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THE LIVER IN SYSTEMIC ILLNESS

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Abbreviations

ALT	alanine aminotransferase	FAP	familial amyloidotic polyneuropathy	NRSSS	national reye syndrome surveillance system
APS	antiphospholipid syndrome	FMF	familial mediterranean fever	OSA	obstructive sleep apnea
AST	aspartate aminotransferase	HBV	hepatitis B virus	OTC	ornithine transcarbamylase
CDC	centers for disease control	HCV	hepatitis C virus	PBC	primary biliary cirrhosis
CPAP	continuous positive airway pressure	HPS	hemophagocytic syndrome	SARS	severe acute respiratory syndrome
CREST	syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia	IL-6	interleukin-6	SCoV	SARS corona virus
		LDH	lactate dehydrogenase	SLE	systemic lupus erythematosus

INTRODUCTION

When patients with abnormal liver tests are encountered, it is often assumed that the liver is the primary culprit in the disease process. However, numerous systemic illnesses and diseases of other organs can produce signs and symptoms that are indistinguishable from primary liver diseases. The hepatic manifestations in these disorders may range from mild enzyme abnormalities to significant liver injury and liver failure. In this chapter, we will review liver involvement in selected systemic disorders such as heart disease, pulmonary disease, amyloidosis, connective tissue disorders, Reye's syndrome, jejunoileal bypass, and hematological disorders. Other systemic disorders with hepatic involvement, such as sarcoidosis, cystic fibrosis, and sepsis, are covered elsewhere in this textbook.

HEART DISEASE

Liver involvement occurs in patients with both acute and chronic heart disease and its spectrum ranges from asymptomatic increases in liver biochemistries to fulminant liver failure. The liver receives a significant portion of the cardiac output and therefore any condition that decreases cardiac output will lead to a fall in hepatic perfusion. The liver is able to compensate for changes in hepatic blood flow via vasoactive mechanisms and by increasing oxygen extraction during periods of hepatic hypoperfusion.[1] However, when critical levels of left or right heart failure are reached, hepatic injury may occur. In right-sided heart failure, it has been suggested that this damage is caused by elevation in right atrial pressure, leading to elevation in hepatic venous pressure that causes distention of hepatic sinusoids and liver cell hypoxia. In left-sided heart failure, decreased cardiac output results in diminished hepatic perfusion, which leads to hepatic hypoxia. In general terms, liver involvement in right heart failure is referred to as *congestive hepatopathy*, whereas liver injury resulting from left heart failure is known as *ischemic hepatitis*. However, these two phenomena often coexist and may be indistinguishable in clinical practice. The final common pathway for liver damage appears to be centrilobular (zone III) hepatocellular necrosis. This portion of the liver lobule is the most vulnerable to hypoxic injury due to the organization of the liver acinus. Highly oxygenated blood enters the hepatic lobule via branches of the hepatic artery and portal vein in the periportal region. As it passes through the hepatic sinusoids toward the terminal hepatic venule, oxygen is extracted and hepatocytes in the centrilobular area are perfused by blood that is the least well oxygenated.[1]

LIVER IN RIGHT HEART FAILURE (CONGESTIVE HEPATOPATHY)

Liver abnormalities in patients with right heart failure are common. Right heart failure can be isolated (due to cor pulmonale or primary pulmonary hypertension) or, more likely, a consequence of left ventricular failure. In a large study of 175 patients with both acute and chronic right heart failure,[2] hepatomegaly was present by physical examination in over 90% and splenomegaly in 20% of these patients.[2] Other findings of right heart failure, such as peripheral edema, pleural effusion, and ascites, were also frequently present (Table 56-1). Ascites is more prominent in patients with chronic right heart failure than in acute right heart failure.[2]

Characteristic changes in histology are seen in the liver of patients with congestive heart failure. On gross inspection, the congested liver appears enlarged and purple with blunt edges.[3] The classically described "nutmeg" appearance is caused by alternative areas of pale, more normal-appearing parenchyma contrasting with congested, hemorrhagic areas that correspond to the centrilobular regions of the liver (Figure 56-1). Microscopically, central veins and sinusoids in the centrilobular region become dilated and engorged with erythrocytes. Inflammation is noticeably absent (Figure 56-2). Adjacent hepatocytes may become compressed and atrophied. With long-standing hepatic congestion, fibrosis and cirrhosis may develop (cardiac cirrhosis) (Figure 56-3).

Hepatic congestion due to the right heart failure results in numerous biochemical abnormalities (Table 56-2). In chronic congestive

Table 56-1. Symptoms and Signs of Congested Livers in 175 Patents with Right-Sided Heart Failure

Symptom/sign	Acute heart failure (%)	Chronic heart failure (%)
Hepatomegaly	99	95
Peripheral edema	77	71
Pleural effusion	25	17
Splenomegaly	20	22
Ascites	7	20

Adapted from Richman SM, Delman AJ, Grob D. Alterations in indices of liver function in congestive heart failure with particular reference to serum enzymes. Am J Med 1961; 30:211.

Table 56-2. Liver Tests of 175 Patients with Right-Sided Heart Failure

Liver tests	Acute heart failure		Chronic heart failure	
	n	Abnormal(%)	*n*	Abnormal (%)
Bilirubin	86	37	57	21
BSP retention	71	87	55	71
Alkaline phosphatase	80	10	55	9
Aspartate aminotransferase	67	48	37	5
Alanine aminotransferase	53	15	29	3
Globulins	100	60	67	37
Prothrombin time	68	84	43	74
Albumin	100	32	67	27
Cholesterol	87	49	60	42

BSP, Bromosulfophthalein.
Adapted from Richman SM, Delman AJ, Grob D. Alterations in indices of liver function in congestive heart failure with particular reference to serum enzymes. Am J Med 1961; 30:211.

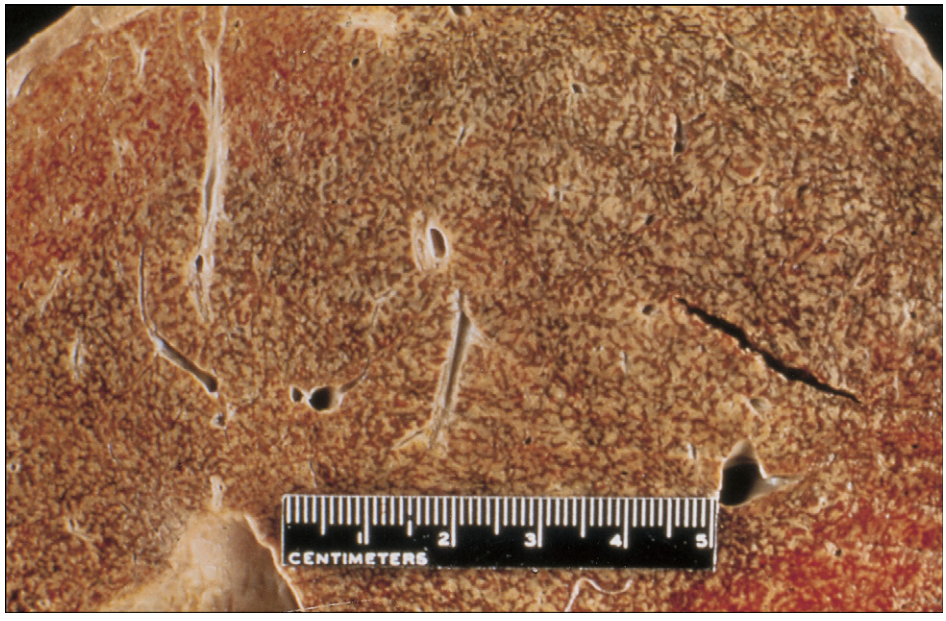

Figure 56-1. Nutmeg liver. In chronic passive congestion of the liver, red cells pool and distend the sinuses around the central vein. These regions develop a darker red-violet color, in contrast to the surrounding tan liver parenchyma. This color stippling is reminiscent of the cut surface of a nutmeg.

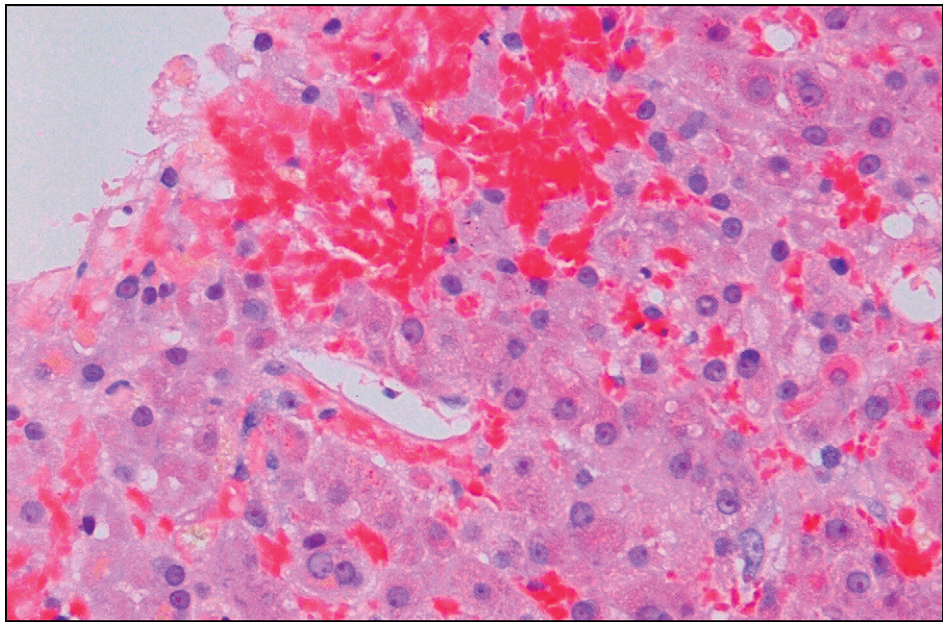

Figure 56-2. Liver congestion. The sinuses around the central vein are distended by normal red cells. As the severity of this lesion increases, the adjacent hepatocytes become atrophic. (Hematoxylin and eosin.)

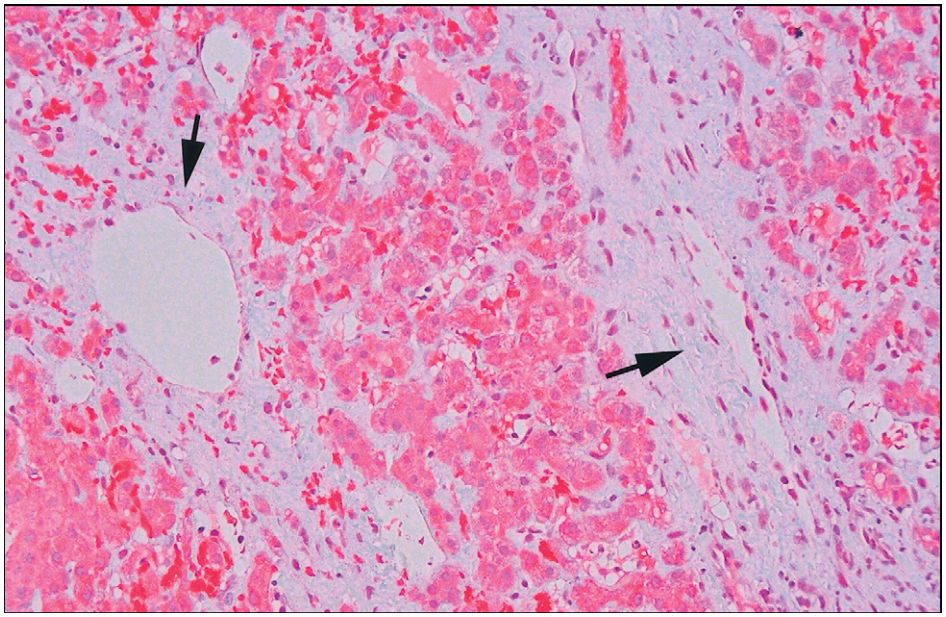

Figure 56-3. Cardiac cirrhosis. Dense fibrous bands emanate from the central veins (arrows) to surround a nodule of regenerating hepatocytes. (Trichrome.)

heart failure, hyperbilirubinema occurs in over 20% of patients.[2] The elevation is generally mild, less than 3 mg/dl, and composed predominantly of unconjugated bilirubin. Serum aminotransferase levels are usually normal or minimally elevated in compensated, chronic congestive heart failure, but may become elevated during exacerbations of heart failure. Prothrombin time is prolonged in the majority of patients with hepatic congestion from right heart failure. Patients anticoagulated with warfarin sodium (warfarin) for dilated cardiomyopathy may have decreased warfarin requirements during exacerbations of congestive heart failure and this effect, if not appreciated, could result in dangerously prolonged prothrombin times. Hepatic biochemical abnormalities generally improve with improvement in cardiac function.

Several signs and symptoms of congestive heart failure (e.g., ascites, pedal edema, mild hyperbilirubinemia) are also seen in patients with decompensated hepatic cirrhosis and distinguishing these two entities may be difficult. In some patients, it is particularly difficult to distinguish cardiac ascites from cirrhotic ascites clinically. In such cases, characterization of ascitic fluid or measurement of hepatic venous pressure gradient may be of assistance. In a prospective study of 13 patients with cardiac ascites, the serum ascites albumin concentration gradient was 1.1 g/dl and the total protein was 2.5 g/dl.[3] Additionally, cardiac ascites had significantly more ascitic fluid red cell counts and higher levels of lactate dehydrogenase.[3]

LEFT HEART FAILURE AND ISCHEMIC HEPATITIS

Ischemic hepatitis can be defined as hepatocellular necrosis associated with a decrease in hepatic perfusion.[4–6] It is relatively infrequent, with a reported incidence of 0.16–1.5% of hospitalized patients. It can affect any age group, although it is most frequently reported in the older population. This undoubtedly reflects the increased risk of underlying cardiovascular disease in older people. When seen in children, it is often associated with congenital heart disease or overwhelming sepsis.[7] The term *ischemic hepatitis* is a misnomer because ischemic liver injury is characterized by centrilobular necrosis in the absence of inflammation. The diagnosis of ischemic hepatitis should be considered in any patient with elevations of liver enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH)) in the setting of documented or suspected systemic hypotension.

Causes and Pathogenesis

Liver is a highly vascular organ, receiving approximately 25% of cardiac output. Seventy percent of the hepatic blood flow is derived from the portal system. The other 30% is delivered by the hepatic artery and liver arterial perfusion expresses a linear relation between blood pressure and blood flow.[8] The liver can maintain normal oxygen uptake by increasing oxygen extraction, with as much as 95% of the oxygen from the blood being extracted in a single pass through the liver.[6] This remarkable compensatory mechanism most likely accounts for the low incidence of liver damage in shock (resistance to ischemia). Nevertheless, these compensatory mechanisms are overwhelmed in some patients with severely diminished hepatic perfusion leading to ischemic liver injury.

Cardiogenic shock from any cause (e.g., myocardial infarction, tamponade) is the most commonly reported risk factor for the development of ischemic hepatitis. Transiently decreased cardiac output seen in patients with arrhythmia or valvular heart disease may also result in hepatic injury even in the absence of bona fide hypotension (? relative hypotension).[9] Episodes of hypotension resulting in ischemic hepatitis may be very brief and sometimes there may not be any documented episodes of hypotension. Although diminished hepatic perfusion from systemic hypotension (either absolute or relative) is essential, a recent study suggested that systemic hypotension or shock alone is insufficient to cause ischemic hepatitis.[10] In this study, 31 patients with ischemic hepatitis were compared to a control group consisting of 31 previously

healthy subjects with major non-hepatic trauma and marked hypotension (mean systolic pressure of 54 ± 22 mmHg lasting for a mean of 19 ± 14 minutes). All 31 patients with ischemic hepatitis had organic heart disease and more than 90% had demonstrable right heart failure. None of the subjects in the control group developed ischemic hepatitis despite profound hypotension. These findings suggest that right heart failure with passive hepatic congestion renders the liver susceptible to ischemic liver injury during transient systemic hypotension.[10] Henrion et al. recently published a paper that described clinical and hemodynamic features of 142 episodes of ischemic hepatitis. When ischemic hepatitis occurred in patients with congestive heart failure or acute heart failure, the hepatic hypoxia resulted primarily from the decreased hepatic blood flow and venous congestion. However, when ischemic hepatitis occurred in patients with toxic or septic shock, oxygen delivery to liver was decreased but oxygen needs were increased, leading to hepatic hypoxia.[11]

Non-cardiogenic causes of ischemic hepatitis include hypovolemic shock from hemorrhage or dehydration, heat stroke, and septic shock.[12–14] Rare episodes of ischemic hepatitis have been reported in patients who ingest vasoactive medication (ergotamine overdose) and after protracted seizures in children.[15,16]

Clinical Syndrome

The clinical picture is usually dominated by the cardiovascular, septic, or hemorrhagic illness that precipitated the hepatic hypoperfusion. A distinctive biochemical pattern is characteristic of this disorder.[17,18] Serum aminotransferase levels rise rapidly after an ischemic episode and peak within 1–3 days (Figure 56-4). With treatment of the underlying illness, serum aminotransferases usually return to near-normal within 7–10 days of the initial insult. Persistent elevation of serum aminotransferase levels beyond this period implies a poor prognosis due to continued hepatic hypoperfusion.

Serum ALT and AST activity are strikingly elevated and may exceed 200 times the upper limits of normal (Figure 56-4). Less marked elevation (<500 U/l) have also been reported in biopsy-proven ischemic hepatitis. Serum LDH activity is also markedly elevated in patients with ischemic hepatitis. When fractionated, serum LDH activity is mostly of hepatic origin.[17] The level of LDH may rise to 30 times the upper limits of normal and parallels the pattern of aminotransferase activity, with a brisk rise and rapid resolution. Of note, the serum LDH is usually only slightly elevated in patients with acute viral hepatitis. Marked elevations of alkaline phosphatase or serum bilirubin are unusual in ischemic hepatitis and cholestasis has not been demonstrated on liver biopsies of those patients. Mild elevations of serum bilirubin may be seen, but this rarely exceeds four times the upper limit of normal.[17]

In one series of patients with ischemic hepatitis, additional biochemical features were noted that might be helpful in diagnosis.[7] All patients in this series had transient abnormalities of serum creatinine and blood urea nitrogen. These changes were sometimes marked, consistent with acute renal failure, but resolved over 7–10 days. The authors speculated that the same hypotensive insult to the liver had similar adverse effects on the kidney. Both hyper-

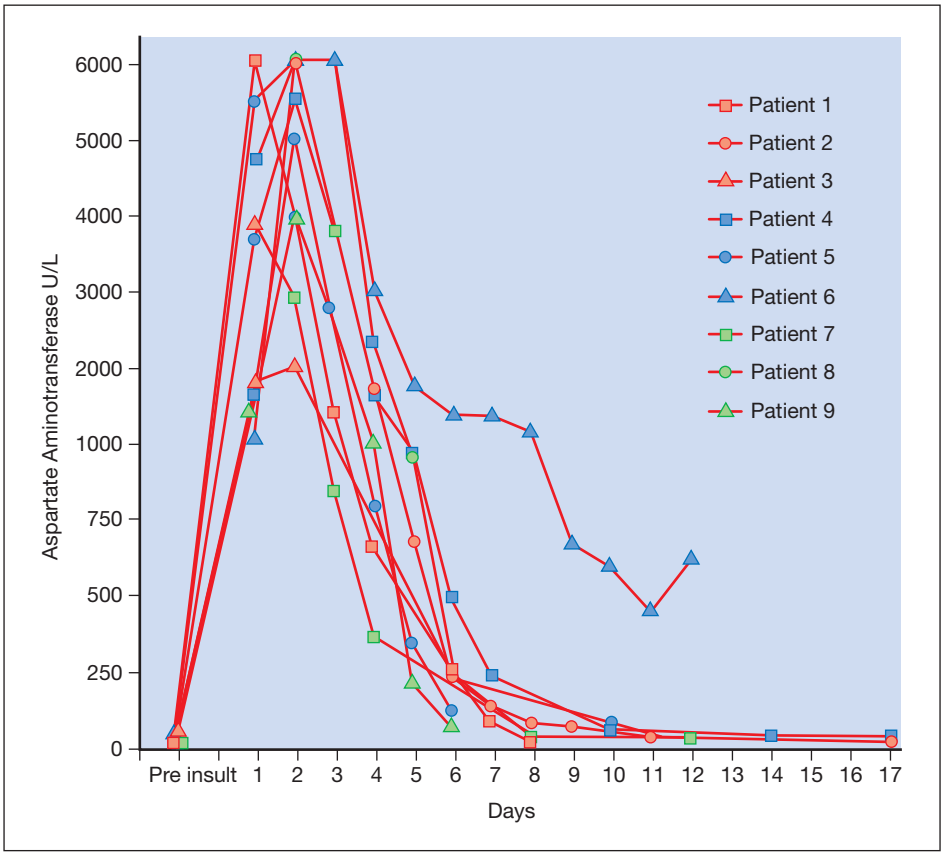

Figure 56-4. Ischemic hepatitis. Serial alanine aminotransferase (ALT) levels in patients with ischemic hepatitis. (Adapted from Gitlin N, Serio KM. Ischemic hepatitis: widening horizons. Am J Gastroenterol 1992; 87:831, with permission.)

glycemia and hypoglycemia can be seen.[5,17,18] In one series, two-thirds of patients with ischemic hepatitis had new-onset hyperglycemia that occurred within 48 hours of their illness.[18] In another report, hypoglycemia was seen in 33% of the patients with ischemic hepatitis.[5]

Histologic studies of ischemic hepatitis are limited. Patients in whom a diagnosis of ischemic hepatitis is being considered are usually critically ill, often with multiorgan failure, making a liver biopsy impractical. Nevertheless, the hallmark of ischemic hepatitis is centrilobular necrosis in the absence of an inflammatory infiltrate.[19] Gibson and Dudley studied 17 patients with these characteristic histologic findings and concluded that a diagnosis of ischemic hepatitis could be made without a liver biopsy in the appropriate clinical setting (patients who had a potential cause for a fall in cardiac output) and a rapid rise in levels of serum aminotransferases and LDH.[17]

Differential Diagnosis

Few primary liver diseases will give such marked elevations of serum aminotransferases followed by rapid resolution. The diagnosis of ischemic hepatitis can be made readily in a patient in the intensive care unit with a rapid and striking increase of serum aminotransferase and LDH activities who has recently suffered a documented, acute hypotensive episode that required pressor support.

Acute viral hepatitis may mimic the clinical picture seen with ischemic hepatitis. Viral hepatitis will usually be accompanied by a symptomatic prodrome or a history of exposure to an infectious agent and serologies will help to exclude a viral etiology. Serum LDH activity is only mildly elevated in viral hepatitis. In patients who have only modest elevations in serum aminotransferases, chronic hepatitis B and hepatitis C should be excluded by history and appropriate serologic tests. Examination of previous liver enzyme results prior to the current illness may be invaluable in distinguishing the acute illness from chronic viral hepatitis.

Special care should be taken to identify all medications taken by the patient prior to admission as well as those started since hospitalization. Drug hepatoxicity can be associated with striking elevations of serum aminotransferase and LDH activities. Acetaminophen toxicity should always be considered in patients with marked elevations of serum aminotransferase levels and renal insufficiency. Amiodarone is an antiarrhythmic agent that is increasingly being used in the management of unstable tachyarrhythmias. Its toxicity should also be considered in the differential diagnosis as several cases of acute hepatitis and fulminant liver failure have been reported with intravenous loading doses of amiodarone.[19–21]

Other causes of marked, acute elevations of serum AST activity include rhabdomyolysis, acute myocardial infarction, acute cholangitis, hepatic trauma, and hepatic infarction, all of which should be distinguishable from ischemic hepatitis by history and additional laboratory investigation.

Treatment and Prognosis

The treatment of ischemic hepatitis is directed at the underlying illness. Therapy to improve cardiac output with inotropes and pressors will improve hepatic perfusion and result in resolution of the ischemic hepatitis. Similarly, volume resuscitation for patients with hemorrhagic shock and appropriate treatment for septic shock will indirectly improve cardiac output and hepatic perfusion.

Special consideration should be given to prescribing medications in patients with circulatory failure and ischemic hepatitis. The clearance of certain medications (e.g., lidocaine, calcium-channel blockers) is dependent on hepatic blood flow and their clearance can be greatly diminished in this setting. Indeed, an association has been reported between the use of calcium-channel blockers and antiarrhythmic agents in patients with ischemic hepatitis and increased mortality, although it was not clear from that study if the worse prognosis was merely related to the presence of more severe cardiac disease.[22] Opiates and analgesics that are often prescribed for these critically ill patients also have the potential to accumulate and cause neurologic and respiratory depression. It has been suggested that the risk of acetaminophen toxicity is increased in patients with underlying cardiomyopathy, even at low doses in the absence of alcohol ingestion.[23]

The prognosis of ischemic hepatitis is largely dependent upon the prognosis of the underlying illness. Short-term mortality has been reported to be as high as 50% in patients with ischemic hepatitis. One-month and 1-year survival rates for patients with ischemic hepatitis in the series by Henrion et al. were 47% and 28%, respectively.[11] However, despite the massive hepatic necrosis that may occur, deaths due to hepatic failure are extremely rare; the cause of death is usually a result of poor cardiac reserve.[4] The aminotransferase levels do not seem to have any prognostic significance. When stratified according to peak AST activity, the survival for patients with AST levels lower than 2000 IU/l was 43%, compared to 41% for patients with a peak AST activity above this value. The pattern of AST activity, however, does seem to have some prognostic value. In patients with ischemic hepatitis who died, the level of serum AST did not drop appreciably from peak values while in those who survived, AST levels rapidly returned towards normal, suggesting improving cardiac function.[4]

LIVER IN CONSTRICTIVE PERICARDITIS

Constrictive pericarditis may masquerade as a primary liver disease.[24–26] Pulsatile hepatomegaly, splenomegaly, and ascites are often present in patients with constrictive pericarditis.[27] Other important physical findings include elevated jugular venous pressure, pulsus paradoxus, and pericardial knock. It has been noted that ascites is more prominent than pedal edema.[28] Histological features are usually non-specific: diffuse centrilobular congestion, necrosis, and fibrosis are the most common, but there may be mild abnormalities such as patchy fibrosis without congestion. Occasionally, there can be prominent sinusoidal dilation and hemorrhagic necrosis with hepatic vein thrombosis, leading to a misdiagnosis of Budd–Chiari syndrome.[29,30] Tuberculosis remains an important cause of constrictive pericarditis, but other etiologies, such as cardiac surgery, connective tissue disorders, subclinical viral pericarditis, and malignancy, are becoming increasingly frequent. Pericardial calcification on chest radiography and low voltage on electrocardiography, when present, are very suggestive of constrictive pericarditis. A recent report indicates that pericardiectomy will improve liver function (assessed by indocyanine green clearance) in most patients with liver injury caused by constrictive pericarditis.[31]

LIVER INJURY DUE TO CHRONIC RESPIRATORY FAILURE

Although most cases of ischemic hepatitis are related to altered hepatic perfusion (e.g., congestive heart failure), it is now clear that severe arterial hypoxemia caused by severe respiratory disease can also lead to hepatic injury independent of hepatic perfusion abnormalities (hypoxic hepatitis).[32–35] A recent study investigated the details of hemodynamic and oxygen transportation abnormalities in 19 consecutive episodes of hypoxic hepatitis caused by acute exacerbation of chronic respiratory failure without left heart failure.[11] These patients had marked arterial hypoxemia (mean PaO_2 34 mmHg and $PaCO_2$ 64 mmHg) with elevated central venous pressure but an elevated cardiac index and low systemic vascular resistance. Oxygen delivery was significantly decreased in these patients, despite reasonable hepatic blood flow, as measured by the low-dose galactose clearance test.[11] The authors suggested that hypoxic hepatitis induced by acute exacerbation of chronic respiratory failure is due to severe arterial hypoxemia in the background of elevated central venous pressure and passive hepatic congestion.[11,33] Most patients with hypoxic hepatitis caused by respiratory diseases have accompanying cardiac dysfunction; however, there are reports of severe obstructive sleep apnea (OSA) leading to hypoxic hepatitis in the absence of any cardiac dysfunction.[33] A recent study suggests that chronic intermittent hypoxemia may cause chronic low-grade hepatic injury in patients with OSA.[36] Chin et al. investigated the relationship between liver enzyme abnormalities and intermittent hypoxemia in 40 obese men with OSA. In this study, the prevalence of unexplained elevations in transaminases in obese patients with OSA was 35%. More interestingly, the authors systematically evaluated the effect of treatment with nasal continuous positive airway pressure (CPAP) on the levels of aminotransferases, insulin, and glucose in 40 obese subjects with OSA. There was a significant decrease in the levels of transaminases after overnight, 1 month, and 6 months of nasal CPAP treatment, with no significant changes in the degree of insulin resistance (Table 56-3).

Table 56-3. Changes in aspartate aminotransferase (AST), Alanine Aminotransferase (ALT), and Insulin Resistance Following Nasal Continuous Positive Airway Pressure (CPAP) Treatment in Obese Patients with Obstructive Sleep Apnea ($n = 40$)

Nasal CPAP treatment	AST before and after treatment (IU/l)	ALT before and after treatment (IU/l)	HOMA before and after treatment
Overnight CPAP	39 ± 28 versus 34 ± 24 ($P < 0.001$)	61 ± 53 versus 61 ± 48 ($P = 0.9$)	3.4 ± 2.2 versus 3.2 ± 1.6 ($P = 0.3$) versus 3.2 ± 1.6 ($P = 0.3$)
CPAP for 1 month	37 versus 25[a] ($P < 0.001$)	60 versus 40[a] ($P = 0.001$)	3.4 ± 2.2 versus 2.8 ± 1.4 ($P = 0.2$)
CPAP for 6 months	37 versus 25[a] ($P < 0.001$)	60 versus 40[a] ($P = 0.001$)	N/A

HOMA, homeostasis model assessment method (a measure of insulin resistance).
[a]Standard deviations for AST and ALT values for 1- and 6-month CPAP were not available in the manuscript.
Adapted from Chin K, Nakamura T, Takahasi K, et al. Effects of obstructive sleep apnea on serum aminotransferase levels in obese patients. Am J Med 2003;114:370.

JEJUNOILEAL BYPASS

Jejunoileal bypass surgery was introduced in the 1960s as a surgical treatment for morbid obesity.[37] Initial enthusiasm for this radical weight-loss procedure was tempered by the recognition of a myriad of associated complications, including electrolyte abnormalities, kidney problems, gallstones, severe malnutrition, and liver disease.[37–41] The hepatic effects of jejunoileal bypass include fatty infiltration, cirrhosis, and progressive liver failure. This procedure is rarely, if ever, performed today, so new diagnoses of liver disease related to jejunoileal bypass are unusual. However, patients who have had surgery decades ago may present with end-stage liver disease, on occasion being referred to centers for consideration of liver transplantation. Rarely, non-alcoholic steatohepatitis has been reported following gastric partitioning surgery.[42]

MECHANISM OF HEPATIC INJURY

Numerous theories have been proposed to explain the liver injury associated with jejunoileal bypass. The bypass procedure results in malabsorption of a number of nutrients, which accounts for some of its weight-loss effects and many of the associated complications. Early researchers noted the similarities of fatty infiltration seen in patients with protein malnutrition and in patients after jejunoileal bypass.[43] Serum levels of essential amino acids were decreased when measured during the period of rapid weight loss and there was a concurrent increase in fatty infiltration of the liver. In a control group of patients who had stable weights after jejunoileal bypass, serum amino acid levels were higher and there was less hepatic steatosis. Nutritional supplements were reported to decrease the extent of hepatic injury in some patients, although others experienced continued deterioration.

Animal models and studies in patients after jejunoileal bypass implicated bacterial overgrowth as a possible etiologic factor in the development of hepatic steatosis. In a dog model of jejunoileal bypass, vibramycin treatment prevented the appearance of fatty liver and death from liver failure.[44] In rats, metronidazole therapy also seemed to ameliorate the postoperative changes to the liver, but to a lesser degree than did protein supplementation.[45] Genetically obese *ob/ob* mice with hepatic steatosis were shown to have age-related increases in the production of endogenous ethanol by the intestinal microflora.[46] Drenick and associates[47] treated patients with metronidazole administered at random time intervals after jejunoileal bypass. In untreated patients, hepatic lipid content as measured by morphologic assessment was elevated and remained abnormal over a 12-month period in most patients. In patients treated with metronidazole, hepatic fat content that was initially elevated following the bypass surgery decreased once the drug was started. In another group, in whom metronidazole was administered intermittently, levels of hepatic fat increased and then decreased in concert with antibiotic therapy. Moreover, in this study there was no correlation between hepatic steatosis and protein malnutrition. The mechanism of hepatic injury, although perhaps related to bacterial overgrowth, remains unknown.

PATHOLOGY OF LIVER DISEASE

The hepatic histology found in patients who have undergone jejunoileal bypass often resembles the changes seen in alcoholic liver disease. The most common findings include macrovesicular steatosis, Mallory's hyaline, sinusoidal fibrosis, and infiltrates of polymorphonuclear leukocytes.[48,49] The histologic changes of hepatic steatosis are often at their worst in the first year after surgery and then may improve in some patients, while others show continued progression to cirrhosis and liver failure.

Vyberg and co-workers[50] performed serial liver biopsies on 34 morbidly obese patients undergoing jejunoileal bypass. Postoperatively, 44% of patients had no or minimal histologic changes, while the remainder had varying degrees of steatosis, steatohepatitis, and perivenular fibrosis. Five to 9 months postoperatively, liver biopsies revealed progression of the hepatic injury in almost all patients. In the group of patients with minimal preoperative changes, 85% had developed moderate to marked steatosis. Those patients with more severe changes preoperatively showed increased steatohepatitis and fibrosis; 18% developed bridging fibrosis and 9% had changes of cirrhosis. Mallory's hyaline was seen in almost one-third of patients.

Nasrallah and colleagues[51] attempted to identify pre- and postoperative variables that may predict histologic liver injury after jejunoileal bypass. Preoperatively, 59% of morbidly obese patients had normal liver histology. There was no correlation between preoperative histology, serum biochemical parameters, use of small amounts of alcohol, or the amount of weight loss and the postoperative histologic changes.

CLINICAL MANIFESTATIONS

Liver injury after jejunoileal bypass may range from asymptomatic elevations of serum hepatic enzymes to cirrhosis with liver failure. It has been estimated that up to 2% of patients died of liver failure following this procedure.[38,52] Liver injury may become clinically apparent within months of surgery or progress insidiously for more than 10 years before presenting with signs and symptoms of cirrhosis. Requarth and co-workers[53] reported the long-term morbidity following jejunoileal bypass in 453 patients. During the follow-up, 24 patients developed acute liver failure (7%) and the actuarial 15-year probability of cirrhosis was 8.1%. In the early stages of hepatic injury associated with jejunoileal bypass, liver enzyme abnormalities do not correlate with histologic findings and are therefore of limited value in identifying patients at risk for liver failure.[51,52,54] Mild elevations of serum aminotransferases and alkaline phosphatase levels may occur, but many patients with significant histologic changes have no biochemical abnormalities. Serial liver biopsies may be helpful in following the progression of liver disease. Once overt liver failure develops, elevation of serum bilirubin, a further fall in serum albumin, and prolongation of prothrombin time will be evident. In these patients, a trial of parenteral vitamin K administration is worthwhile to exclude malabsorption as a contributing cause to the coagulopathy.

Patients who are discovered to have progressive liver injury may benefit from reversal of the bypass operation.[41,55] In one series, 9 patients with cirrhosis had reversal of the bypass to re-establish continuity of the small intestine. Seven patients survived for at least 3 years after the surgery. Follow-up liver biopsies showed histologic improvement in 4 patients with decreased steatosis and inflammation, while 3 had no obvious changes on liver histology. Two patients died of liver failure shortly after the reversal procedure; both of these patients had preoperative ascites, indicating that once decompensation has occurred the prognosis is very poor.

For patients who have already developed decompensated cirrhosis, liver transplantation may be the only therapeutic option available to improve quality of life and prolong survival.[56–59] In general, it is believed that jejunoileal bypass should be reversed either during or immediately after the liver transplantation.[57,58] One should avoid the takedown of jejunoileal bypass in patients with advanced liver disease prior to transplantation because such surgical interventions are poorly tolerated. If the jejunoileal bypass is not reversed, there is a substantial risk of recurrent steatosis and progressive liver damage in the allografts.[59] In such patients, liver biopsies should be performed on a regular basis during the post-transplant period to detect progressive liver damage. Morbid obesity is common in the post-transplant period when jejunoileal bypass is reversed, but allograft abnormalities are uncommon despite such weight gain.[57–59]

CONNECTIVE TISSUE DISEASES

Patients with connective tissue disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, and scleroderma may have clinical and biochemical evidence of associated liver disease. The severity of liver involvement can range from asymptomatic elevations of serum aminotransferases to cirrhosis and liver failure. Unusual liver lesions such as nodular regenerative hyperplasia have been reported with increased frequency in patients with connective tissue disorders. Over the last decade, there have been numerous reports associating chronic hepatitis C infection with Sjögren's syndrome. An excellent review was recently published by Abraham and colleagues that provided a detailed review of the hepatic manifestations of autoimmune rheumatic diseases.[60]

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is an autoimmune disorder involving skin, kidneys, cardiovascular system, and central nervous system. Strict criteria reflecting multiorgan involvement have been established by the American College of Rheumatology in order to diagnose SLE uniformly and distinguish it from other connective tissue disorders; patients are required to have four of 11 criteria before a diagnosis of SLE is established.[61] These criteria need not be present at one time, but may develop sequentially over many years. Liver test abnormalities are not a part of these diagnostic criteria and the liver is generally not a major target for end-organ damage in patients with SLE. Nevertheless, many patients with SLE may have clinically significant liver disease.

Runyon and associates[62] reviewed over 200 patients who met the criteria for SLE. Twenty-one percent of patients had abnormal liver enzymes at some point during their illness and these elevations could not usually be attributed to other non-hepatic etiologies or comorbid conditions. In 20% of patients, the first liver enzyme elevations were noted during an exacerbation of SLE. Elevations of aminotransferase and alkaline phosphatase levels were usually mild – less

than fourfold the upper limits of normal. However, more severe liver disease occurred, approximately 25% of the patients with abnormal liver enzymes were jaundiced, and 3 patients died of liver failure. Liver biopsy specimens were available from 33 patients and revealed a variety of hepatic lesions, including non-specific portal inflammation, chronic active hepatitis, and established cirrhosis. The most common finding was hepatic steatosis that was seen in over one-third of patients.

In an autopsy study published in 1992, Matsumoto and associates[63] studied liver specimens and clinical data from 52 patients with SLE. None of these patients died as a result of liver failure. One-third of these patients had abnormalities of at least two different liver enzymes. The most common finding was hepatic congestion, although the authors felt that this lesion was most likely a result of the terminal event. As in the previous study, hepatic steatosis was very common and was found in 73% of patients. Twelve percent of patients had chronic hepatitis. Of interest, 21% of patients had histological evidence of arteritis, a finding previously considered rare in patients with SLE. Hepatic infarction occurred in 1 patient. Nodular regenerative hyperplasia, a lesion characterized by diffuse nodularity in the absence of associated fibrosis, was seen in 3 patients.

Hemophagocytic syndrome (HPS) can be seen in patients with SLE.[64,65] HPS is a clinicopathological entity characterized by systemic proliferation of benign hemophagocytic cells of monocyte–macrophage–histiocyte lineage. It is characterized by fever, cytopenia, liver dysfunction, and lymphadenopathy. This complication developed in nearly 10% of the patients with SLE seen at Yokohama City University Hospital over a 10-year period.[64]

The interpretation of any studies of liver disease in patients with SLE is complicated by comorbid conditions and the potential for drug toxicities that may mimic chronic liver disease. All of the above-mentioned studies were performed prior to the availability of hepatitis C testing. Thus, hepatitis C virus (HCV) cannot be excluded as a cause for some of the liver enzyme elevations or the abnormal hepatic histology. This is particularly important since substantial number of patients with SLE received blood transfusions prior to 1991. In addition, most patients in these studies received varying doses of prednisone and this could explain the frequent finding of hepatic steatosis in these patients.

Hepatic injury from salicylates may also be a factor in producing some of the liver dysfunction associated with SLE and other connective tissue disorders.[66] The salicylate-induced hepatotoxicity appears to be dose-dependent. Hepatic injury is not evident at doses less than 2.5 g/day or with a blood salicylate level <25 mg/dl. Furthermore, there is a correlation between blood salicylate levels and the serum ALT activity.[67] Features of a hypersensitivity reaction, such as fever or rash, are usually absent. The elevation in the liver enzymes reflects hepatocellular injury, with elevations of serum aminotransferases, sometimes exceeding 1000 U/l. Discontinuation of aspirin results in prompt improvement of liver enzymes with no chronic sequelae.

Ascites has been reported in several patients with SLE in the absence of liver disease or other secondary conditions.[68] The pathogenesis of ascites in these patients is due to serositis with associated weeping of lymphatics. Ascites may be present even when SLE is relatively quiescent and other symptoms or signs of the disease are inactive. Increased immunosuppression with prednisone may be beneficial in reducing SLE-related ascites, once other etiologies have been carefully excluded.

RHEUMATOID ARTHRITIS

Elevations of alkaline phosphatase are the most frequently reported liver test abnormalities associated with rheumatoid arthritis, and may be seen in as many as 50% of patients, while serum aminotransferase levels are usually normal.[69] The source of alkaline phosphatase, bone versus liver, is somewhat controversial. In studies of alkaline phosphatase fractions, almost one-third of patients with rheumatoid arthritis had elevated levels of hepatobiliary alkaline phosphatase, suggesting liver involvement. However, other serum enzymes, such as 5′-nucleotidase and γ-glutamyltranspeptidase, that are often used a supplementary assays to support the hepatic origin of alkaline phosphatase, are frequently normal in patients with rheumatoid arthritis.[69,70] Furthermore, these enzymes have been shown to have higher levels in the joint space than in serum, implying that they may originate from inflamed joints. Other investigators have demonstrated that the degree of total alkaline phosphatase elevation varies with the number of joints involved.[71] Finally, the pattern of alkaline phosphatase fractions may vary over time.[72] Thus, abnormal serum liver-associated enzymes in patients with rheumatoid arthritis must be interpreted with caution.

A number of liver diseases have been reported in patients with adult and juvenile rheumatoid arthritis (Table 56-4). In 1997, Ruderman and associates[73] published an autopsy study of hepatic histology in 182 patients with rheumatoid arthritis. The most common finding was hepatic congestion, although it is likely that this lesion was a result of the terminal event. As in SLE, hepatic steatosis was common and was found in 23% of the patients. Eleven percent of patients had fibrosis, 2.7% had established cirrhosis, and 5% had evidence of amyloidosis. Other disorders that are described in association with rheumatoid arthritis, such as primary biliary cirrhosis (PBC) and nodular regenerative hyperplasia, were not seen in this series.

Nodular regenerative hyperplasia has been reported in association with rheumatoid arthritis, often with Felty's syndrome and active joint disease (Figure 56-5).[74] Features of portal hypertension such as varices and ascites are common in this latter group of patients.[63] The pathogenesis of nodular regenerative hyperplasia is not known, although some authors have suggested it is related to drug toxicity or underlying portal venous thromboses.[63,74] The latter hypothesis is intriguing given the frequency of antiphospholipid syndrome (APS) in patients with connective tissue diseases, the same

Table 56-4. Liver Disease Associated with Adult and Juvenile Rheumatoid Arthritis

Adult rheumatoid arthritis	Juvenile rheumatoid arthritis
Hepatic steatosis	Acute hepatitis
Primary biliary cirrhosis	Chronic non-specific hepatitis
Autoimmune hepatitis	Massive liver enlargement
Nodular regenerative hyperplasia	Drug toxicity
Amyloidosis	
Salicylate or methotrexate hepatotoxicity	

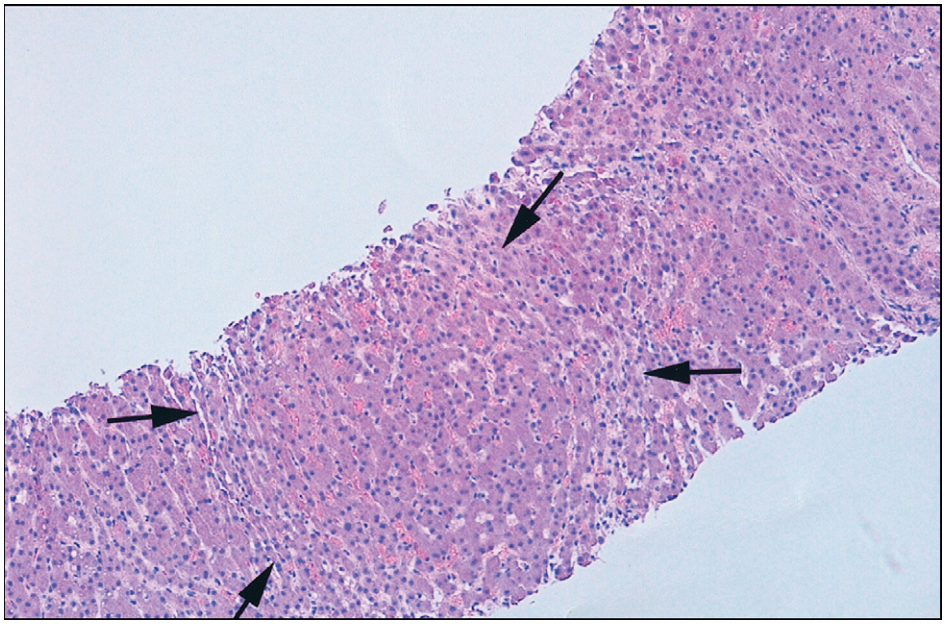

Figure 56-5. Nodular regenerative hyperplasia**.** Thin bands of atrophic hepatocytes (arrows) outline a central focus of hepatocyte regeneration, producing a nodular appearance throughout the liver. The reticulin in the atrophic areas is condensed but there is no fibrosis. (Hematoxylin and eosin.)

population with an increased incidence of nodular regenerative hyperplasia.

As with SLE, drug toxicities, particularly aspirin and other salicylates, may play a role in the liver abnormalities associated with rheumatoid arthritis. Gold therapy may cause intrahepatic cholestasis with features of a hypersensitivity reaction, including a skin rash and eosinophilia.[75–77] Prolonged, high-dose gold salt therapy has also been reported in 1 patient to produce a dose-related form of toxicity characterized by jaundice and severe hepatocellular necrosis. Liver biopsy revealed submassive hepatic necrosis with lobular and portal inflammation. Brown-black pigment, identified as gold granules, was seen in macrophages, and electron microscopy demonstrated gold particles in lysosomes. It was believed that hepatic injury occurred once the concentration of gold exceeded the lysosomal storage capacity.[78] Perhaps the most controversial issue in drug therapy and hepatotoxicity involves the use of methotrexate for the treatment of rheumatoid arthritis. This topic is reviewed elsewhere (Chapter 26).

ANTIPHOSPHOLIPID SYNDROME

APS is characterized by the presence of antiphospholipid antibodies (anticardiolipin antibodies and/or lupus anticoagulant) in association with venous/arterial thromboses, recurrent fetal loss, and thrombocytopenia. Although APS can be a primary disorder, it is frequently seen in patients with SLE and other connective tissue disorders. The most commonly described hepatic manifestation of APS is Budd–Chiari syndrome.[79,80] Pelletier and colleagues[81] reported that, of their 22 patients with APS, 4 had Budd–Chiari syndrome, with no other cause of hepatic vein thrombosis. Several other liver disorders have been reported in patients with APS and these are summarized in Table 56-5.[79–83]

Table 56-5. Liver Complications in Antiphospholipid Syndrome

Budd–Chiari syndrome
Hepatic veno-occlusive disease
Nodular regenerative hyperplasia
Transient elevation of hepatic enzymes due to multiple fibrin thrombi
Infarction of liver
Autoimmune hepatitis
HELLP syndrome

HELLP, hemolysis, elevated liver enzymes, and low platelet count.

SJÖGREN'S SYNDROME

Sjögren's syndrome is an autoimmune disorder that mainly affects exocrine glands and usually presents as a persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands. PBC is common in both primary and secondary forms of Sjögren's syndrome. In a study of 300 patients with primary Sjögren's syndrome, 7% of the patients had elevated antimitochondrial antibody titers.[84] Of these, 60% had elevations of alkaline phosphatase. Liver biopsies revealed changes of early PBC, even in many patients with normal liver enzymes.[84]

Over the last decade, there have been numerous investigations exploring the relationship between HCV and Sjögren's syndrome. In 1992, Haddad and colleagues[85] postulated a causal relationship between Sjögren's syndrome and HCV. The reported prevalence of HCV in patients with Sjögren's syndrome depends on the methods of detection, population studied, and the criteria for diagnosing primary Sjögren's syndrome. In European patients, the prevalence ranges between 14 and 19% by third-generation enzyme-linked immunosorbent assay and 5–19% by the second-generation immunoblot (RIBA-2) method, whereas HCV prevalence by RIBA-2 was only 0–1% in American patients.[86] HCV prevalence is much lower when the polymerase chain reaction method is used to detect HCV or when more objective criteria are applied to define primary Sjögren's syndrome.[87] Based on the current evidence, HCV seems to be a rare cause of primary Sjögren's syndrome except in patients with liver involvement or cryoglobulinemia.[86] Furthermore, HCV is

a sialotropic virus and morphological evidence of sialadenitis is found in a significant proportion of patients with chronic HCV infection.[86–90] In HCV-related sialadenitis, the lymphocytic infiltrate is predominantly pericapillary (unlike periductal, in primary Sjögren's syndrome) and clinical symptoms of dryness are infrequent.

SCLERODERMA

Reynolds and colleagues[91] described 6 patients with typical PBC and varying features of scleroderma and CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia). Since then, the association between these two autoimmune disorders has been well established. The close immunologic association between PBC and scleroderma is supported by the finding of positive antimitochondrial antibodies in more than one-quarter of patients with scleroderma and anticentromere antibody in one-quarter of patients with PBC. In a recent study of 40 patients with systemic and localized scleroderma, liver biopsy-confirmed PBC was seen in 5 patients (12.5%).[92] Sometimes, patients with PBC develop symptomatology consistent with scleroderma. In a review of 558 patients with PBC, 4% were found to have symptoms of CREST syndrome.[93] Clinical manifestations of CREST often antedated the development of PBC by as much as 28 years.

REYE'S SYNDROME

Reye's syndrome is an acute illness characterized by encephalopathy and fatty infiltration of the liver. It was first reported in 1963 by Reye and colleagues, who described 21 Australian children who developed loss of consciousness, vomiting, fever, and hypoglycemia that occurred shortly after a viral prodrome.[94] Over 80% of patients in this series died. At autopsy, extensive fatty infiltration was noted in the liver and kidney, and to a lesser extent in the myocardium and pancreas.

EPIDEMIOLOGY

The Centers for Disease Control (CDC) define a case of Reye's syndrome as one in which there is:

1. acute, non-inflammatory encephalopathy, manifested clinically by alterations in the level of consciousness and documented, when such results are available, by the measurement of 8 or fewer leukocytes per cubic millimeter of cerebrospinal fluid or by the presence of cerebral edema without perivascular or meningeal inflammation in the histological section of the brain;
2. hepatopathy documented by liver biopsy or autopsy or a threefold or greater rise of AST, ALT, or serum ammonia;
3. no other more reasonable explanation for the cerebral or hepatic abnormalities.[95,96]

Reye's syndrome predominantly affects children in the first decade of life, but up to 20% of patients may be older than 15 years and, thus, this condition may be seen by adult gastroenterologists and hepatologists.[96–98] A study demonstrated decreasing incidence of Reye's syndrome based on the epidemiological characteristics of 1207 cases reported to the National Reye Syndrome Surveillance System (NRSSS) from December 1, 1980 through November 30, 1997.[96] A peak of 555 cases was reported in surveillance year 1980. From 1987 through 1993, no more than 36 cases were reported each year, and from 1994 through 1997, no more than 2 cases were reported each year (Figure 56-6).[87] A similar decline in the incidence of Reye's syndrome has been noted in the UK and elsewhere (Figure 56-7).[98]

Since the original description of Reye's syndrome, epidemiologic studies have suggested an association between Reye's syndrome and the use of aspirin during influenza or varicella viral infections.[96,98–101] Before 1990, the incidence of Reye's syndrome was higher in years with epidemics of influenza B than in years with epidemics of influenza A (H3N2 or H1N1), but this association was not found subsequently.[96] Patients who developed Reye's syndrome were much more likely to have received salicylates during a prodromal

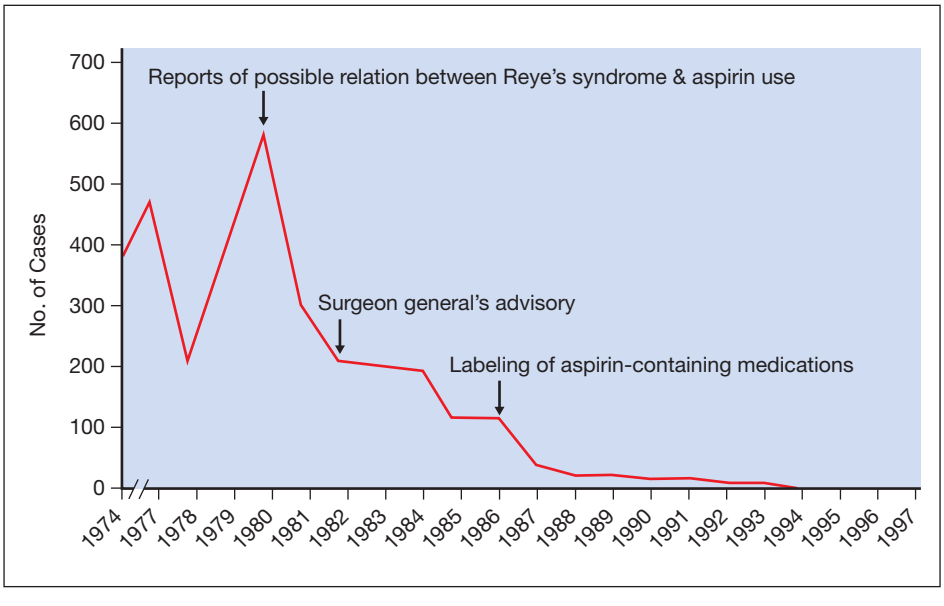

Figure 56-6. Number of reported cases of Reye's syndrome in relation to the public announcement of the epidemiologic association of Reye's syndrome with aspirin ingestion and the labeling of aspirin-containing medications. (Reproduced from Belay ED, Bresee JS, Holman RC et al. Reye's syndrome in the United States from 1981 through 1997. N Engl J Med 340:1377, 1999, with permission.)

illness than were those who did not develop the syndrome.[100,101] In a previous study from the CDC, the odds ratio of developing Reye's syndrome in association with a viral illness treated with aspirin was 16:1.[101] Children chronically treated with salicylates for illnesses such as juvenile rheumatoid arthritis and Kawasaki's disease are also at increased risk for Reye's syndrome.[96,102] Based upon these observations, in 1986, aspirin and aspirin-containing medications were labeled with an advisory not to administer to children with flu-like illnesses. The declining incidence of Reye's syndrome in the USA and UK is temporally associated with public health warnings about the risk of Reye's syndrome after the use of aspirin in children with varicella and influenza-like illnesses.[96,98] In countries where aspirin is inadvertently used in children with viral illnesses, Reye's syndrome continues to be a significant problem.[103] Erroneous diagnosis of Reye's syndrome was not uncommon when presumptive criteria were used to establish the diagnosis. Several inherited metabolic disorders present with signs and symptoms that are indistinguishable from Reye's syndrome (see below). When the charts of 49 patients originally diagnosed with Reye's syndrome were blindly reviewed, only one case was felt to be truly due to Reye's syndrome.[104] In UK, 12.7% patients that were originally reported with Reye's syndrome between 1981 and 1998 were subsequently diagnosed with an inherited metabolic disorder.[98] Because Reye's syndrome is now very rare, it has been suggested that any infant or children suspected of having this disorder should undergo investigation to exclude the presence of inborn metabolic disorders that can mimic Reye's syndrome.[96]

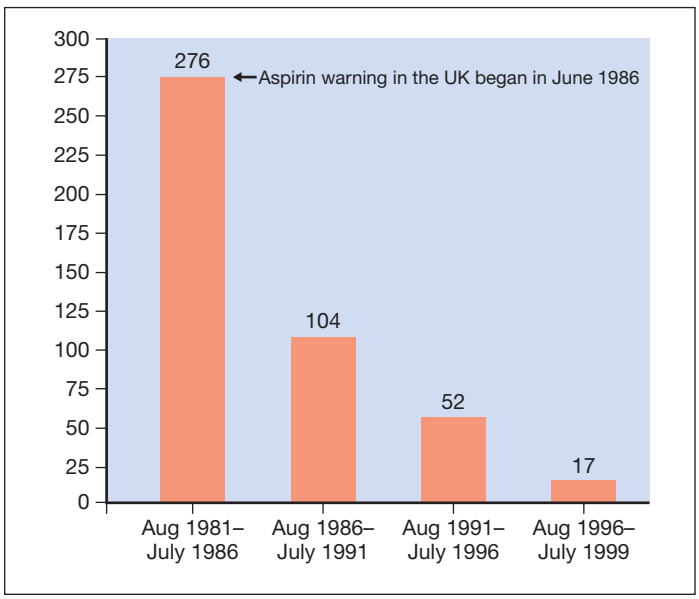

Figure 56-7. Number of cases of Reye's syndrome reported to the British Paediatric Surveillance Unit. (Adapted from Hall SM, Lynn R. Reye's syndrome. N Engl J Med 1999; 341:845, with permission.)

HISTOPATHOLOGY AND PATHOGENESIS

Liver specimens in patients with Reye's syndrome exhibit several characteristic histologic abnormalities (Figure 56-8). Microvesicular steatosis and decreased or absent glycogen stores are common and appear to correlate with severity of illness and survival.[105] There is minimal hepatocellular necrosis associated with these lesions. Hepatic glycogen content in biopsies taken within 24–48 hours of the onset of encephalopathy was significantly lower in patients who died. These lesions also appear to evolve over time so that in serial biopsy specimens glycogen stains and microvesicular steatosis may initially worsen and then improve within 1–2 weeks of the onset of encephalopathy. In survivors, liver biopsies performed 1–13 months after clinical improvement showed essentially normal histology, indicating that the hepatic lesions of Reye's syndrome are completely reversible.

Electron microscopic studies of the liver in Reye's syndrome have also demonstrated characteristic findings that are consistent with the presumed pathogenesis of the disease. Ultrastructural study has shown that mitochondria within the hepatocytes of children with

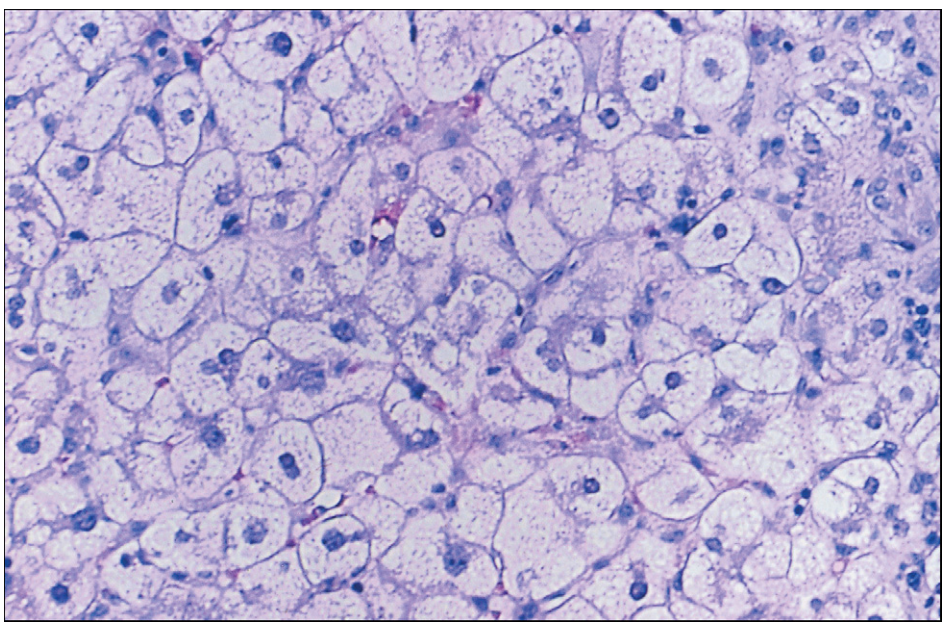

Figure 56-8. Liver in Reye's syndrome. In Reye's syndrome the hepatic architecture is preserved and the portal tracts are unremarkable. The hepatocyte cytoplasm is finely vacuolated due to accumulated lipid. Note that the nuclei remain in the center of the cell, a feature of microvesicular steatosis. (Hematoxylin and eosin.)

Reye's syndrome are swollen and irregularly shaped with expansion of the matrix space.[106] These changes also regress in parallel with clinical improvement. An excellent review of metabolic abnormalities seen in Reye's syndrome and other inherited disorders was published in 1994.[107] Hyperammonemia may result from a decrease in the activity of enzymes involved in the urea cycle, carbamyl phosphate synthetase and ornithine transcarbamylase (OTC), due to damage to hepatic mitochondria. Both of these enzymes are normally found predominantly within the mitochondria; however, in patients with Reye's syndrome, OTC activity is shifted to the cytosol, presumably due to damage to the mitochondrial membrane.[108] The decreased levels of enzyme activity are transient and correlate with the clinical status of the patient.[109] Increase in nitrogen load due to muscle breakdown has also been reported in patients with Reye's syndrome and contributes to the profound hyperammonemia present in this disorder.[107]

The metabolism of fatty acids is also impaired in patients with Reye's syndrome. Numerous intermediate metabolites are abnormally elevated in the liver, plasma, or urine of these patients and high levels of these compounds are believed to inhibit further mitochondrial enzymes involved in ureagenesis, gluconeogenesis, and fatty acid oxidation.[107] Salicylates may inhibit mitochondrial enzymes involved in fatty acid oxidation, which may explain the association between these drugs and the development of Reye's syndrome.[107] Furthermore, in mice, infection with influenza virus potentiated the inhibitory effects of salicylates on mitochondrial fatty acid oxidation.[110] Some of the deleterious effects of salicylates on mitochondrial structure and function may be cytokine-mediated; pretreatment with α-interferon ameliorated salicylate-induced damage to isolated rat liver mitochondria.[111]

CLINICAL FEATURES, DIFFERENTIAL DIAGNOSIS, AND TREATMENT

Reye's syndrome is predominantly seen in young children and adolescents but has been reported to occur infrequently in adults.[112–114] Belay et al. found that 8% of the cases in the USA involved patients who were 15 years of age or older.[96] Other illnesses, such as Jamaican vomiting sickness and drug toxicity from valproic acid or fialuridine, may present with similar changes of microvesicular steatosis. Several inborn metabolic disorders often present with signs and symptoms that are indistinguishable from Reye's syndrome.[115–117] The most common metabolic disorder mimicking Reye's syndrome is medium-chain acyl-coenzyme A dehydrogenase deficiency.[117] The majority of these inherited disorders are specific enzymatic defects that usually become evident before the age of 3 years. These disorders are characterized by recurrent episodes, the presence of similar disorder in the siblings, frequent hypoglycemia, cardiac enlargement, and muscle weakness. The most consistent distinguishing features of Reye's syndrome on electron microscopy are ultrastructural changes in liver tissue, specifically the proliferation of smooth endoplasmic reticulum and peroxisomes, and the presence of enlarged and pleomorphic mitochondria with loss of dense granules.[116–118] In enzymatic defects with Reye's manifestations, in contrast, the mitochondria are normal in size and appearance.

The illness begins with a viral prodrome that may begin to resolve. Within several days, patients present with intractable vomiting and mental status changes, ranging from irritability to mild encephalopathy with confusion and disorientation that may progress to deep coma. Serum aminotransferase levels are elevated as much as 50 times the upper limits of normal. Prothrombin time is usually prolonged and serum ammonia is elevated. Serum bilirubin levels are almost invariably normal or just slightly elevated so that jaundice is conspicuously absent in Reye's syndrome.[112]

Treatment of Reye's syndrome is generally supportive, with careful attention to hypoglycemia and electrolyte disturbances. High-concentration glucose solutions are required to maintain adequate serum glucose levels. With neurologic deterioration, consideration should be given to intracranial pressure monitoring in order to guide the effects of various interventions, such as hyperventilation and mannitol infusions, that may be used to decrease intracranial pressure. In the report from the CDC that described the outcomes of 1207 cases of Reye's syndrome reported to NRSSS, the overall case fatality rate was 31.3%.[96] The level of consciousness at the time of admission was a strong predictor of death; the mortality rate increased from 17.8% in stage 0 (alert and wakeful) to 89.6% in stage 5 patients (unarousable, areflexia, and fixed pupils) (Table 56-6). Additionally, age 5 years and serum ammonia concentration 45 μg/dl were independent predictors of mortality. Residual neurological deficits were reported in 9.8% of patients; the deficits were mild in 6.9% and severe in 2.8%.[96] Patients with serum ammonia > 45 μg/dl had significantly higher risk of neurological complications (relative risk, 4.1; 95% confidence interval, 1.2–14.0).[96]

STAUFFER'S SYNDROME

Stauffer's syndrome is a paraneoplastic syndrome of liver test abnormalities in patients with renal cell carcinoma, first described in 1961 by Stauffer.[119] In the early literature, its incidence in patients with renal cell cancer ranged from 4 to 40%.[120–122] Its true incidence is difficult to ascertain from these early reports due to their inability adequately to exclude hepatic metastases as a cause for liver test abnormalities. In a recent study that reviewed the records of 365 patients with renal cell carcinoma, 21% had paraneoplastic elevation of alkaline phosphatase. Hepatic and bone metastases were excluded by computed tomography scans and bone scans.[123]

Recent evidence suggests that interleukin-6 (IL-6) is responsible for causing various paraneoplastic syndromes seen in renal cell

Table 56-6. Outcome of Reye's Syndrome According to the Level of Consciousness

Stage	Total	Outcome			
		Complete recovery	CNS sequelae		Death
			Mild	Severe	
0–1	505	391 (77%)	16 (3%)	4 (0.8%)	94 (19%)
2–3	473	289 (61%)	32 (6.7%)	10 (2.1%)	142 (30%)
4–5	128	15 (12%)	5 (4%)	8 (6.2%)	100 (78%)

CNS, central nervous system.
Adapted from Belay ED, Bresee JS, Holman RC, et al. Reye's syndrome in the United States from 1981 through 1997. N Engl J Med 1999; 340:1377, with permission.

carcinoma. The following evidence supports IL-6 as the cytokine involved:

1. when given systemically, IL-6 induces findings similar to paraneoplastic syndromes associated with renal cell carcinoma (fever, elevated alkaline phosphatase);[124,125]
2. IL-6 is expressed by most of the renal cancer cell lines and a strong correlation exists between serum IL-6 and paraneoplastic elevation of alkaline phosphatase;[126,127]
3. administration of anti-IL-6 monoclonal antibodies normalized the alkaline phosphatase levels in patients with Stauffer's syndrome.[128]

Strickland and Schenker reviewed 29 published cases of nephrogenic hepatic dysfunction in whom sufficient data were available to apply strict criteria for the diagnosis.[129] Fever and weight loss were the most common symptoms. Hepatomegaly was present in two-thirds of patients. Elevation of alkaline phosphatase was the most common biochemical abnormality, occurring in 90% of reported cases, while abnormalities of serum aminotransferases and serum bilirubin were much less common. Histologic examination of the liver in patients with nephrogenic hepatic dysfunction has shown only non-specific changes. Steatosis, mild focal hepatocyte necrosis, portal lymphocytic infiltration, and Kupffer cell hyperplasia have all been reported.[120,129,130]

The importance of recognizing this syndrome lies in the decision concerning resection of the tumor and differentiating these benign liver enzyme abnormalities from metastatic disease. Abnormalities of hepatic function usually resolve within 1–2 months after the primary tumor has been resected and, indeed, this is an important feature in the diagnosis of this syndrome.[119–122,129,130] With recurrence of renal cell carcinoma, clinical and biochemical characteristics of nephrogenic hepatic dysfunction may again become evident.[130]

AMYLOIDOSIS

Hepatic involvement is common in patients with systemic amyloidosis. It is disorder of abnormal protein deposition in various organs. On histological examination, all amyloid proteins show extracellular, amorphous, eosinophilic hyaline-like material. This material stains with Congo red dye and shows apple-green birefringence when examined under polarized light. The precursor proteins, although vastly different chemically, share the conformational property of forming beta-pleated sheets as they precipitate. It is the beta-pleated sheet arrangement that leads to the characteristic histochemical findings.

PRIMARY AND SECONDARY AMYLOIDOSIS

Amyloid is currently classified by placing an A in front of the abbreviation for the precursor protein (Table 56-7). There are at least 16 different variants. Many of these occur only focally in aged or tumorous organs and do not directly involve the liver.

Primary or AL amyloidosis is related to the deposition of immunoglobulin light- or heavy-chain protein.[131,132] This is probably the most common form of systemic amyloidosis in this country. Immunoglobulin is a normal component of the humoral immune system and can normally be found in the serum in a 2:1 ratio, kappa to lambda. In lymphoplasmocytic disorders such as multiple myeloma or Waldenströms's macroglobulinemia, there is an overproduction of portions of the immunoglobulin molecule, generally the light chain. The light-chain protein itself or its breakdown products then precipitate out of the serum to form amyloid. Most patients with amyloidosis have precipitated lambda light chains, suggesting that this form is more likely to produce beta-pleated sheet arrangement.

AA or secondary amyloid is associated with chronic infections such as osteomyelitis or tuberculosis. Cytokines associated with the inflammation, such as IL-1, IL-6, and tumor necrosis factor, stimulate the liver to produce serum amyloid A.[133,134] This protein is an injury-specific component of high-density lipoprotein. The normal human AA protein exists as three isoforms and coded by three genes on the short arm of chromosome 11 (11p). This protein is continuously produced during chronic infections.[135] People vary greatly in their ability to clear this protein. While most individuals cleave

Table 56-7. Different Types of Amyloidosis

Variant	Precursor protein	Sites involved	Disease	Mutation
AL	Immunoglobulin light chain	Systemic	Myeloma	
ATTR	Transthyretin	Systemic	Hereditary	Chromosome 18; Val30Met most common
AA	(Apo)serum AA	Systemic	Chronic infection	AA gene on 11p; FMF 16p
$A\beta_2M$	β_2-microglobulin	Systemic	Chronic hemodialysis	
AApoAI	Apoprotein AI	Nerves, kidney, liver	Hereditary	Chromosome 11; Gly26Arg most common
ALys	Lysozyme variants	Kidney	Hereditary	
AGel	Gelsolin	Cornea, nerves, skin	Hereditary	
AFib	Fibrinogen a-chain	Kidney	Hereditary	
ACys	Cystatin C	Cerebral blood vessels	Hereditary	
Aβ	Aβ-protein precursor	Brain	Alzheimer's disease	Chromosome 21
APrPsc	Prion protein	Nervous system	Spongiform encephalopathy	PRNP gene Chromosome 20
ACal	(Pro)calcitonin	Thyroid	Medullary carcinoma	
AIAPP	Islet amyloid protein	Islet of Langerhans		
AANF	Atrial natriuretic factor	Heart		
APro	Prolactin	Aging pituitary	Prolactinoma	

amyloid A into small peptides, some patients can only cleave it into larger sizes consistent with the amyloid subunit.

Familial Mediterranean fever (FMF) is an autosomal recessive disorder associated with recurrent episodes of fever, arthritis, serositis, and skin rash. It is predominantly seen in non-Ashkenazi Jewish, and Turkish people. These patients develop renal disease and ultimately renal failure, which can be prevented with colchicine administration. Recently a genetic defect has been located on the short arm of chromosome 16 in patients with FMF.[136,137] The defect occurs in a gene coding for a protein known as pyrin/marenostrin. It is unclear how this gene product interacts with the serum A protein to produce amyloidosis.

Mutations in the transthyretin gene are associated with familial amyloidotic polyneuropathy (FAP).[138] This is the most common type of heritable amyloidosis. The transthyretin gene product is a normal serum protein largely produced by the liver and it carries serum thyroxin and retinal-binding protein. The protein is a tetramer of identical subunits that is encoded by a single gene on chromosome 18. At least 78 different amino acid substitutions occurring at 51 different sites in the transthyretin gene have been reported.[138] Most of these mutations are amyloidogenic. Although inherited as an autosomal dominant disorder, symptoms generally do not arise until the third to fourth decade of life. The disorder has been seen in Portugal, Sweden, Japan, and the USA. The US kindreds usually exhibit the defects associated with their country of origin. The clinical onset can be quite variable among these ethnic groups, even in those patients with the same mutation. The patients usually present with a lower-limb nephropathy, which progresses to the upper limbs. Autonomic nervous system involvement is also usually extensive, often resulting in diarrhea. Changes in the joints, skin, and cornea are also present. Rarely, other organs can be involved.

Patients undergoing chronic hemodialysis develop amyloid secondary to precipitation of the β_2-microglobulin protein.[139] β_2-Microglobulin is a normal serum protein. The hemodialysis itself is thought to produce localized excess concentrations of this precursor, resulting in the deposition of amyloid. Generally, the musculoskeletal system and the kidneys are involved.

Although amyloid is relatively homogeneous in its appearance, it is clear that its etiology can be quite variable. The mechanism of amyloid formation is likewise complex and probably various mechanisms are at work, depending on the type of amyloid. For instance, in the FAP disorders it is thought that the inheritable mutation causes beta-plated sheet-type fibrils to form upon normal proteolysis. This contrasts with secondary amyloidosis where not only overexpression of the AA protein but perhaps abnormal proteolysis results in the deposition of fibrils.

CLINICAL FEATURES, DIAGNOSIS, AND TREATMENT

Amyloidosis can present as renal dysfunction/renal failure, heart failure/cardiomyopathy, peripheral neuropathy, skin rash, and blood dyscrasias.[140] The most common finding related to the liver is hepatomegaly.[141] Several other forms of presentation of hepatic amyloidosis are summarized in Table 56-8. Jaundice and cholestasis can be one of the initial manifestations of hepatic amyloidosis.[142–148]

Table 56-8. Manifestations of Hepatic Amyloidosis

Hepatosplenomegaly
Splenomegaly
Ascites
Prolongation of prothrombin time
Due to acquired factor X deficiency
Cholestasis
Jaundice
Acute liver failure
Spontaneous rupture

When present, it is an ominous finding and suggests a short survival time. Amyloid can also present catastrophically as liver failure or hepatic rupture.[149] Ascites due to sinusoidal occlusion can also be a presenting symptom.[150] Generally the transaminases are minimally elevated, although they can be quite high in the rare cases of fulminant failure. Jaundice is also infrequent except for the rare cholestatic cases. Imaging studies may show an infiltrative process but are generally not helpful in gauging the extent of disease.

Demonstration of amyloid deposition is generally required to make the diagnosis. Fat pad aspirations are the easiest and most common approach to diagnose amyloidosis. If that is negative, rectal or skin biopsies are obtained, and finally biopsies of affected organs as needed. Amyloid deposition in the liver occurs in three basic patterns. The most common pattern is protein deposition in the spaces of Disse (Figure 56-9). As the material accumulates, it encroaches on the hepatocytes, causing extensive atrophy. Amyloid increases the mass of the liver, producing hepatomegaly, but only rarely compromises sinusoidal blood flow, leading to portal hypertension. Another pattern is deposition of amyloid only in the walls of hepatic arterioles and the third pattern is globular clusters of amyloid, again in the space of Disse. The latter pattern appears to be most uncommon. The Congo red stain is the mainstay of diagnosis.[138,151] While commonly used as a diagnostic test, the Congo red stain can be difficult to perform correctly. The characteristic staining is highly dependent on the pH, salt concentration, and thickness of the material stained. Any variation in the above parameters can greatly affect the quality of staining. The Congo red staining is relatively specific for amyloid when properly performed; however, under some conditions, one can also see staining of fibrin, elastin, and collagen. However, these are usually not birefringent under polarized light. The staining properties with Congo red are related to the beta-pleated sheet arrangement of the proteins. Generally, all types of amyloid stain with the Congo red dye. However, in some patients with AL amyloid, it may be very difficult to obtain a satisfactory staining reaction. In these cases, it may be useful to attempt other stains, such as Thioflavin T and S, crystal violet, and methyl violet. Electron microscopy has been a gold standard for detection of amyloidosis. Ultrastructural examination shows non-branching fibrillar structures of indefinite length with a width of approximately 9.5 nm.

Therapy is generally directed at treating the underlying condition.[152,153] In the case of primary amyloid, therapy directed against the underlying lymphoplasmocytic neoplasm can sometimes improve the survival.[154,155] Liver transplantation has been performed

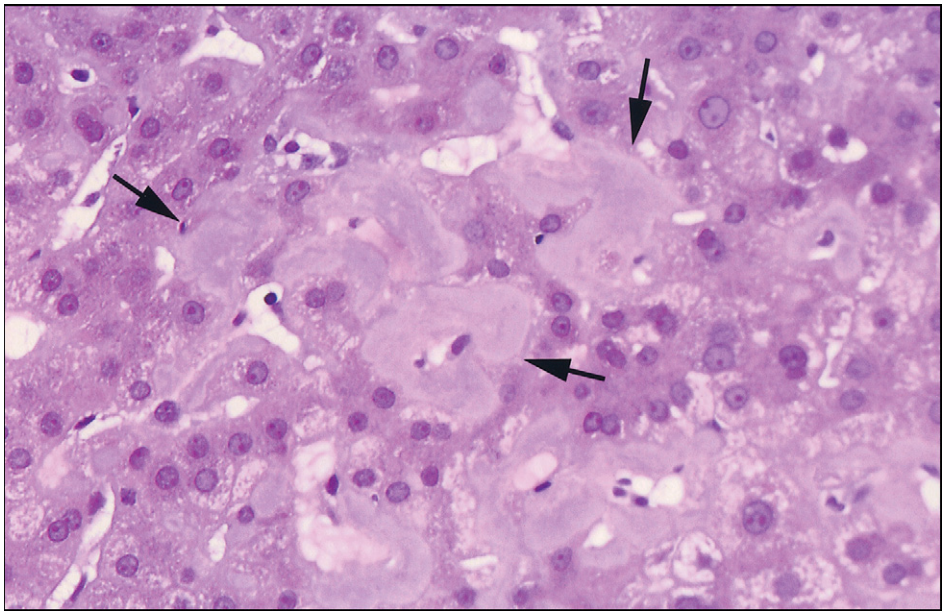

Figure 56-9. Liver in amyloidosis. Amyloid is usually deposited in the space of Disse (arrows). As the deposits increase, the hepatocytes become sunken ribbons. (Hematoxylin and eosin.)

in this disorder and short-term survivors have been noted.[156] Stem cell transplantation therapy has also been employed, with mixed results.[157,158] However, generally the disease progresses and fatal complications from cardiac or renal failure eventually ensue. In the cases of amyloidosis due to chronic infections, eradication of underlying infection should be attempted. Colchicine is the treatment of choice in patients with FMF. Orthotopic liver transplantation has been very successful in patients with FAP.[159–166] Most centers recommend transplantation in patients with FAP as soon as symptoms occur, as liver transplantation has been shown to diminish the disease progression. In general, there is little improvement in the autonomic dysfunction that is already established.[165,166] Patients with advanced disease, including both upper and lower motor neuron symptoms, generally do poorly.[165,166]

LIVER IN HEMATOLOGIC DISEASES

SICKLE-CELL ANEMIA

Patients with sickle-cell anemia may have a variety of hepatic abnormalities involving both the hepatic parenchyma and the biliary tract. These abnormalities may be present during the asymptomatic phase of sickle-cell disease as well as during the episodes of sickle crisis. The incidence of hepatic involvement is very difficult to estimate due to the confounding effects of chronic hemolysis that may elevate serum bilirubin and aminotransferase activity. Of 100 consecutive patients seen as outpatients or inpatients at a university hospital, 24% had one or more chronic abnormalities of liver tests.[167] The vast majority of the abnormalities were due to concurrent illnesses ranging from chronic viral hepatitis to congestive heart failure.[155] Similarly, in another series, serum alkaline phosphatase was abnormal in 64% of patients with sickle-cell disease, although it appears that the alkaline phosphatase was mostly of bone origin.[168] Thus, the true incidence of hepatic involvement is greatly dependent upon the criteria used to define liver disease in this population.

HEPATIC CRISIS

Hepatic crisis in sickle-cell disease is characterized by right upper quadrant abdominal pain, jaundice, hepatomegaly, and fever. This constellation of findings is also suggestive of acute cholecystitis or cholangitis and differentiating these entities may be difficult. It has been estimated that 7–10% of hospitalizations for sickle-cell anemia were complicated by hepatic crises.[169,170] The most marked serum biochemical abnormality during hepatic crisis is elevation in serum bilirubin. Total bilirubin is usually less than 15 mg/dl, although extreme levels of hyperbilirubinemia, greater than 50 mg/dl, may occur. This marked hyperbilirubinemia may not necessarily be associated with a worse prognosis.[171–173] A large component of this bilirubin is the direct fraction, which may be as much as 50% of the total bilirubin in many cases. Serum aminotransferases are abnormal, with levels usually less than 10 times the upper limits of normal. Elevation of serum LDH activity, disproportionate to the increase of serum aminotransferases, is also common and reflects the ongoing hemolysis associated with sickle crisis.[168] Evidence of extrahepatic sickle crisis, such as joint and flank pain, is usually, but not invariably, present. With general supportive care, clinical improvement is seen within several days, although hyperbilirubinemia may persist for several weeks. Deaths related to fulminant hepatic failure in the absence of other identifiable etiologies have been reported.[168] Recent data suggest that acute hepatopathy due to sickle-cell anemia should be considered a contraindication to percutaneous liver biopsy.[174] Out of 14 patients with sickle-cell disease who had percutaneous liver biopsy, 5 (36%) had serious hemorrhage and 4 of them died due to bleeding complications. All of those who had bleeding complications had acute sickling crisis at the time of their liver biopsy.

BILIARY TRACT DISEASE

Pigment gallstones are frequently found in patients with sickle-cell anemia: estimates of the prevalence range between 40 and 80%.[168,175–177] The incidence varies directly with the age of the

patient.[168] Choledocholithiasis was found in 18% of 65 patients undergoing cholecystectomy.[168]

Hepatic crisis will resolve quickly with supportive care while cholecystitis and cholangitis will ultimately require endoscopic and/or surgical intervention. Therefore, establishing the correct diagnosis is especially important. There is a suggestion that the operative complications of cholecystectomy in patients with sickle-cell anemia are greater than in the general population.[165] Schubert reviewed published reports on 97 patients who underwent cholecystectomy and found 15% of patients had complications that were deemed serious, including pneumonia, seizures, and sickle crisis.[168,178] Thus, cholecystectomy should be reserved for those patients with documented gallstones whose symptoms are clearly of biliary tract origin or for those in whom hepatic crisis and biliary tract disease cannot be adequately differentiated.[168,178] Careful preoperative management with special attention to transfusion requirements and volume status is important.

VIRAL HEPATITIS

As expected from the large numbers of transfusions required by many patients with sickle-cell anemia, viral hepatitis has been reported to occur, although from published reports, the incidence is difficult to determine. In patients with liver test abnormalities, the incidence of hepatitis B virus (HBV) or histologic changes of chronic hepatitis have ranged from 5 to 47%.[167,175,179,180] The reported prevalence of hepatitis C in patients with sickle-cell anemia is 10–35%.[181–183] Not surprisingly, the risk of hepatitis C was directly related to the number of transfusions received. The impact of hepatitis C infection on the natural history of patients with sickle-cell anemia is currently unknown.

HEPATIC HISTOLOGY

Several studies have evaluated the histopathologic changes in the livers of patients with sickle-cell disease.[171,180,184,185] These studies included biopsies from patients during hepatic crisis as well as biopsies during quiescent periods. Hepatic sinusoidal distention, erythrocyte sickling, and erythrophagocytosis was found in almost all patients (Figure 56-10).[180] In a study of pregnant women given prophylactic red cell transfusions, erythrocyte sickling and erythrophagocytosis were present in all patients in the absence of hepatic crisis.[184] Thus, these changes appear to be characteristic of sickle-cell anemia and do not correlate with aminotransferase levels or activity of liver disease.

The presence of other histologic lesions may also be detected in the livers of patients with sickle-cell anemia and further confuse the clinical picture. Massive iron deposition is frequently identified by routine iron stains in the majority of patients.[179,180,184] Also, of 19 patients with sickle-cell anemia on whom biopsies were performed because of abnormal liver tests, 9 (47%) had changes consistent with acute or chronic viral hepatitis.[180] Cirrhosis has been reported to occur in 15–20% of patients with sickle-cell anemia and may be due to hypoxic injury from sickling and intrasinusoidal sludging of erythrocytes, chronic viral hepatitis, or massive hemosiderosis.[168,180,186]

HODGKIN'S LYMPHOMA

Hepatic involvement in Hodgkin's lymphoma has been reported to occur in 5% of patients at the time of diagnosis, 30% during the course of the disease, and up to 50% at the time of autopsy.[187]

The histology of liver involvement in malignant lymphomas has been reviewed.[174] The extent of tissue sampling correlates with the ability to stage hepatic involvement in Hodgkin's disease accurately; percutaneous liver biopsy has the lowest yield while laparoscopy and laparotomy have similar yields. A diagnosis of hepatic involvement in Hodgkin's disease requires the finding of the Reed–Sternberg cell (Figure 56-11). Non-specific inflammatory infiltrates are seen in 50% of liver biopsies in patients with Hodgkin's disease and, alone, do not constitute grounds for diagnosing hepatic involvement. Non-caseating epithelioid granulomas may be seen in 25% of patients with Hodgkin's disease.[188,189] Granulomas may be seen in the portal tract and the hepatic lobules and do not necessarily indicate hepatic involvement by Hodgkin's disease.

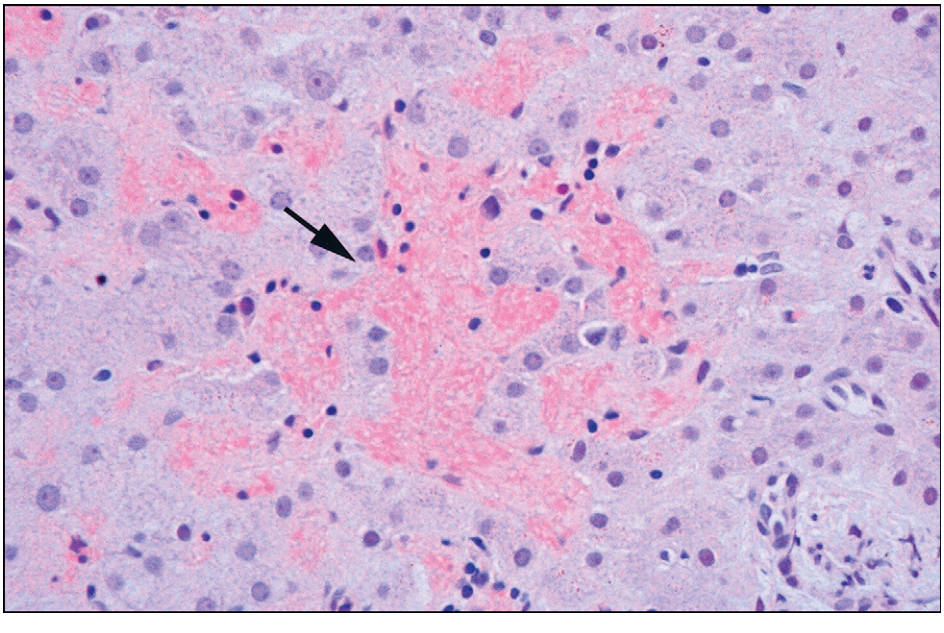

Figure 56-10. Liver in sickle-cell anemia. Numerous sickled red blood cells distend the sinuses of the liver (arrow). (Hematoxylin and eosin.)

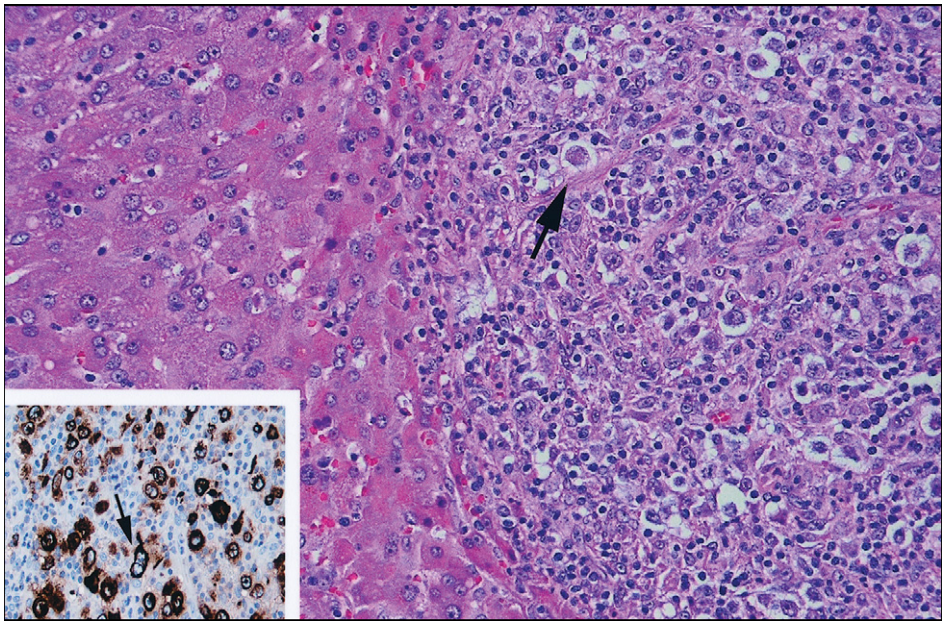

Figure 56-11. Liver in Hodgkin's lymphoma. Classic Reed–Sternberg cell (arrow) is seen in a polymorphous background of lymphocytes, plasma cell, and eosinophils which greatly expands a portal tract. (Hematoxylin and eosin.) The inset shows the Reed–Sternberg cells marked with anti-CD-30. (Modified immunoperoxidase method.)

Elevation of serum alkaline phosphatase levels is the most frequently abnormal liver test found in patients with Hodgkin's disease. In a review of 111 inpatients with Hodgkin's disease, 41% had abnormal serum alkaline phosphatase levels.[190] Patients with more advanced stages of Hodgkin's disease were more likely to have elevations of this enzyme; 14% of patients with stage I or II disease and 65% and 81% of patients with stage III or stage IV disease, respectively, had abnormal serum alkaline phosphatase levels. The elevations were generally mild – 1.5–2 times the upper limits of normal – although more marked increases were noted in patients with stage IV disease. The liver was felt to be the source of the alkaline phosphatase in the majority of patients, although several patients, adolescents with potential for bone growth, had elevation in the bone fraction.[190] Abnormalities in alkaline phosphatase were seen in several patients in the absence of hepatic involvement, more commonly in patients with fever as a systemic manifestation of Hodgkin's disease. Thus, in some patients abnormal serum alkaline phosphatase could represent the equivalent of an acute-phase response.

Jaundice occurs infrequently in Hodgkin's lymphoma, except in the late stages of the illness. The most frequent cause of jaundice is intrahepatic infiltration by the tumor, which was seen in 45% of jaundiced patients at the time of autopsy.[187,191,192] Extrahepatic biliary tract obstruction occurs much less frequently and accounts for only 5–10% of jaundiced patients.[191–193] A small number of patients with Hodgkin's lymphoma have been described who have evidence of severe intrahepatic cholestasis with dramatic elevations in serum bilirubin and alkaline phosphatase levels in the absence of tumor infiltration or bile duct obstruction.[173,179] The etiology of this syndrome is not known but one report suggested that it could be related to vanishing bile duct syndrome.[194,195] An association between primary sclerosing cholangitis and Hodgkin's lymphoma has also been suggested.[196] Acute liver failure with encephalopathy, jaundice, and coagulopathy has also been reported in patients with Hodgkin's and non-Hodgkin's lymphoma either due to direct hepatic involvement,[197,198] or as a paraneoplastic syndrome.[199]

NON-HODGKIN'S LYMPHOMA

Hepatic involvement in non-Hodgkin's lymphomas occurs very frequently, with estimates ranging between 24 and 43%.[200,201] The hepatic infiltrate usually involves the portal triads and has a nodular appearance (Figure 56-12). Epithelioid granulomas may also be seen in the liver of these patients. Immunophenotyping using monoclonal antibodies may be performed on snap-frozen liver biopsy tissues in order to characterize the infiltrates.[202] Rarely, primary hepatic lymphoma in the absence of systemic lymphoma has been reported.[203,204]

The clinical manifestations of hepatic infiltration with non-Hodgkin's lymphoma are similar to that seen with Hodgkin's disease. Patients may remain asymptomatic despite extensive hepatic infiltration. Mild to moderate elevations in serum alkaline phosphatase and moderate to marked elevations of LDH activities may be present. In contrast to Hodgkin's disease, non-Hodgkin's lymphomas are more likely to produce jaundice as a result of extrahepatic obstruction, usually at the porta hepatis, rather than by direct hepatic infiltration.[187] Reactivation of chronic hepatitis B in patients receiving cytotoxic therapy is well documented.[205,206] Recent data suggest that lamivudine can prevent such reactivation of hepatitis B in patients receiving chemotherapy.[207] While some reports have suggested that HCV may have a role in the development of non-Hodgkin's lymphoma,[208,209] other reports have failed to confirm such an association.[210,211]

Patients with lymphoma with severe liver dysfunction (due to either lymphoma involvement or coexisting liver problem) pose a significant therapeutic problem due to their inability to tolerate conventional chemotherapeutic agents. Ghobrial and colleagues summarized their experience with 41 such patients seen at the Mayo Clinic over a 5-year period. The authors found that mechlorethamine, high-dose corticosteroids, and rituximab are safe and effective in this patient population.[212]

MULTIPLE MYELOMA

Liver may be directly involved by plasma cell infiltrate in up to 30% patients with multiple myeloma. The patients generally present with

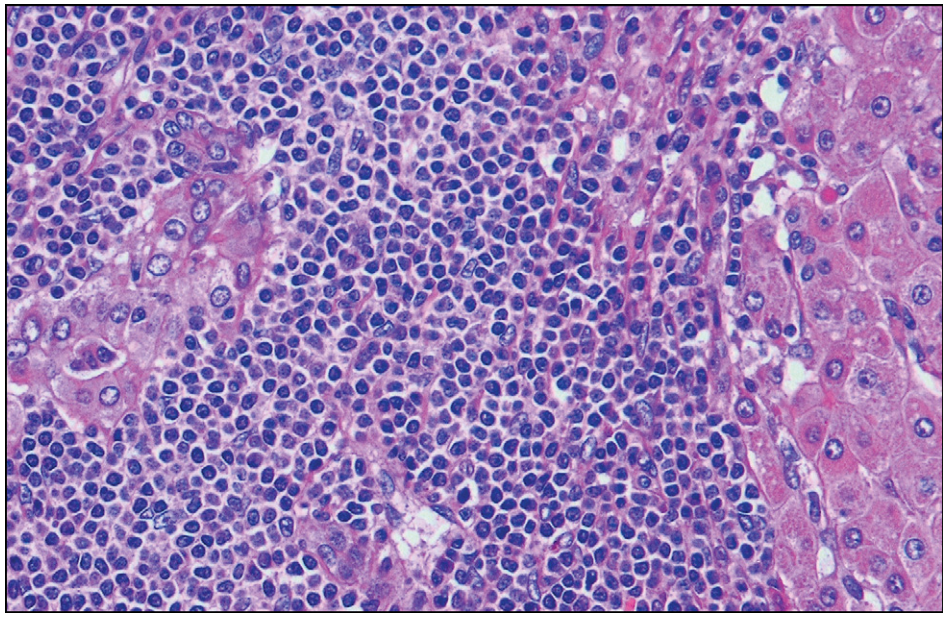

Figure 56-12. Hepatic B-cell lymphoma. Sheets of small lymphocytes surround a regenerative liver nodule. The portal tract also appears to be involved. The B-cell nature of the infiltrate can be confirmed by immunohistochemistry or flow cytometry. (Hematoxylin and eosin.)

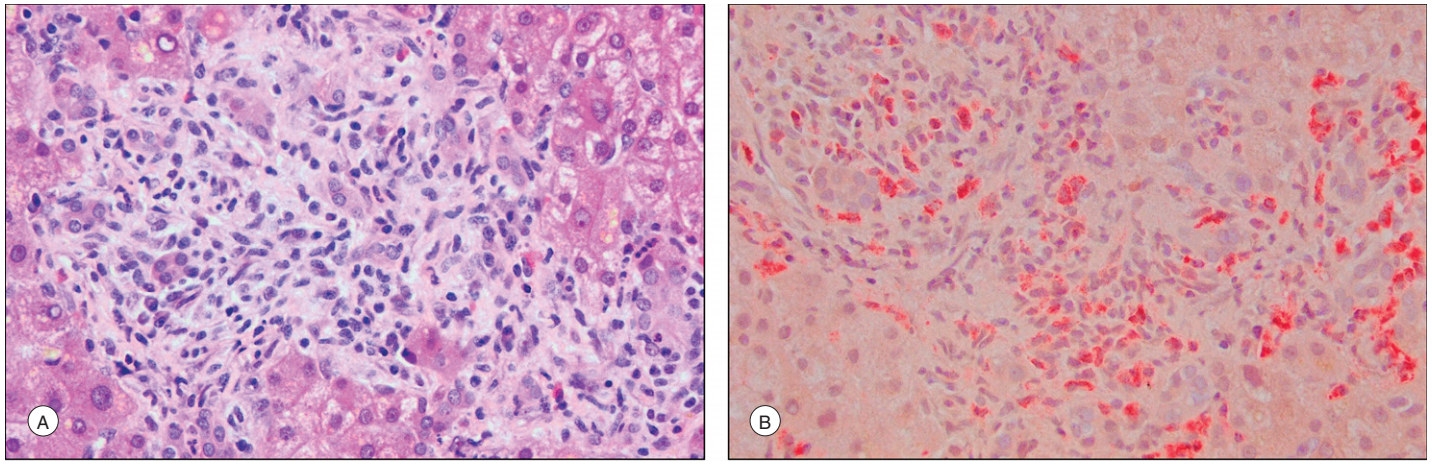

Figure 56-13. (**A**) Hepatic mastocytosis. (Hematoxylin and eosin.) It may involve the portal tracts, lobule, or both. The lesion is a stellate region of fibrosis occupied by lymphocytes, eosinophils, and cells with larger pale nuclei – the mast cell. (**B**) Hepatic mastocytosis (Leder). In this section of the liver the numerous mast cells (red) of systemic mastocytosis stand out against the background counterstain (chloroacetate esterase (Leder) stain).

hepatomegaly or ascites.[213] It is important to distinguish myeloma liver involvement with myeloma from autoimmune hepatitis. In myeloma, the plasma cell infiltrate predominantly involves the sinusoids, with relative sparing of the portal tracts. This is distinct from autoimmune hepatitis, where the infiltrate is predominantly in the portal area. Another pattern of liver injury in myeloma patients is nodular regenerative hyperplasia.[214]

Waldenström's macroglobulinemia is a neoplastic disorder of B-lymphocytes and plasma cells that has been alluded to previously.[215] The neoplastic cells secrete immunoglobulin heavy chain, which has rarely been associated with the development of amyloidosis. The lymphoplasmacytic tumor can directly involve the liver. Clinical liver disease in these patients is often mild, with minimal elevation of transaminases and alkaline phosphatase. Their symptoms are usually referred to the extrahepatic problems associated with the disease. Histologically, the infiltrate shows expanded portal tracts with lymphocytes and plasma cells, and larger atypical cells with occasional mitotic figures.

MASTOCYTOSIS

Mastocytosis is commonly seen in children as a skin rash, urticaria pigmentosa. However, the disease can become systemic and involve the liver, especially in adult patients.[216] When seen in adults, it often presents with fever, hepatosplenomegaly, steatorrhea or diarrhea, and weight loss. The liver chemistries are usually minimally abnormal; radiologic studies are often not contributory. A liver biopsy demonstrates the characteristic lesions that are similar to those seen in other organs, including spleen and lymph nodes. This lesion is characterized by irregular areas of fibrosis containing numerous eosinophils and a background of lymphocytes and other mononuclear cells (Figure 56-13).[217] These mononuclear cells are mast cells that may be recognized by a number of methods. Because the

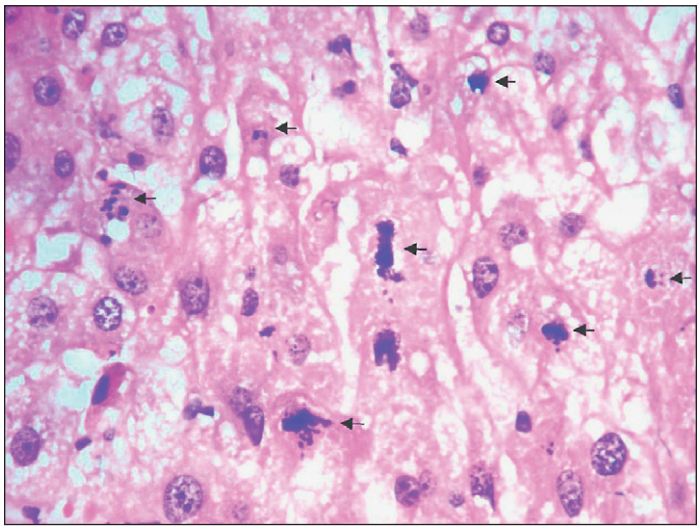

Figure 56-14. Lobular portion of liver from a patient with severe acute respiratory syndrome (SARS) showing marked regenerative activity characterized by numerous mitotic figures (arrows). (Reprinted from Chau TN, Lee KC, Yao H, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. Hepatology 2004; 39;302, with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons.)

cells are often degranulated, toluidine blue staining may not be helpful. Chloroacetate esterase staining, however, is usually diagnostic; the cells also exhibit *c-kit* (CD-117). These fibrotic clusters may be located either in the portal tracts or in the parenchyma. When the lesions abut the central veins, they may be responsible for the rare cases of portal hypertension associated with the disease.[218,219]

LIVER MANIFESTATIONS IN SARS

Severe acute respiratory syndrome (SARS) is a serious infectious disease that spreads via airborne droplets and can result in severe acute pulmonary inflammation and epithelial damage. Studies have confirmed that a novel corona virus called SARS corona virus (SCoV) is the etiologic agent. Liver test abnormalities are seen in up to 50–60% of patients who were hospitalized with SARS, and the most common liver test abnormality is mild elevation in serum transaminases.[220–223] Transaminase levels peak during the second week of illness and their levels improve with successful recovery.[223] This phenomenon of mildly elevated transaminases is likely a nonspecific response to severe systemic illness with hypoxemia and possibly related to multiple medications. Occasionally, transaminase levels may be significantly elevated with peak ALT values ranging between 500 and 1000 IU/l.[224] Chau and colleagues described the liver histology in 3 patients with SARS who had markedly elevated transaminases with no evidence of organ failure.[224] All three biopsies had hepatocyte apoptosis and in 2 patients there were marked accumulation of cells in mitosis (Figure 56-14). Liver biopsies also exhibited balloon degeneration of the hepatocytes and mild to moderate lymphocytic infiltration. Reverse transcriptase polymerase chain reaction was positive for SCoV in liver tissue from all 3 patients, suggesting that this pattern of liver injury may indeed represent a form of SARS-associated viral hepatitis.[225]

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