4. (A) Newly formed septa (arrows) and regeneration nodules ($\times 100$) of pre-resection cirrhotic liver and (B) slender septa (arrows) and pseudolobules of the remnant liver of the same patient (Case 1) three days after left hepatic lobectomy ($\times 100$).

It is quite clear that a cirrhotic liver remnant never shows a postoperative increase in size even after one year. In contrast, a noncirrhotic liver remnant does increase in size.

When an hepatic lobe (especially the right lobe or an extended right hepatic lobe) is removed portal flow to the liver remnant will be increased immediately. Accordingly, in case of major hepatic lobectomy, the remaining noncirrhotic left lobe will immediately increase its bulk due to vascular engorgement and edema. However, the new circumstances created by hepatic lobectomy can not be immediately adjusted by a cirrhotic liver remnant and as a result will increase portal pressure. In the author's series of 33 hepatic lobectomies for cirrhotic hepatoma, two patients resulted in ruptured esophageal varices, one on the third and the other on the seventh day after right hepatic lobectomy. The ruptures were probably due to this increased portal pressure.

The increase in the size of the residual lobe of noncirrhotics seen in the later stage is, however, due to true regenerative hyperplasia which will contribute to the restoration of normal liver function. In fact Vajrabukka et al.⁸ had found histologic evidence of regenerative hyperplasia including increased mitotic activity within three days after partial hepatectomy for blunt injury of a normal liver. In our series we also found remarkable regenerative nodule or enlarged liver cells with basophilic cytoplasm and hyperchromatic or double nuclei in the biopsy specimens taken from the noncirrhotic liver remnant on the fifth, eleventh and twenty-seventh postoperative days.

As to regeneration of cirrhotic liver tissue after hepatic lobectomy, although Valdoni et al.⁷ reported

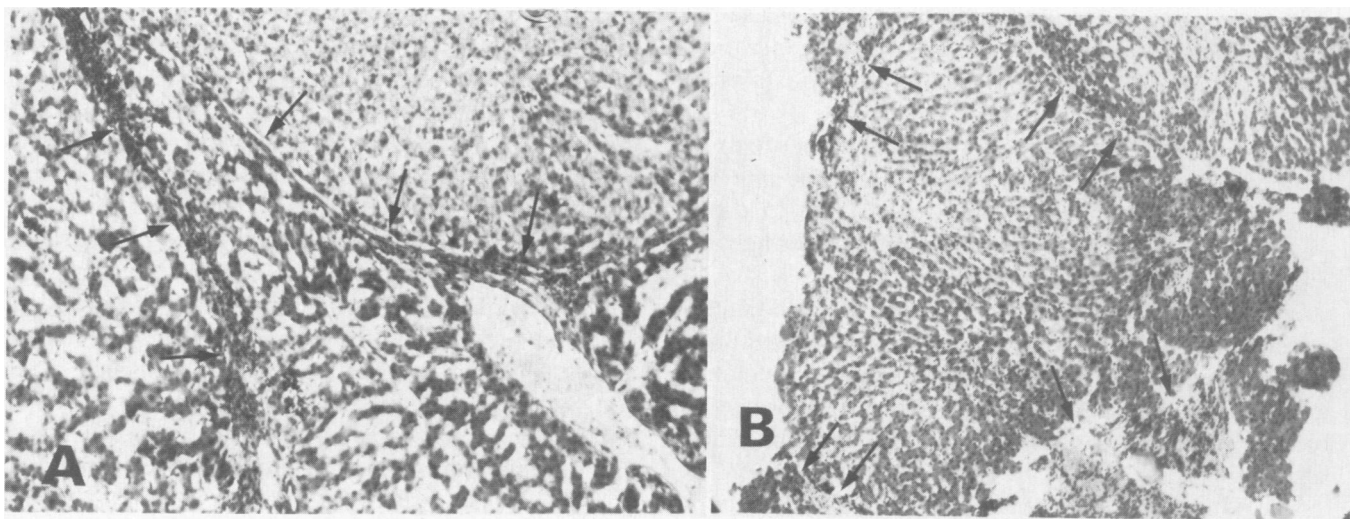


FIG. 5. (A) Formation of septa (arrows), pseudolobules and one regeneration nodule ($\times 100$) of pre-resection cirrhotic liver and (B) slender septa (arrows) and pseudolobules of the remnant liver of the same patient (Case 4) two years and eight months after left hepatic lobectomy ($\times 60$).

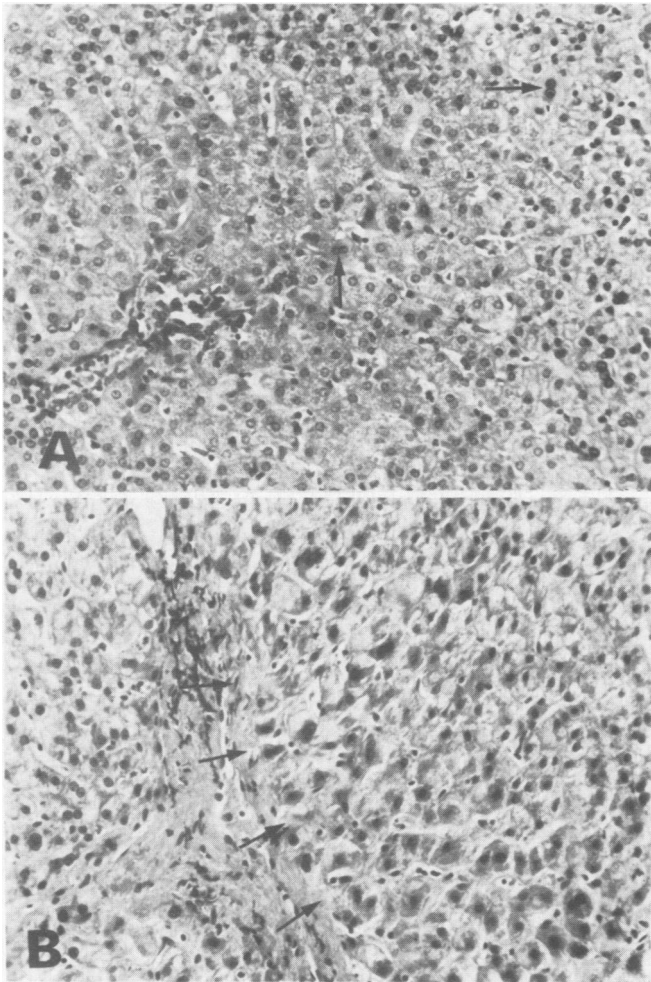


FIG. 6. (A) Normal liver structure with a few cells with double nuclei (arrows) ($\times 200$) of pre-resection noncirrhotic liver and (B) a regeneration nodule (arrows) ($\times 200$) appeared in the liver remnant of the same patient (Case 5) five days after right hepatic lobectomy.

marked hypertrophy of the residual liver, an histologically marked increased of the islands of liver parenchyma and a thinning of fibrous bands in a cirrhotic patient who died 21 days after partial hepatectomy, we failed to see any change in size of cirrhotic liver remnant by repeated liver scanning and by metal crips study.³ Histologic examinations of the cirrhotic liver remnant obtained by repeated needle biopsies in our series also showed that cirrhosis persisted regardless of the length of time that elapsed after hepatic lobectomy. Moreover 39.3% of 33 hepatic lobectomies for hepatomas associated with cirrhosis in our series developed hepatic failure. This was particularly true when a right lobectomy was performed as 66.6% of the patients died of hepatic failure. A few cirrhotic hepatoma patients survived left hepatic lobectomy and remained free from cancer and in good condition for one and half a year to 2 years and 8 months. Nevertheless their liver

functions still showed high level of Bromsulphalein retention. Therefore, it is difficult to say whether the cirrhotic liver remnant will normalize impaired liver function after hepatic resection.

The time difference in completing liver regeneration between the group of liver cyst patients and non-cirrhotic hepatoma patients, might be explained as follows. A nonparasitic liver cyst is a benign disease. It grows very slowly and may take 1–3 years or more to totally occupy the right lobe. Consequently, the left lobe will have enough time to adapt to the increased blood flow and may already have had some regenerative hyperplasia before hepatic lobectomy. This is probably the reason why the remaining left lobe regenerates within three months after right hepatic lobectomy in cyst patients. In hepatoma patients the hepatoma grows very quickly. Usually it takes only two or three months before the mass becomes so large that surgery is indicated. During this short period the nonaffected lobe may have little chance to adapt to the increasing blood flow. This may be the reason why, in hepatoma patients, the remaining left lobe takes a longer time to complete the regenerative process. In the same respect, Aronsen, Bengmark et al.¹ reported that the normal liver did not seem to be completely restored to normal size six months after operation. They studied regeneration by repeated liver scanning in two patients who had had liver resection for blunt injuries. A normal liver always has equal blood flow to each lobe, so there is no reason for any lobe to undergo a regenerate process before liver resection. Therefore, unlike the cases of either long- or short-term disease, the normal liver may need more time to complete regeneration after hepatic resection.

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