Dynamics of Normal and Injured Human Liver Regeneration After Hepatectomy as Assessed on the Basis of Computed Tomography and Liver Function

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We compared liver volume and function kinetics after partial hepatectomy according to extent of resection and severity of coexisting liver disease in 57 adults with uneventful postoperative courses. Liver volume and massiveness of resection, or resection rate, were estimated on computed tomography. Patients were categorized into three groups on the basis of reaction rate: small (<30%), medium (30%-50%) and large (>50%). The regenerative patterns of normal livers in the medium and large groups consisted of three phases: a rapid increase during the first month, some decrease in the second month and a final, slower increase. This contrasted with the pattern of injured livers with chronic hepatitis or cirrhosis, which generally showed a phase of less rapid, gradual increase. The regeneration rate (volume gain, cm^3/day) during the first month was found to be proportional to resection rate in the presence or absence of liver disease. Normal livers regenerated at least twice as rapidly as injured livers in patients with comparable resection rates. Normal livers reached plateau levels within 1 to 2 mo regardless of the massiveness of resection, whereas regeneration took 3 to 5 mo in injured livers. Liver function (albumin, bilirubin) recovered concomitantly with liver volume in the medium group, whereas in the large group they generally returned to their initial values behind volume restoration, particularly in cirrhotic patients. In conclusion, human liver regeneration is strongly influenced by the massiveness of the resection and presence of coexisting liver disease. However, we found that some cirrhotic livers can regenerate, albeit more slowly and less completely, as long as the extent of hepatectomy remains within safe functional limits. (HEPATOLOGY 1993;18:79-85.)

It is well known that normal livers in human beings (1) and animals (2) have enormous regenerative capacity after hepatectomy. Extensive research has been conducted on human liver regeneration after hepatectomy by means of repeated liver scanning (3-6), angiography (7) and metal clips attached to the remnant liver (8). These methodologies, however, have not provided accurate posthepatectomy liver-volume changes, leading to inconsistent evaluation of rapidity, pattern and time of completion of restoration in normal liver compared with injured liver. Liver weight, measured volume and radioisotope scan profiles are generally not used as indexes of evaluating liver regeneration because liver volume may change with deposition of lipids, glycogen or other materials not directly related to the proliferative response (9). DNA or RNA synthesis or cells in mitosis, which would provide a more accurate index of proliferation, are nearly impossible to measure at frequent intervals *in vivo*. Therefore restoration of liver mass, together with improvement in liver function, is the simplest index of regeneration. Its use is encouraged by evidence that the number of cells in residual liver (10) or total hepatic DNA volume (11) correlates with liver mass after hepatectomy.

In recent years, the advent of easy-to-repeat, noninvasive techniques such as computed tomography (CT) (12) and ultrasonography (13, 14) have made it possible to accurately determine liver volume. Consequently, human liver regeneration after hepatectomy has been assessed with CT (15-17), ultrasonography (18) or single-photon CT (19). We have followed hepatectomized patients with extensive CT scan follow-ups, which allow us to investigation of liver dynamics after hepatectomy, particularly in injured livers subjected to massive resection.

PATIENTS AND METHODS

Subjects. Fifty-seven hepatectomized patients (January 1980 to December 1988) with uneventful postoperative courses were studied (Table 1). Indications for hepatectomy included 49 hepatomas, 6 metastatic cancers and 2 benign tumors. Fifty-two of the patients underwent right or left lobectomies, and five had left lateral segmentectomies. The average age of the patients was 56 yr. Patients were classed in one of three groups on the basis of liver pathology (normal liver, chronic hepatitis and posthepatitic cirrhosis) as classified by the International Association for the Study of the Liver (20).

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TABLE 1. Preoperative data

Characteristics	Normal liver			Chronic hepatitis			Cirrhosis		
	Small-range (n = 3)	Middle-range (n = 6)	Large-range (n = 7)	Small-range (n = 3)	Middle-range (n = 11)	Large-range (n = 10)	Small-range (n = 4)	Middle-range (n = 6)	Large-range (n = 7)
Age (yr)[a]	60 ± 14	57 ± 11	45 ± 13	57 ± 9.5	56 ± 8.6	59 ± 3.0	59 ± 8.2	61 ± 11	47 ± 10
PHRR[a]	20 ± 2.1	41 ± 7.9	67 ± 7.5	23 ± 5.1	39 ± 6.0	62 ± 7.3	21 ± 3.6	38 ± 8.4	56 ± 7.9
Procedure									
Lobectomy	2	6	7	3	11	10	–	6	7
LLS	1	–	–	–	–	–	4	–	–
Total bilirubin (mg/dl)[a]	0.5 ± 0.1	0.5 ± 0.08	0.5 ± 0.2	0.7 ± 0.1	0.8 ± 0.3	0.7 ± 0.2	1.1 ± 0.8	0.6 ± 0.1	0.7 ± 0.3
Albumin (gm/dl)[a]	3.6 ± 0.2	3.8 ± 0.36	3.8 ± 0.24	3.5 ± 0.3	3.5 ± 0.4	4.0 ± 0.5	3.3 ± 0.2	3.5 ± 0.3	3.6 ± 0.4
ICG_{R15} (%)[a]	8.0 ± 2.0	8.9 ± 5.6	7.5 ± 3.0	14 ± 3.0	15 ± 4.0	11 ± 2.8	23 ± 11	21 ± 5.6	13 ± 5.1
TLV (cm^3)[a]	1,267 ± 168	1,077 ± 190	987 ± 267	1,078 ± 52	1,167 ± 263	1,265 ± 212	1,019 ± 399	1,152 ± 428	1,134 ± 357

TLV = total liver volume excluding tumor volume; LLS = left lateral segmentectomy.
[a]Data expressed as mean ± S.D.

Each group was further subdivided into three classes on the basis of the degree of parenchymal hepatic resection rate (PHRR) (21). The patients with PHRRs of less than 30% were placed in the small-range resection class; PHRRs of 30% to 50% were the middle-range resection class and PHRRs of 50% or more were the large-range resection class. Postoperative CT was performed 2 wk and 1, 3, and 5 to 6 mo after hepatectomy.

Liver Volume and PHRR Estimation. Serial transverse scans at 1-cm intervals were performed from the dome to the most inferior portion of the liver. Each slice of the liver was outlined, and area was calculated with an electroplanimeter. The right and left lobes of the liver were defined by a line passing through the gallbladder and the inferior vena cava, and the left lateral segment was defined by the left sagittal fissure on CT slices. PHRR (21) for each lobe or left lateral segment was preoperatively estimated as follows: ([Volume of liver resected] − [Volume of tumor]/[Volume of entire liver] − [Volume of tumor]) × 100. Volumes of remaining areas were determined by adding the volumes of the individual areas.

Regeneration Rate. Rate of regeneration during the first postoperative month (cubic centimeters per day) was defined as (Liver volume 1 mo after hepatectomy − estimated residual liver volume at surgery)/30 days. Final restoration was defined as the volume ratio of postoperative liver over the original liver volume, excluding tumor mass.

Preoperative Data. Preoperative data, including liver function test results in each group and class, are shown in Table 1. All patients were classified as Child class A. Liver function parameters, such as serum total bilirubin and albumin, were not significantly different between the corresponding resection classes across the three groups or in the three classes in each group. However, patients with cirrhosis had higher retention rates of indocyanine green (ICG) 15 min after intravenous injection of 0.5 mg/kg (ICG_{R15}) than did those with normal livers. Additionally, in each group, patients with increased PHRRs had lower ICG_{R15}. This occurred because the safe limit of a hepatectomy was determined with a multiple-regression equation taking into account PHRR, ICG_{R15} and age (22).

Statistical Methods. Data are expressed as mean ± S.D. Statistical analysis was performed with Student's t test. A p value less than 0.05 was considered significant.

RESULTS

Mode of Liver Volume Changes in Individual Cases. Serial liver volume changes are shown in Figures 1, 2, and 3 in selected patients who underwent serial CTs over periods of more than 3 mo.

In most cases of small-range resection, residual liver volumes increased significantly within 2 to 4 wk of surgery in normal and injured livers. However, the cirrhotic group included two patients without prominent restoration (Fig. 1).

In middle-range resection, residual liver volumes of normal livers (Fig. 2, upper panel) showed rapid restoration and returned to initial size within 1 mo. In chronic hepatitis and cirrhosis (Fig. 2, middle and bottom), rapidity of the increase in liver volumes and final restoration rates were less than those of normal liver. Additionally, an early transient peak in liver volumes, followed by reduction, was found in some normal and chronic hepatitis cases, but not in the cirrhotic patients, whose restorative process showed a more gradual pattern.

After large-range resections, all but one patient with normal livers demonstrated early, rapid restoration (Fig. 3, upper panel). An early transient peak within 1 mo was found more commonly than in the middle-range resection class. Furthermore, two patients had second-step increases after several months of a constant level of restoration. In patients with chronic hepatitis, the early rapid restorations were less remarkable, and transient peaks were less commonly observed (Fig. 3, middle). Patients with cirrhotic livers had slower and less complete restoration (Fig. 3, bottom). However, several cirrhotic patients had rapid restoration after middle- or large-range resection. On a microscopic level, macronodules from the livers of cirrhotic patients who had rapid restoration were separated by slender, incomplete strands of fibrosis, whereas cirrhotic livers with incomplete restoration were characterized by irregular, broader septal scars surrounding regenerative nodules.

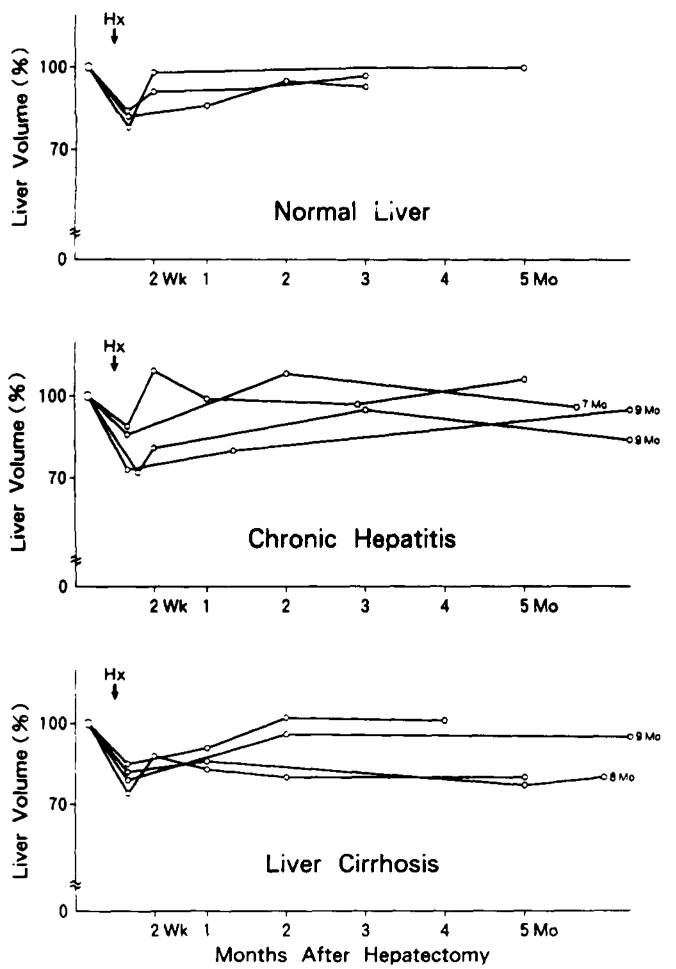

FIG. 1. Serial liver volume changes in patients who underwent small-range resection. *Hx* = hepatectomy.

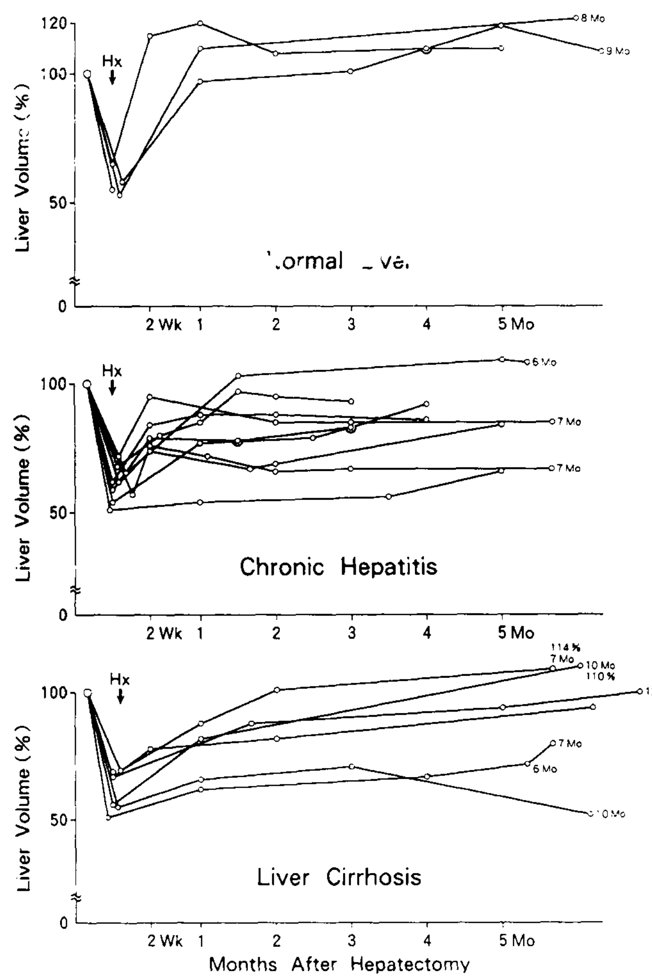

FIG. 2. Serial liver volume changes in patients who underwent middle-range resection. An early, rapid increase in liver volume is apparent in normal livers compared with injured livers. *Hx* = hepatectomy.

Liver Volume Changes and Restorations. Mean serial changes in liver volume, expressed as percentage of postoperative liver volume to preoperative size excluding tumor mass, were compared between the middle- and large-range resection classes (Fig. 4), both of which showed large liver volume alterations after hepatectomy.

In middle-range resection, normal livers quickly regained initial volumes and exceeded these volumes in 1 mo; this was followed by gradual return to preoperative size. In contrast, injured livers regenerated at significantly slower rates and were restored to only 80% of their initial volumes in 2 to 3 mo. We saw no significant difference in the pattern of restoration between chronic hepatitis and cirrhosis.

In large-range resection, the differences in restoration patterns between normal and injured livers found in middle-range resections were more prominent in the large-range resections. Approximately 90% of initial volume was regained within 2 to 3 mo in normal livers, whereas injured livers were only restored to 76% to 82% of initial volume in 3 to 5 mo.

Regeneration Rates During the First Month. Regeneration rates during the first month in the middle- and large-range resections were compared in selected patients who underwent CT scans 1 mo after hepatectomy. In middle-range resections, the mean regeneration rate of normal livers was 14 ± 3.5 cm^3/day, significantly greater than the rate in chronic hepatitis (5.2 ± 2.6 cm^3/day) and 5.8 ± 2.8 cm^3/day in cirrhosis (Fig. 5).

Regeneration rates in the large-range resections were significantly greater than those of the corresponding group in middle-range resection (Fig. 6). A comparison of regeneration rates in the three groups revealed a rate of 20 ± 5.0 cm^3/day in normal livers; this was significantly greater than the rate of 11 ± 6.5 cm^3/day in chronic hepatitis and 8.5 ± 6.1 cm^3/day in cirrhosis.

Regeneration rates during the first postoperative month were plotted against resection rates, allowing comparison of the regeneration rate curves for normal and injured livers (Fig. 7). In both normal and injured livers, regeneration rates increased with greater re-

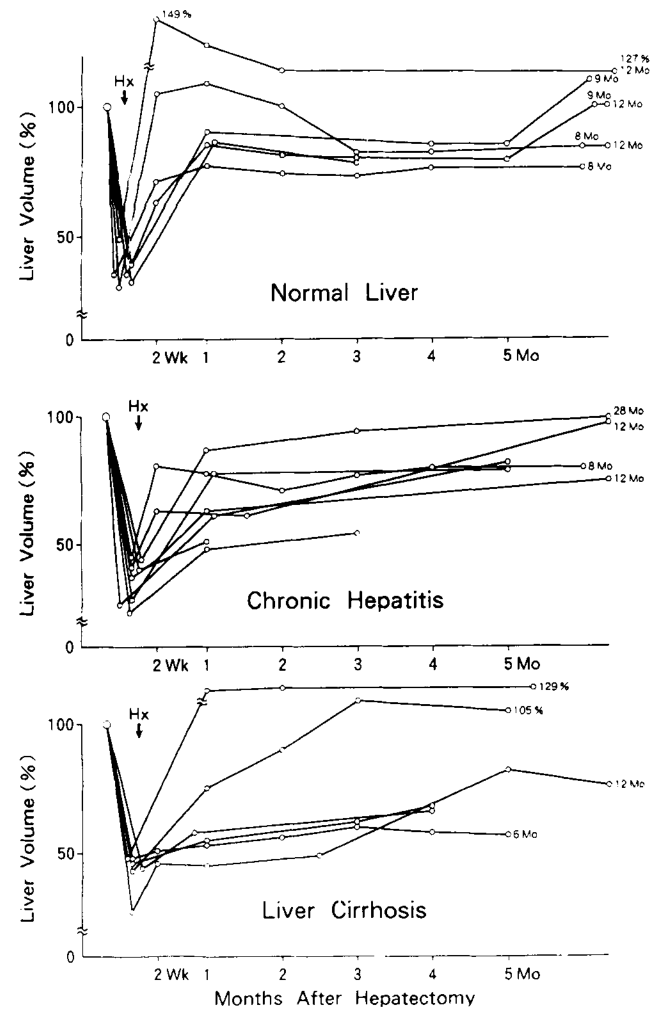

FIG. 3. Serial liver volume changes in patients who underwent large-range resection. An early, rapid increase in liver volume is apparent in normal livers and some injured livers. *Hx* = hepatectomy.

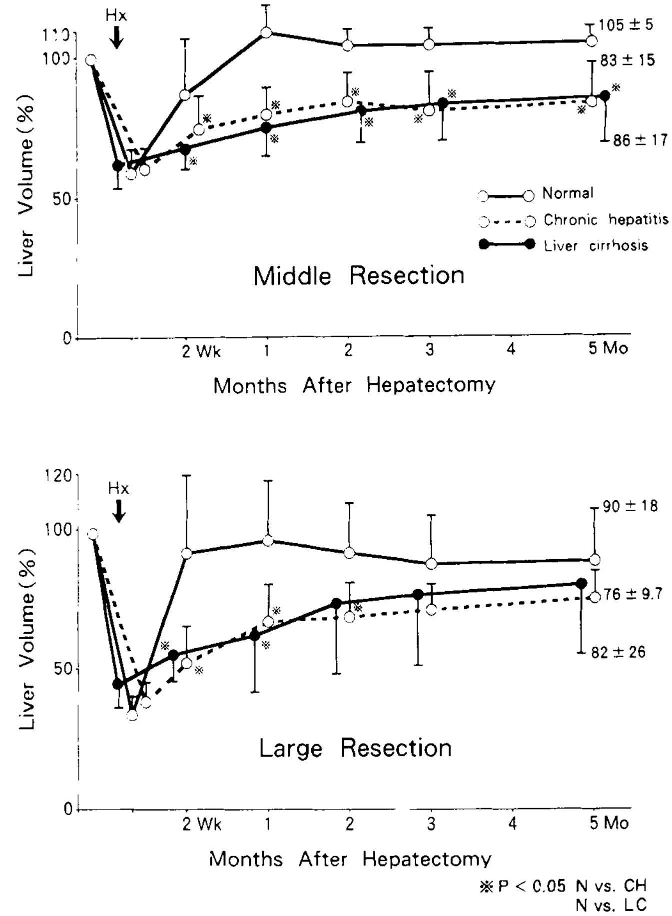

FIG. 4. Mean regenerative process in middle-range (top) and large-range (bottom) resections. Regeneration is more rapid and restoration more complete in normal livers than in injured ones. *Hx* = hepatectomy.

section rates, albeit with greater regeneration rates in normal livers than in injured ones.

Liver Function After Hepatectomy. Serum total bilirubin and albumin were followed in the middle- and large-range resection groups.

Albumin levels in normal livers did not significantly change in the 4 wk after surgery but then increased above preoperative levels (Fig. 8). In contrast, albumin levels in injured livers dropped below the preoperative baseline value over the first 1 to 2 mo after surgery, following discontinuation of protein-replacement therapy, and were restored to their initial values in 3 or 4 mo. Total bilirubin level was elevated immediately after hepatectomy but returned to normal within 4 wk in all three groups (Fig. 8).

In all three groups albumin levels declined during the first postoperative month despite protein-replacement therapy. Thereafter we noted progressive increases in the normal and chronic hepatitis groups to initial values by 4 to 5 mo after surgery. However, albumin levels in cirrhosis had not reached preoperative levels by 5 mo. Total bilirubin level sharply increased and returned to normal within 2 wk in normal liver and 1 mo in chronic hepatitis. In contrast, total bilirubin levels in cirrhosis tended to remain elevated for 3 to 4 mo (Fig. 9). Persistent hypoalbuminemia and hyperbilirubinemia were particularly noted in cirrhotic patients, who were seen to have poor restoration of liver volume over 5 mo.

DISCUSSION

Only a few studies (15-17) have used new modalities to compare the differences in regeneration after major resection of normal and injured livers. The numbers of patients in these studies and lengths of observation were too small to support any definite conclusions on regeneration rate and mode. Moreover, massiveness of hepatectomy, which strongly influences the restorative process, has been conventionally expressed by the anatomical extent of resected segments. We previously found that PHRR is a more accurate estimation of the massiveness of resection (21). Because of this finding, in this study we measured restoration in patients classified according to their PHRR. Initial liver volumes were estimated with CT as preoperative liver volume minus tumor volume.

Liver regeneration rates have been found to be

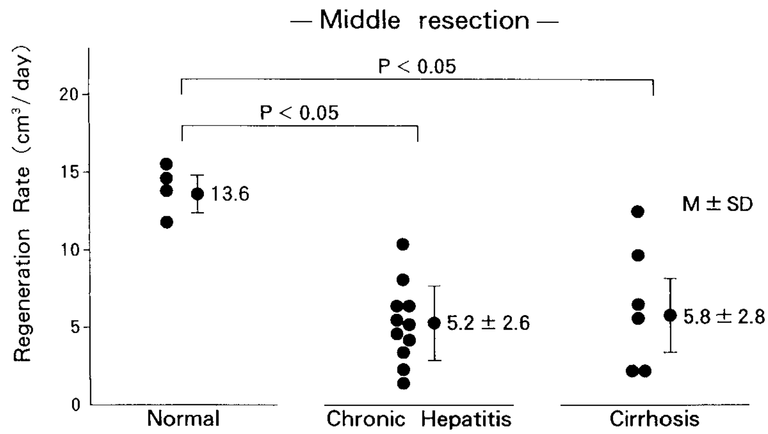

FIG. 5. Regeneration rate during the first month in middle-range resections. Regeneration rates of normal livers are significantly greater than those of injured ones.

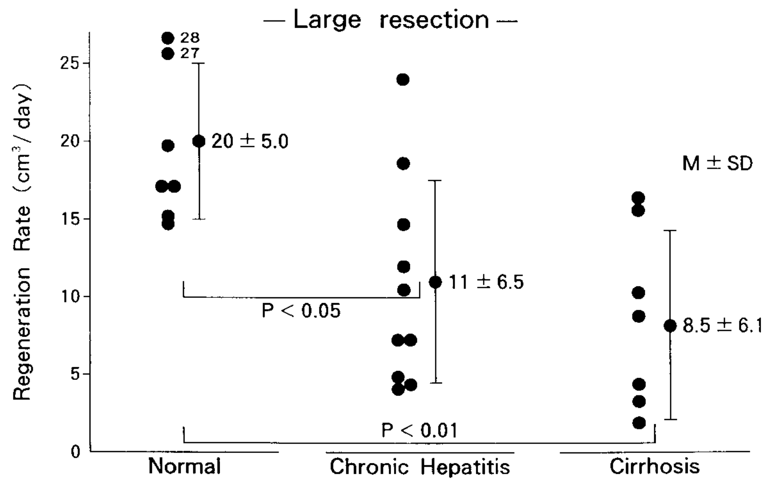

FIG. 6. Regeneration rate during the first month in large-range resections. Regeneration rates of normal livers are significantly greater than those of injured livers.

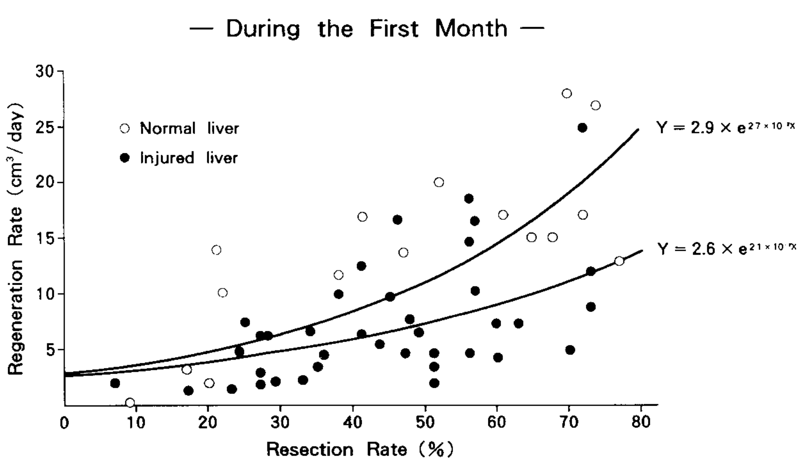

FIG. 7. Regeneration rates as a function of resection rates as estimated with CT. Resection and regeneration rates are proportional, with a greater regeneration rate in normal livers than in injured livers.

proportional to massiveness of resection in animals (1, 9, 23, 24). This occurs when the resection rate is more than 9% to 12% of total liver volume (the threshold necessary to induce DNA synthesis in the remaining liver [23]). This is consistent with our observations in human liver. In a given resection range, normal livers regenerated at least twice as rapidly as injured livers during the first month. Normal liver with a PHRR of more than 50%

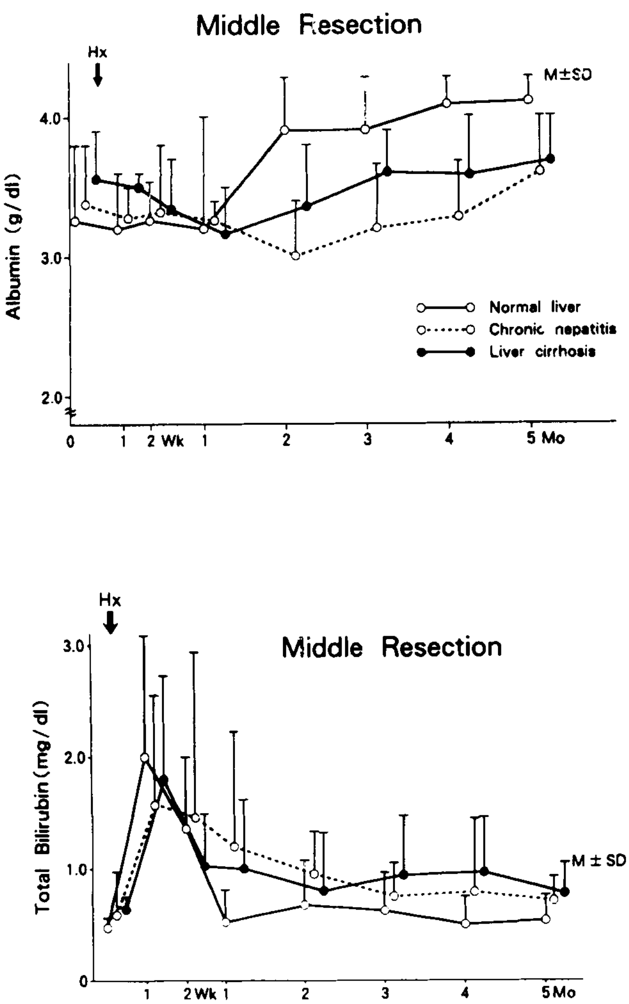

FIG. 8. Changes in serum albumin (top) and total bilirubin (bottom) levels in middle-range resections.

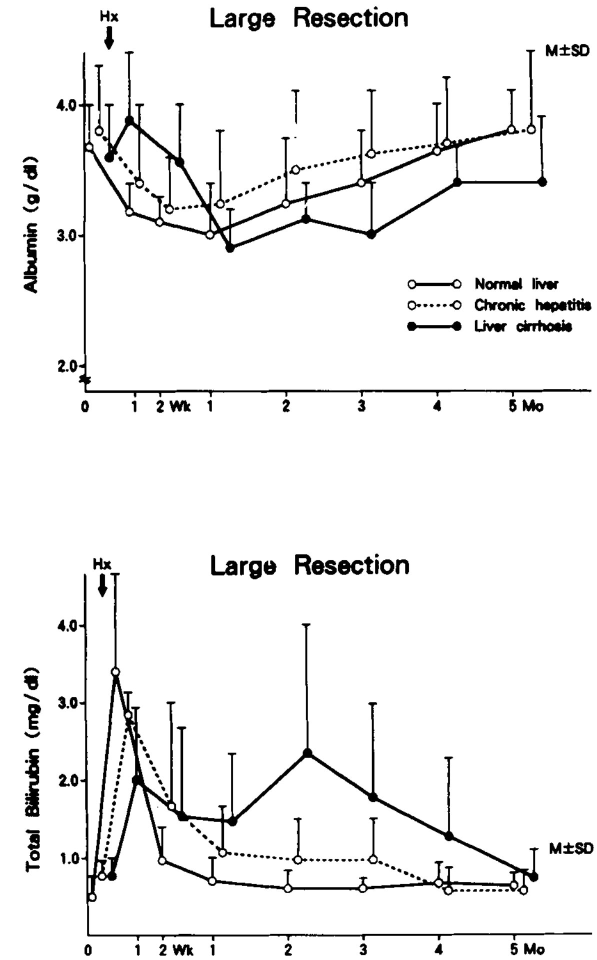

FIG. 9. Changes in serum albumin (top) and total bilirubin (bottom) levels in large-range resections.

grew as much as 20 gm/day during the first month. The rate may in fact be as high as 30 to 40 gm/day in the first 2 wk.

The pattern of regeneration differed considerably in normal and injured livers. The regeneration process in normal liver consisted of three consecutive phases after massive resection. It included an early rapid increase in the first 2 postoperative wk, subsequent decline in size and, finally, a further slow increase. In contrast, the regeneration process in injured liver generally consisted of a slow and gradual increase in size. This difference in the regenerative pattern found in human liver is contrary to data obtained in an animal study comparing regeneration in normal and experimentally induced cirrhosis (24). The second phase, consisting of a decline in liver volume 1 to 2 mo after hepatectomy, may be partially due to reduction of developed vascular engorgement or edema (25). This phenomenon was shown to be more distinct in normal liver with less collateral circulation surrounding the liver than in injured liver with developed collateral circulation.

No consistent data have been reported concerning the amount of time needed for complete restoration after hepatectomy: Data range from 2 to 3 mo (3-6) to 4 to 6 mo (1, 18, 23). This discrepancy may be due to methodological differences in observation, diversity of massiveness of resection or the presence or absence of coexisting liver disease. In our study, normal livers reached constant volumes within 1 to 2 mo regardless of degree of resection; this took 3 to 5 mo in injured livers, although there was great variation among cirrhotic livers. Some normal livers with massive resection had cyclic increases in volume even after 6 mo. Such cyclic acceleration during the late phase has been found in human beings (7, 16, 17) and in animals (2, 9, 25). Normal livers generally regained their original volumes, whereas injured livers did not.

Liver function recovered concomitantly with restoration of liver size in middle-range resections, both in normal and injured liver. On the other hand, concomitant recovery was not always found in large-range resections, particularly after resection of cirrhotic livers. Restoration of albumin levels followed the restoration of liver volumes in normal and injured livers, although bilirubin levels decreased to normal simultaneously with restoration of liver volume. Greater extent of resection and more severe coexisting liver disease correlated with lagging functional recovery, particularly in synthetic capacity. This suggests that protein synthesis is utilized for constitution of liver parenchyma rather than excretion of albumin in larger resections.

In conclusion, regeneration of human liver is influenced by the massiveness of resection and severity of coexisting liver disease. Lin et al. (4) did not detect any change in the size of the cirrhotic remnant on repeated scanning after hepatic lobectomy. Our study also finds that cirrhotic livers generally have poor restoration of liver volume and concomitant poor recovery in liver function. However, we also found that a few well-compensated cirrhotic livers regained approximately 80% of initial liver size with return to preoperative liver function, albeit with some delay compared with that in normal liver.

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