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POST-TRANSFUSION CHRONIC LIVER DISEASE

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To document the sequelae of acute hepatitis among recipients of commercial and volunteer blood and to assess factors influencing the development of chronic hepatitis (CH), 47 patients with post-transfusion hepatitis were followed prospectively from the time they received their transfusions. Twenty-nine had prolongation of at least 2-fold serum glutamic pyruvic transaminase (T) elevations for more than 20 weeks, and were classified as CH. When the patients with CH were compared to those with only acute hepatitis (abnormal T for less than 20 weeks), no difference was found with respect to age, sex, number of units transfused, incubation period, presence or absence of symptoms, occurrence of jaundice, maximum T, receipt or development of hepatitis B surface antigen or antibody, underlying illness, or area of the hospital where the patient was treated. Liver biopsies in 15 of the 29 revealed chronic active hepatitis in 9, chronic persistent hepatitis in 2, unresolved hepatitis in 4. Five of the 9 patients with chronic active hepatitis were without symptoms. None of these died or have developed cirrhosis. Because chronic liver disease frequently developed after acute post-transfusion hepatitis among multiply transfused hepatitis B surface antigen-negative blood recipients, close follow-up, including liver biopsy, is warranted in such patients with prolonged transaminase elevations.

The development of chronic liver disease (CLD) such as chronic active hepatitis (CAH) or postnecrotic cirrhosis from acute hepatitis (AH) has been inadequately documented. There are reports of symptoms[1] and/or abnormal liver function tests[2] persisting long after an acute episode of nonparenteral hepatitis, but in these cases CLD was never histologically confirmed. In fact, when large series of patients with prior nonparenteral hepatitis (usually icteric) were studied months to years later, it appeared that this illness only rarely resulted in chronic disease.[3] Similarly, there are many reports of patients with clinical, biochemical, and/or histological evidence of CLD and a preceding history of AH.[4-6] Up to 50% of patients[4] with CAH have a typical history of an "acute" episode of hepatitis. Whether this is the initiating process in a subsequent chronic disease, or merely the first acute exacerbation of an already established underlying disorder, is not clear.

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The course of acute parenteral hepatitis (PH) may be prolonged. Retrospective and short term prospective[7-11] studies have shown that this illness may have a protracted course and may be associated with the subsequent development of CLD. Accordingly PH may be considered one of the etiologies of chronic hepatic disease.[5, 12]

Why two different types of presumed viral hepatitis should differ in their respective propensity to cause chronic disease is unclear. However, the association of the hepatitis B surface antigen (HB_sAg)[13] with one of the viruses that can produce PH has enabled researchers to study this problem. An association between CLD and serological evidence of HB_sAg has been demonstrated.[14-19] Persistent hepatitis B antigenemia appears to be related to the development of CAH.[20-23] Finally, acute HB_sAg-positive hepatitis may develop into CAH in up to 10% of the cases.[24]

Because of this relationship between HB_sAg, PH, and CLD, it might be postulated that the screening procedures recently introduced[25] to avoid transfusing HB_sAg-positive blood would also eliminate the association between CLD and PH by eliminating a common link, HB_sAg. In order to look at this question, an ongoing study of post-transfusion hepatitis (PTH) was reviewed with regard to the frequency of development of CLD. The roles of other factors such as age, sex, initial course

of the hepatitis, associated illnesses, and other characteristics of the blood transfused were considered. Finally, histological documentation of the chronic sequelae of PTH was obtained.

Materials and Methods

In order to evaluate certain sensitive HB_sAg screening tests, a study was begun in 1972[26] in which recipients of blood units that were positive by reverse passive hemagglutination[27] or Abbott solid state radioimmunoassay[28] (RIA) were prospectively followed as were control recipients of all HB_sAg-negative units. Where quantities permitted, the transfused units were rescreened with confirmatory RIA[29] and tested for antibody to HB_sAg (anti-HB_s) by passive hemagglutination and RIA.[30, 31] These blood recipients were monitored with biweekly determinations of serum glutamic pyruvate transaminase (T) and of HB_sAg and anti-HB_s. All of the blood units used in these patients were HB_sAg negative when previously screened by immunodiffusion or counterelectrophoresis, and were rescreened by the more sensitive assays after transfusion. PTH was defined as an otherwise unexplained rise in the T level to at least 5 times the upper limit of normal. Every abnormal T was verified by a second determination and every patient considered to have hepatitis was interviewed and examined by one of the authors (R. L. K.). Those who were subsequently classified as PTH had no other apparent cause for the abnormal T. The onset of hepatitis was considered to be from the time the T first became abnormal.

All patients who had T levels more than twice the upper limit of normal for more than 20 weeks were classified as chronic hepatitis (CH). The liver biopsies were performed after at least 26 weeks of abnormal T values. Those who consented and in whom there were no other medical contraindications were admitted for biopsy. All but two of the biopsies were performed percutaneously with a 1.4-mm Menghini needle. The other two biopsies were done using a Vim-Silverman needle during an open surgical procedure (surgical treatment for ulcer disease). The biopsies were reviewed by three of the authors (S. S., G. L. G., R. L. K.) independently, as well as by the Division of Surgical Pathology. Two of the authors (S. S. and G. L. G.) read the biopsies "blind," i.e., without any knowledge of the clinical or biochemical status of the patients. Using the criteria listed below the reviewers agreed in the diagnoses offered.

CH, arbitrarily defined by biochemical criteria only, was the otherwise unexplained persistence of an abnormal T level for more than 20 weeks. After liver specimens were obtained those biopsied were further classified as unresolved hepatitis (UH), chronic persistent hepatitis (CPH), or CAH, using the following histological criteria. CPH was defined as the presence of an inflammatory infiltrate limited to the portal areas with no evidence of significant hepatocyte necrosis or breakdown of the limiting plate. CAH was defined as the presence of breakdown of the limiting plate of the portal triad with round cell infiltration and hepatocyte destruction in the neighboring hepatic parenchyma, so-called "piecemeal necrosis," associated with an inflammatory cell infiltrate and varying degrees of intralobular hepatocellular necrosis and fibrosis. UH was diagnosed by the presence of focal hepatitis (hepatocyte necrosis with inflammatory cell infiltrate), but with normal intervening hepatocyte architecture.

Two groups of patients were compared, namely those whose T abnormality lasted less than 20 weeks and remained normal at least 6 months thereafter (the AH group), and those who developed CH. They were compared with regard to age, sex, presence or absence of symptoms or jaundice (bilirubin >3 mg per 100 ml), maximum T, incubation periods, number of units received, receipt of HB_sAg and/or anti-HB_s, serological response, underlying disease, and the hospital service on which care was received. All of the patients in this study had adequate states of nourishment and this factor was not assessed. Because we obtained more reliable histories of alcohol ingestion from the patients followed longer (i.e., the CH patients), this parameter could not be compared fairly between the two groups. Statistical evaluations were performed either by the χ^2 or by Student's t-test method.[32]

Results

The study group was composed of 24 recipients of HB_sAg-positive blood of whom 16 developed PTH, and 81 recipients of HB_sAg-negative blood, 30 of whom developed PTH. There were 20 recipients of blood initially HB_sAg positive but for which insufficient serum was available for confirmatory testing, and of these, 8 developed PTH. Thus, 54 of 125 patients (43%) developed PTH.

This high frequency of PTH has been reported and discussed previously,[26] and may reflect the extensive use of commercial blood at this center. Of the blood transfused in this patient population, 85% came from commercial sources. Each of the patients who developed PTH received at least one commercial blood unit. Six patients were lost to follow-up 3 to 19 weeks after their hepatitis developed, and they will not be further considered. A 7th patient subsequently found to be HB_sAg positive before transfusion will not be considered. Of the remaining 47, 29 (62%) developed CH and 16 of these still had abnormal T values when last tested. In addition, one other patient died of his underlying disease over 20 weeks after the onset of the PTH with T values still abnormal, and another patient only showed normalization of enzymes when begun on prednisone therapy. Figure 1 shows the distribution of the duration of illness to date in these 47 patients. It should be noted that, although 20 weeks was arbitrarily selected as the minimum duration for CH, only 5 of these 29 patients had

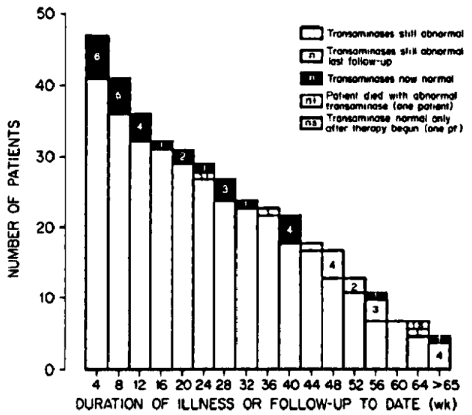

FIG. 1. Duration of abnormal transaminases to date in 47 patients with post-transfusion hepatitis.

documented normalization of the abnormal T by 32 weeks.

There was no difference in the age distribution between the two groups (table 1). The higher proportion of males in the CH group (76 versus 56%) was not statistically significant ($P > 0.10$). Although the 18 patients whose PTH was less than 20 weeks appeared to have received almost twice as many units of blood, this is an artifact due to 1 patient who received 75 units. If this 1 patient is deleted, the two groups are comparable in this respect also (table 1).

Similarly, there was no apparent difference between the two groups with respect to the initial presentation of their hepatitis (table 2). The incubation periods were only calculated for those who received blood within a 14-day period, which excluded 5 patients with AH and 8 patients with CH. There was no significant difference between the two groups composed of the remaining patients. Approximately 70% of the patients in each group had symptoms, although in many cases the symptoms were minimal, and often the patient attributed them to his or her underlying disease. Jaundice was observed in approximately one-third of each group. There was no difference in the maximum T levels between the two groups.

Considering only those patients in whom confirmatory determinations of HB_sAg or anti-HB_s in the transfused blood could be made, there was no difference in the frequency of HB_sAg or anti-HB_s receipt between the AH and CH groups (table 3). Subtyping of the HB_sAg was not performed. There was no difference between the two groups in the subsequent development of HB_sAg (table 3). Although patients with AH developed anti-HB_s more

TABLE 1. *Patients with AH only compared to those who developed CH: age-sex-transfusion characteristics*[a]

	AH (N = 18)	CH (N = 29)
Age		
Range (yr)	23–75	20–85
Mean	48	50
Sex		
M	10 (56%)	22 (76%)
F	8 (44%)	7 (24%)
No. of units transfused		
Range	2–75 (2–28)[b]	3–26
Mean	17 (13)[b]	10

[a] AH, acute hepatitis that resolved within 20 weeks; CH, chronic hepatitis.

[b] Numbers in parentheses, number of units excluding 1 patient who received 75 units.

TABLE 2. *Patients with AH only compared to those who developed CH: characteristics of initial hepatitis*[a]

	AH (N = 18)	CH (N = 29)
Incubation period[b] (wk)		
Range	3–25	2–28
Mean	10	14
Symptoms		
+	11 (61%)	22 (76%)
–	7 (39%)	7 (24%)
Jaundice		
+	7 (39%)	7 (26%)
–	11 (61%)	22 (74%)
Maximum transaminase (X upper limit normal)		
Range	5.6–66.3	5.2–51.3
Mean	18.9	22.3

[a] AH, acute hepatitis that resolved within 20 weeks; CH, chronic hepatitis; +, present; –, absent.

[b] Only for those patients who received all blood within 14-day period: excludes 5 patients with AH and 8 patients with CH.

TABLE 3. *Patients with AH only compared to those who developed CH: serological characteristics*[a]

	AH (N = 18)	CH (N = 29)
	No. (%)	*No.* (%)
Received HB_sAg[b]		
+	7 (44)	8 (32)
–	9 (56)	17 (68)
Received anti-HB_s[c]		
+	11 (73)	20 (80)
–	4 (27)	5 (20)
Developed HB_sAg		
+	2 (11)	1 (3)
–	16 (89)	28 (97)
Developed anti-HB_s		
+	9 (50)	8 (28)
–	9 (50)	21 (72)

[a] AH, acute hepatitis that resolved within 20 weeks; CH, chronic hepatitis; HB_sAg, hepatitis B surface antigen; anti-HB_s, antibody to hepatitis B surface antigen; +, present; –, absent.

[b] At least one unit of blood transfused to the remaining 2 patients with AH and 4 patients with CH was positive by initial radioimmunoassay testing, but there was insufficient quantity in the aliquot to do confirmatory testing.

[c] The remaining 3 patients with AH and the 4 patients with CH received at least one unit of blood that could not subsequently be tested for anti-HB_s due to insufficient quantities of aliquot.

TABLE 4. *Patients with AH only compared to those who developed CH: underlying disease*[a]

	AH (N = 18)	CH (N = 29)
	No. (%)	*No.* (%)
Leukemia-lymphoma	1 (6)	1 (3)
Other malignancy	2 (11)	9 (31)
Gastrointestinal bleeding	3 (17)	6 (21)
Cardiac surgery	3 (17)	4 (14)
Orthopedic surgery	2 (11)	3 (10)
Vascular surgery	1 (6)	3 (10)
Trauma	1 (6)	2 (7)
Abdominal surgery	2 (11)	1 (3)
Chronic renal disease	1 (6)	0 (0)
Obstetrical surgery	1 (6)	0 (0)
Overdose and anemia	1 (6)	0 (0)

[a] AH, acute hepatitis that resolved within 20 weeks; CH, chronic hepatitis.

often (50 versus 28%), this was not a significant difference ($P > 0.10$).

The patients in both groups were separated with regard to their underlying disease in table 4. The AH and CH groups were comparable in all respects. The proportion of malignant disease was 2 times greater in the CH group (34 versus 17%) but this was not statistically significant ($P > 0.10$). In the groups with malignant disease there was no clinical evidence of hepatic metastases nor were any seen in the liver biopsies obtained. Alkaline phosphatases were normal or near normal in all patients. The two groups did not differ as to the service on which they were hospitalized.

The authors felt unable to obtain a reliable history of alcohol consumption from all patients to compare the two groups. However, as the study was carried on and several members of our staff became very familiar with some of the patients and their families, we obtained histories showing that some of the patients had been heavy drinkers in years past. These close relationships between our staff, the patients, and their families tended to occur in those patients with persistently abnormal T levels, as they would be seen more frequently and were followed well beyond the initial 9-month period. This was particularly so in those who underwent biopsy. Although all 15 patients denied alcohol consumption in recent years, at least 4 of the 9 with CAH had histories of "heavy" alcohol consumption in years past. In contrast, none of the other 6 biopsied patients or their families related such histories.

Of the 29 patients who developed CH, 15 underwent liver biopsies. These were obtained 26 to 59 weeks (average 31 weeks) after the onset of their hepatitis. The remaining 14 patients were not biopsied for a variety of reasons, such as advanced age of the patient, unavailability, significant underlying disease precluding biopsy and/or treatment, or resolution of the abnormal T levels. None of these 14 patients had any clinical or biochemical evidence of hepatic deterioration. Nine of the biopsied patients had the histological finding of CAH, 2 had CPH, and 4 had UH. A representative example of each finding is shown in figures 2 to 4, respectively. Four of the patients with CAH and 1 patient with UH had symptoms referable to their hepatic dysfunction.

Discussion

Screening blood products for HB_sAg before transfusion reduces the frequency of acute PTH,[26, 33] presumably by reducing the frequency of passage of the hepatitis B virus. If this virus is responsible for the significant

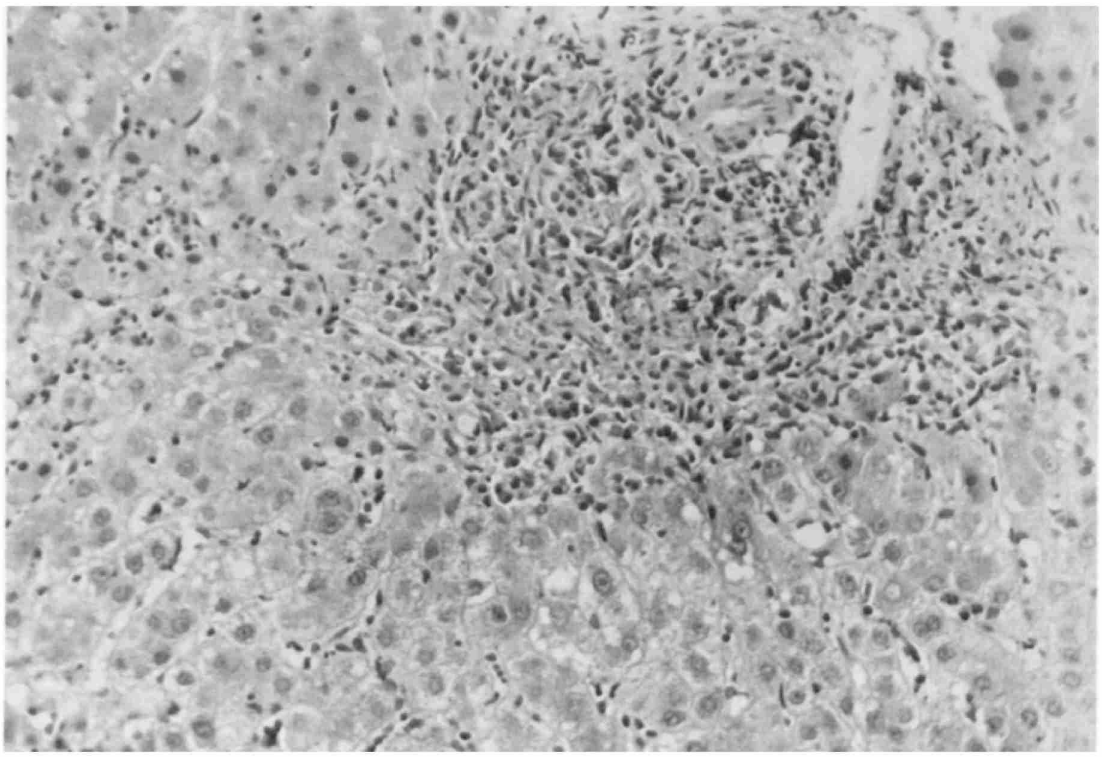

FIG. 2. Chronic active hepatitis with piecemeal necrosis of the limiting plate of hepatocytes and delicate fibrous lobular infiltration (original magnification · 66).

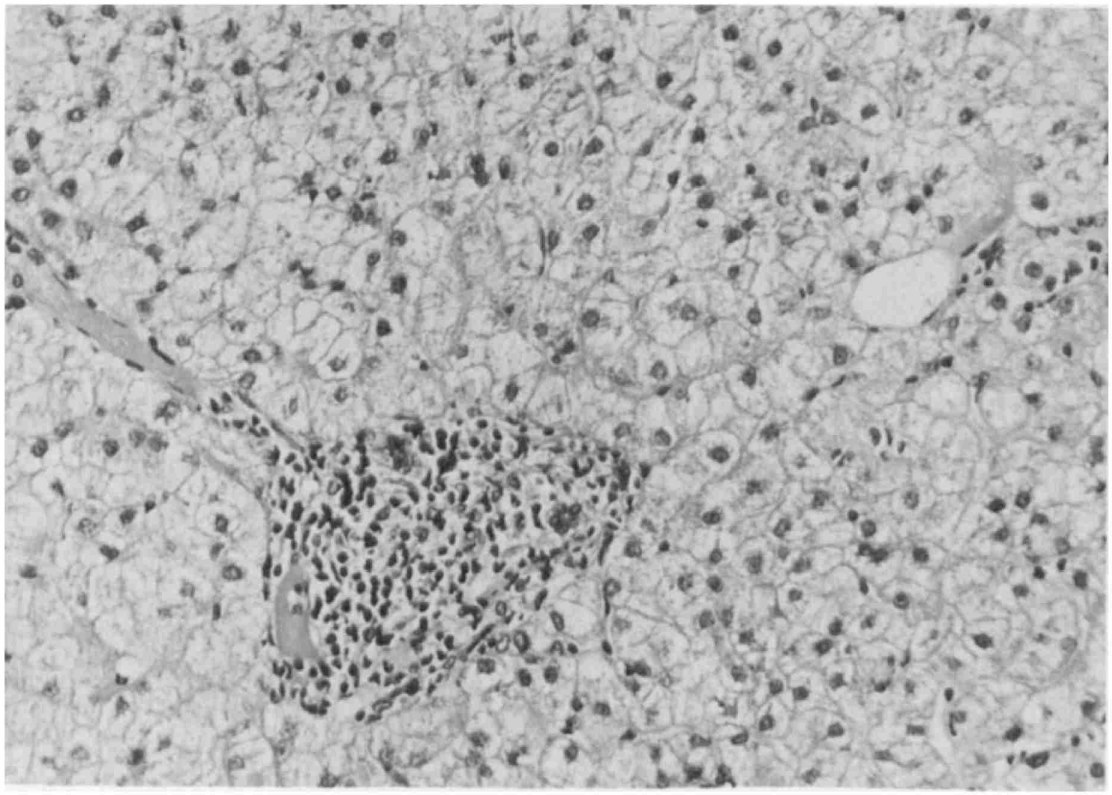

FIG. 3. Chronic persistent hepatitis with dense portal lymphocytic aggregation (original magnification × 66).

amount of CLD seen in patients who develop PH, then the screening procedures might reasonably be expected to reduce the incidence of chronic disease. From the presented data, however, the problem does not seem that simple.

There was a high incidence (43%) of PTH in the initial series, possibly related to the very high proportion (85%) of commercial blood used. Commercial blood could not be evaluated as a factor in the development of CH as all 54 patients who developed PTH received at least one commercial unit. Of note, however, was that 62% of the patients with PTH who were followed at least 20 weeks continued to have abnormal T levels beyond that time. This occurred in spite of the fact that all of the blood they received was negative when screened for HB_sAg by immunodiffusion or counterelectrophoresis. Thus, screening for HB_sAg by these methods does not appear to prevent the development of CH from acute PTH. When the transfused units were tested by more sensitive HB_sAg assays (RIA and reverse passive hemagglutination), there was no difference between the AH and CH groups in the frequency of HB_sAg receipt (44 versus 32%, $P > 0.10$).

Indeed, other factors may influence the development of CLD. Those in whom the hepatitis has a more insidious onset or who is anicteric may be more likely to develop CAH,[10, 19, 22] as are older patients. CAH may be more common in women,[5, 6] especially in the HB_sAg-negative disease.[34] There is the theoretical possibility that the passive infusion of anti-HB_s during transfusion may result in immune complex formation and CLD.[35] The factors of alcoholism and dietary deficiency, separate and together, have also been considered[36] as possible contributing causes. CAH is often postulated to be a disorder of the immunological system ("autoimmune")[5, 6, 26] and, in some cases, HB_sAg or liver tissue may act as the antigen in antigen-antibody complexes.[12, 37] Host factors play a role, as can be demonstrated in renal dialysis patients, in whom hepatitis tends to be a smoldering, chronic disease.[13] Finally, other viruses in addition to hepatitis B may lead to chronic disease.

There was no apparent association in this series between the development of CH and sex, number of units received, service the patient was on, incubation period, occurrence of jaundice, maximum T, or presence of symptoms. There was no difference in the two groups with respect to age, but the average age in each group was 48 and 50, respectively. As hepatitis in the elderly is associated with a more prolonged course, this may be one reason for the high proportion (62%) of CH in this series. The development of antigenemia did not show any

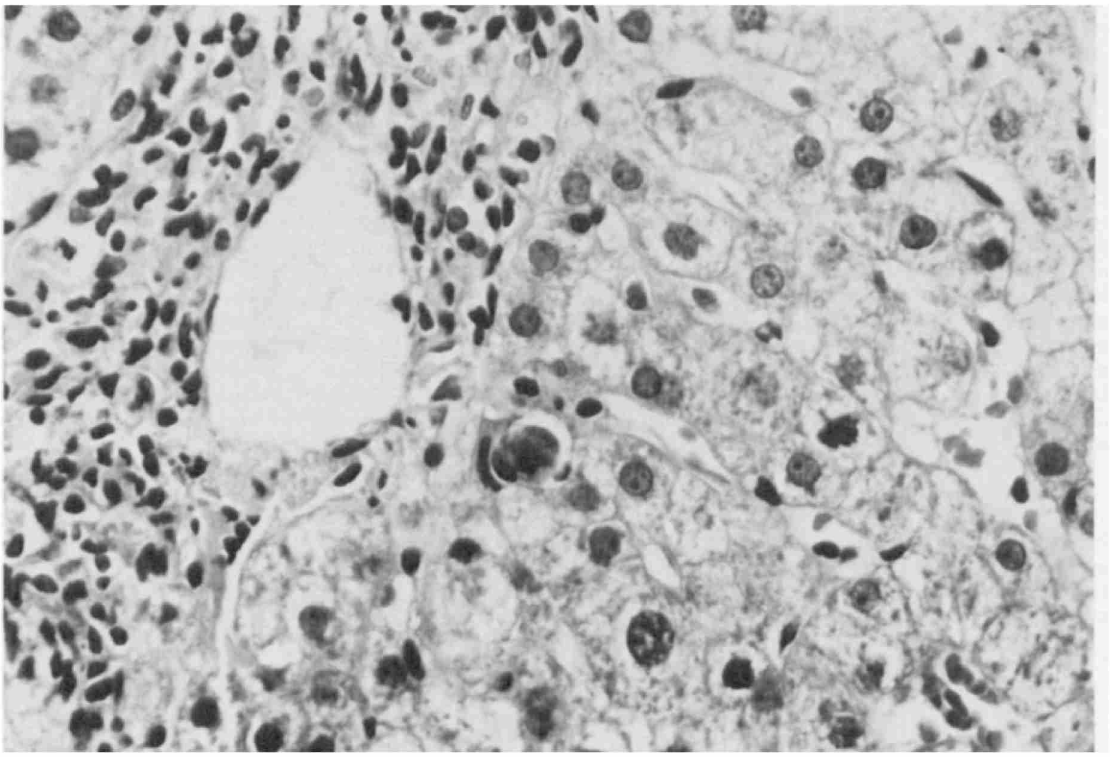

FIG. 4. Unresolved hepatitis with peripheral lobular hepatocytic necrosis (original magnification · 132).

relationship to the development of CH. Similarly, CH was not associated with the receipt of anti-HB_s. Although there was a lower frequency of anti-HB_s development in the CH group (28 versus 50%), this was not significant ($P > 0.10$).

It was of note that there was a higher (but not statistically significant) proportion of patients with malignancies in the CH group (34 versus 17%, $P > 0.10$). None of these patients had clinical, biochemical, or histological evidence of hepatic metastases. Most of them had tumors that do not usually metastasize to the liver early, the alkaline phosphatases in these patients were either normal or minimally elevated (but less than would usually be expected if an infiltrative process was involved in the liver), those who were biopsied had no evidence of metastatic spread, and most of them subsequently had reduction or even complete resolution of their T elevations without any specific therapy aimed at their malignancy. This higher frequency of malignancy in the CH group and the trend for the CH patients to fail to develop anti-HB_s might raise the possibility of CH occurring in patients with impaired immune defenses. However, this is only a speculation, as the numbers are small, and, in fact, fail to achieve statistical significance in both instances.

The histological lesion of CPH and UH have been considered to have good prognosis untreated, and have been described in patients convalescing from hepatitis with few or no symptoms.[38] In distinction, the lesion of CAH has been associated, at least in symptomatic patients with high grade T activity, with progressive liver disease resulting in cirrhosis and frequently death. This disease has been shown to be responsive to therapy.[24]

Viewed in this perspective, it is of interest that 5 of the 9 patients with CAH on biopsy had no significant symptoms of liver disease. The other 4 were managed with steroids and azathioprine, but, even in these cases, only 1 patient had a clinical picture of severe fatigue, anorexia, and weight loss. The other 3 patients had more subtle symptoms of mild fatigue, and all underwent very extensive medical evaluations, looking for other causes of their symptoms before liver biopsy and treatment. None of the biopsies showed bridging necrosis. One of the patients with mild fatigue had evidence of cirrhosis on biopsy. Whether the histological lesion of CAH ultimately has the same poor prognosis in asymptomatic patients as it does in those with symptoms remains to be established.[39] Thus far, however, there has been no death or evidence of hepatic failure in any of these patients. Moreover, there has been no histological progression or resolution in the 4 patients with follow-up biopsies.

It was of interest that all 4 patients with clear histories

of heavy alcohol consumption in the past had histological evidence of CAH. Although these numbers are small, they permit speculation as to the role of alcohol either as the primary cause of CLD in these patients (although they all had normal T levels and no clinical evidence of CLD at the time of transfusion) or as a predisposing factor in the development of more severe hepatic reaction when stressed with a bout of acute viral hepatitis.

The 15 patients who underwent liver biopsy represent a selected group of the 29 with CH, and thus it would not be expected that 60% (9 of 15) of the total group would have CAH. However, at least 31% (9 of 29) of the patients in this series had this histological lesion.

In conclusion, although HB_sAg screening does reduce the frequency of acute PTH, the problem of chronic sequelae of acute PTH remains. The question is raised whether the development of CLD in some people may be related to subtle abnormalities in their immune defenses. Past alcoholism may also be a factor in the development of CAH. The prognosis of asymptomatic patients with the histological lesion of CAH is unknown. Finally, all patients who receive blood transfusions should be carefully followed for the development of abnormal T levels and those who do develop PTH should be watched for persistence of these abnormal levels. Consideration should be given to liver biopsy in any patient whose T level remains abnormal beyond 20 weeks, even if the patient is having few or no symptoms.

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