Atlas of Liver Pathology, Chapter 8: Biliary Tree Disease

Introduction

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- Intrahepatic ("Pure") Cholestasis
- Classic Large Duct Obstruction
- Diseases Affecting the Intrahepatic Biliary Tree
  - Primary Biliary Cirrhosis
  - Primary Sclerosing Cholangitis
  - Miscellaneous Biliary Tree Diseases
- Miscellaneous Diseases with Significant Involvement of the Biliary Tree

Introduction

There has been a shift in recent years with regards to the histopathology of biliary tree diseases. Formerly the greatest interest was in separating obstructive processes in the extrahepatic biliary tree from parenchymal liver disease. Refinement of imaging techniques has largely obviated this frequently challenging task. These techniques have greatly increased our knowledge of biliary disease, including an increased understanding of the intrahepatic portions of the biliary tree. As biliary intelligence has increased, interest has shifted from larger to ever smaller ducts. For example, primary sclerosing cholangitis, a disease virtually unrecognized 30 years ago, is now encountered in clinical practice with some frequency, and is a common cause of hepatic damage requiring transplantation.

Biliary tree disease is commonly manifested to the diagnostic pathologist by the appearance of cholestasis in the liver biopsy. The term cholestasis implies an arrest in bile flow, bile being a secretory product produced by hepatic parenchymal cells and modified by contribution from the bile duct lining cells. Bile formation and transportation both have been studied in great detail at the biochemical and ultrastructural level; these elegant studies will not be considered here. Rather we shall confine ourselves to the morphological manifestations of cholestasis, and how structural alterations in the liver might give a clue as to the nature of the process affecting the biliary tree.

To the naked eye, cholestasis is manifested by a green or green-black mottling of the liver (Figure 8-1). This color usually becomes more apparent after the hepatic tissue has been exposed to formalin for some time, although, paradoxically, exposure to aqueous formalin ultimately results in a "washing out" of a significant portion of the bile pigment.

Microscopically, bilirubin is the easiest pigment to identify in standard H&E sections. It can be identified in canaliculi, in hepatocytes, and in Kupffer cells. Involved canaliculi are dilated (Figure 8-2) because of the plugs of inspissated bile. The dilated canaliculi are almost always preferentially in zone 3; there is often a curious variability to the severity of canicular involvement even around individual central veins.

Cholestasis within hepatocyte cytoplasm is ordinarily accompanied by prominent canicular plugs, but is occasionally seen in the absence of such change. This phenomenon is most common in an adverse reaction to drugs or toxins. The granules tend to be larger, more rounded, and have a distinct green-yellow hue with bright light (Figure 8-3). This helps differentiate them from lipochrome. In difficult cases, a specific bile stain can be employed (Figure 8-4).

In chronic or severe cholestasis, Kupffer cell clusters containing deposits of bilirubin and other PAS positive pigments may become quite prominent (Figure 8-5). The composition of bile in tissue tends to vary, since it is a mixture of glycocalyx, cholesterol, bile salts and membrane
fragments in differing proportions; this probably accounts for its variable PAS positivity even in the same section.

Several other phenomenon may occur in cholestasis. The liver cells may become arranged in tubules or rosettes around dilated canaliculi. This is most commonly seen in steroid associated cholestasis and in hepatic adenomas, particularly those related to androgen use. Hyperlipidemia is associated with impairment of bile flow, and lipid accumulation may result in the appearance of xanthoma cells (Figure 8-7). Inflammation may appear in zone 3; this is largely lymphocytic. Finally, in cholestasis of long duration, a phenomenon which has been referred to as cholate stasis appears. This is related to retention of bile acids. It predominantly affects zone 1 hepatocytes. These cells become swollen and vacuolated with a coarsely clumped cytoplasm. Copper accumulation is common at this stage (Figure 8-8 A and B); this is to be expected, since the main pathway for excretion of dietary copper under normal circumstances is through the bile.

Eventually these processes can lead to hepatocyte necrosis and subsequent fibrosis. This process has been referred to as biliary piecemeal necrosis (Figure 8-9); it is distinguished from classical piecemeal necrosis by the cholestasis related features just described and by the relative paucity of the lymphocytic infiltrate.

A good general approach to a liver biopsy specimen containing identifiable pigment would consist of the following (Figure 8-10). First and foremost, one must exclude parenchymal liver disease. In this regard, it is particularly important to consider the possibility of alcohol related liver disease, which is often clinically subterranean and can mimic biliary tree disease clinically, biochemically, and morphologically (see Chapter 6). Once the judgment has been made that any parenchymal changes can be explained as the result of, rather than the cause of cholestasis, one's attention should be directed to the triads. If these are essentially normal, pure intrahepatic cholestasis (see below) should be considered. If there is uniform proliferation of interlobular ducts in all the triads with an associated stromal edema and neutrophilic infiltrate, consider large duct obstruction. If, on the other hand, there is a great deal of variability from one triad to the next, some showing duct proliferation, some showing duct destruction, and either associated with ductular proliferation, consider strongly those processes affecting the intrahepatic biliary tree.

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**Intrahepatic ("Pure") Cholestasis**

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It is not infrequent to encounter a biopsy specimen in which the only finding is the presence of cholestasis. A fairly limited number of differential diagnostic possibilities will account for most of these (Figure 8-11, Table 8-1). Of these processes, an adverse reaction to drugs is far and away the most commonly encountered. Of drugs, those encountered with great frequency include oral contraceptives (Figure 8-12), erythromycin estolate, androgens and phenothiazine. Occasionally there may be a portal eosinophilia as a clue to the drug reaction. The history of drug exposure must be sought carefully and specifically; in particular this may be neglected with oral contraceptives, which the patient may not consider to be a "drug".

A patient with Gilbert's syndrome or a patient with hemolysis may present with mild jaundice but is not ordinarily biopsied if those possibilities have been considered and documented clinically. The occasional patient coming to biopsy shows this pattern of pure (bland) cholestasis.

The post-operative state may be followed by a mild to moderate jaundice due mainly to elevation of the conjugated bilirubin; this occurs in the first week post-operatively. The jaundice
starts one or two days after surgery and peaks in less than two weeks. The surgery is usual major; typical sites are abdominal or thoracic. The pathogenesis is probably multifactorial, with impairment of perfusion intraoperatively, destruction of red cells from blood transfusions, and possible post-operative infection contributing. Halothane toxicity and large duct obstruction are the main differential.

Familial recurrent intrahepatic cholestasis of pregnancy occurs in the last trimester of pregnancy and is thought to be due to the increased sensitivity of these patients to endogenous gonadal and placental hormones. These patients also have a tendency to develop cholestasis if exposed to oral contraceptives. The situation is harmless and resolves after delivery.

Patients with Hodgkin's disease can develop jaundice because of parenchymal involvement by the disease, because of common bile duct obstruction by enlarged involved lymph nodes, or because of an unknown mechanism leading to "pure" cholestasis.

Patients with infection and sepsis may have a bland cholestasis, but may also have some degree of cholangitis (see below). Miscellaneous uncommon causes of pure or bland intrahepatic cholestasis include: benign recurrent intrahepatic cholestasis (Summerskill-Tygstrup disease); passive venous congestion; sickle cell disease; amyloidosis; sarcoidosis; hepatic dysfunction in renal carcinoma; and a variety of metabolic disorders (see Chapter 10).

**Atlas of Liver Pathology, Chapter 8: Biliary Tree Disease**

**Classic Large Duct Obstruction**

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Although the recognition and confirmation of an obstructive lesion in the large ducts of the biliary tree outside the liver are no longer a major clinical challenge frequently issued to the hepatic pathologist, recognition of the changes associated with such lesions is essential. Without such knowledge the pathologist cannot understand fully the changes associated with diseases of the small ducts, and the occasional case still slips through the clinical diagnostic armamentarium to be identified first only at biopsy or autopsy (Figure 8-13).

The patient with large duct obstruction will be jaundiced. Typically there is a significant elevation of the serum bilirubin with the direct reacting fraction predominantly early on; the absolute level is dependent on duration. The alkaline phosphatase is ordinarily elevated three to five fold and bears a rough relationship to the bilirubin level, in contrast to primary biliary cirrhosis and primary sclerosing cholangitis (see below). In chronic cases, hyperlipidemia may be present. Careful attention must be paid to the results of imaging studies. Ultrasound, CT scans, and ERCP have usually documented the presence of obstruction and often have provided evidence as to the cause of obstruction. The typical causes remain: stone, tumor, benign stricture, extrinsic compression, and (rarely in the US) parasitic infection. The benign stricture may be post-operative, or may be part of the syndrome of primary sclerosing cholangitis which involves large and small ducts (see below). Occasionally the abnormal common bile duct will be examined histologically (Figure 8-14).

Although the exact sequence of events following obstruction of the human extrahepatic biliary tree cannot be documented, cumulative clinical experience has given a fairly good idea of the temporal sequence of histologic events after complete duct obstruction (Figure 8-15).

The very earliest change to be seen after duct obstruction is cholestasis evident as bile plugs in canaliculi in zone 3; at this time the histological picture is identical to that seen in bland cholestasis. This occurs in a matter of days. The next change is seen in the portal triads. This is best seen in the smaller portal triads; the accumulation of edema fluid transforms the usual triangular configuration to one which is more oval or circular (Figure 8-16). This edema may give a somewhat lamellar appearance around the larger septal ducts as it separates out the
collagen fibers; these ducts may appear slightly dilated. A cellular infiltrate begins to appear
around the ducts; while histiocytes and lymphocytes are often seen, the presence of readily
evident neutrophils is the key feature. There is a proliferation of ductules, usually at the marginal
areas of the triads (Figure 8-17). Periductular neutrophils and edema are essentially invariable
(Figure 8-18). This proliferation may be typical (with lumina and basement membranes) or
atypical (with solid cords of cells). Characteristically there is an irregular branching of these
structures.

As the days progress to weeks and months the cholestasis progresses from being confined
to zone 3 to involving the whole hepatic lobule. The bile plugs may look more inspissated. A
number of changes occur in the hepatocytes. There is a transformation to the tubular or
pseudoglandular pattern, and feathery degeneration may appear. Cells exhibiting this latter
phenomenon are large, pale, and rounded, with irregular strands of cytoplasm traversing the
areas of pallor; there may also be some bile staining (Figure 8-19). Because of the associated
hyperlipidemia, small droplets of fat may appear in the cytoplasm of clusters of phagocytic cells,
resulting in cells called xanthoma cells (Figure 8-20). Sometimes hepatocytes may take on these
lipid droplets, and are referred to as pseudoxanthoma cells; it may be virtually impossible to
distinguish hepatocytic from non-hepatocytic cells in such circumstances. Lytic necrosis of
individual hepatocytes or groups of hepatocytes may occur; when such groups are bile stained
they are referred to as a bile infarct (Figure 8-21). There may be extravasation of bile into large
spaces in the parenchyma with formation of bile lakes (Figure 8-22). Changes of superimposed
infection may appear (see below). Changes of cholate stasis (periportal Mallory bodies and
deposition of copper) may also appear.

There is ultimately progression to cirrhosis if the ductal obstruction is not relieved. The
pattern of scarring is quite characteristic, with the architecture of the liver being replaced by a
series of garlands resembling the pieces of a jigsaw puzzle (Figure 8-23). While this condition
has most commonly been referred to as secondary biliary cirrhosis, it has been argued by some
that biliary fibrosis would be a more appropriate name (see Chapter 9). The period of time for
the development of secondary biliary cirrhosis depends on such host factors as age and the
presence of complicating infections; it has been documented to occur in merely a matter of
months, but ordinarily requires a year or more.

There is no single feature that is pathognomonic for large duct obstruction. While bile
lakes and bile infarcts are rarely seen outside of obstruction, they can be misleading on occasion.
It should be emphasized strongly that more important than any particular feature or group of
features is the uniformity of the changes throughout the liver. Most of the triads are similar in
appearance and virtually all are affected in a patient with an obstructed common bile duct. The
surrounding liver inevitably shows readily evident canalicular bile plugs. This uniform
involvement in the presence of striking cholestasis is in sharp contrast to the variability from one
triad to the next so characteristic of small duct diseases.

Obstruction of the biliary tree predisposes to infection, and superimposed bacterial
infection can be recognized as a suppurative (ascending) cholangitis. This is characterized by
neutrophils in the walls of the bile ducts and focally filling the lumena of ducts, often dilating or
destroying them (Figure 8-24). The predisposition to infection is much greater than those whose
obstruction is due to stones rather than to tumor.

In Oriental countries, recurrent infections involving the biliary tree are much more
common than in the West. This has been referred to as recurrent pyogenic cholangiohepatitis.
There is an equal sex incidence, and patients tend to be young adults. Stones are commonly
present in the common bile duct and intrahepatic duct, but the gallbladder is often curiously free
of stones. There are recurrent bouts of sepsis, usually due to E. coli, with subsequent hepatic
abscesses and scarring. There may be secondary atrophy of the left hepatic lobe. Some have
suggested a relationship to parasitic infection (Clonorchis sinensis or helminths).
Primary Biliary Cirrhosis:
The term primary biliary cirrhosis (PBC) has been in use somewhat over 40 years. While the term is usually inaccurate (most patients are not yet cirrhotic at the time of diagnosis) it has withstood the test of time, and remains the term most commonly used to refer to this peculiar autoimmune disease affecting almost exclusively middle aged women. While the term chronic nonsuppurative destructive cholangitis has been used as a synonym for PBC and is scientifically more accurate, it is not widely used, and has the disadvantage of being applicable to a number of other diseases, most notably primary sclerosing cholangitis (see below).

Over 90% of patients are female. The typical age range is 40 to 60 years of age at the time of onset, although cases in the 20 to 70 years of age range certainly occur. The most common symptom is pruritus, being present in over two thirds of the patients. The number of patients being discovered at the asymptomatic stage has risen dramatically in recent years due to the advent of widespread laboratory screening. The typical pattern is an extremely high alkaline phosphatase (often in the 500-1000 IU/l range) with a disproportionately low, and often normal, bilirubin.

These patients are often seen first by a dermatologist because of their intense pruritus; some 30% of them have cutaneous xanthelasmas. Even at the asymptomatic stage there may be striking hepatomegaly. There is an increased frequency in these patients of diseases of an autoimmune nature; these include: sicca syndrome, CREST syndrome, rheumatoid arthritis, thyroiditis, systemic lupus, and celiac disease. These diseases may dominate the clinical presentation.

When the disease is suspected, several clinical tests may prove useful. There is often a striking elevation of the serum IgM. The serum cholesterol level may be increased, and there may be other evidence of hyperlipidemia. Of paramount importance is an assay for the presence of the antimitochondrial antibody. Elevated titers of this antibody are present in over 95% of cases of PBC, and are uncommonly elevated in other diseases. There is clearly some heterogeneity in antimitochondrial antibodies; nine types (designated anti-M1-M9) have been described, based on immunological methods. Of these, anti-M2, anti-M4, anti-M8, and anti-M9 are clearly associated with PBC, with anti-M2 bearing the closest relationship to the disease (it is virtually always present in PBC). Modern molecular techniques have shown that anti-M2 itself is heterogeneous, there being a series of M2 autoantigens identified with the functionally related enzyme family, the 2-oxo-acid dehydrogenases. While these elegant studies dissecting the molecular anatomy of the antimitochondrial antibody will undoubtedly increase the specificity of the test and increase our understanding of PBC, the more refined tests are not widely clinically available. Nevertheless, it is important to keep these facts in mind when dealing with the results of an antimitochondrial antibody assay result seemingly at odds with the clinical-pathological picture.

The disease process is most readily recognized on biopsy in its earlier stages; even patients who are completely asymptomatic may have significant histological alterations. There is a multifocal attack affecting segments of bile ducts in the 40-75 micron range early on. There is a surrounding cellular infiltrate rich in lymphocytes and plasma cells; eosinophils are also usually conspicuous (Figure 8-25). The basement membrane may be damaged and become focally
discontinuous (Figure 8-26). The bile duct epithelial cells may show damage, becoming irregular or vacuolated, and showing an increase in intraepithelial lymphocytes. There may be a vague papillary piling up of the epithelium, and there is often compromise of lumenal diameter (Figure 8-27). The most important finding is the florid duct lesion (Figure 8-28); the damage to the bile duct epithelium elicits a granulomatous response. The granuloma is clearly related to the damaged duct, often seeming to wrap around the duct for a considerable segment. This lesion is nearly pathognomonic for PBC; the occasional case of sarcoid may show a striking periductal location of granulomas. Clinical features should clearly discriminate sarcoid and PBC. In addition to the periductal granulomas, patients with PBC may have scattered parenchymal granulomas as well. The florid duct lesion is not universally present in all cases of PBC, even those with biopsies taken at an early stage; step sections will increase the yield. At times lymphoid aggregates with germinal centers will be present in portal triads related to damaged ducts (Figure 8-29); while helpful, they do not provide as strong evidence in support of the diagnosis of PBC as do the granulomas. Such lymphoid aggregates are also frequently seen in chronic hepatitis C, another disease process in which there may be damage to the small bile ducts (see below).

At the same time as the larger bile ducts are being damaged, there is also often destruction of the smaller ducts. It is quite common to find triads in PBC in which the interlobular bile ducts have been obliterated. While there is usually no residual scar, such triads can be readily recognized in that they contain well formed arterioles without the expected slightly larger accompanying interlobular bile duct (Figure 8-30).

As the interlobular and septal ducts are destroyed, ductular proliferation may occur. Although one is usually uncomfortable with the presence of neutrophils in a patient with PBC, it is certainly not uncommon to find polymorphonuclear leukocytes surrounding proliferating ductules at this stage. The proliferating ductules can be seen extending into the surrounding parenchyma and there is an associated fibrosis. This lesion of biliary piecemeal necrosis (Figure 8-31) differs from classic piecemeal necrosis of chronic active hepatitis by containing less lymphocytes, although lymphocytes are certainly present in PBC.

As the disease progresses, periportal parenchymal cells will show striking features of cholate stasis. Copper deposition is quite common (Figure 8-32), and Mallory bodies are not infrequent. Xanthoma cells may be present. In addition to xanthoma cells, there is quite frequently a striking prominence of the Ito cells (Figure 8-33). These cells appear to be increased in numbers; they are certainly larger and more evident than usual because of the increase in number and size of their lipid vacuoles. This change in Ito cells reflect alterations in Vitamin A metabolism which commonly accompany interlobular bile duct (Figure 8-30).

Eventually cirrhosis with the garland or jigsaw puzzle pattern typical of biliary cirrhoses appears. It is important to remember that the disease progresses with different foci in the liver being at varying points in their life history, so the various stages described in PBC are often seen simultaneously depending on the extent of the biopsy. Generally four stages are described in the histopathologic evolution of PBC, although several investigators have employed slightly different criteria for these stages. Recently it has been suggested that a staging scheme applicable to both PBC and primary sclerosing cholangitis (Figure 8-34) be used. While there are obvious difficulties with staging, this exercise does provide useful information in managing these patients, especially since they are particularly likely to undergo liver transplantation.

The differential diagnosis from chronic active hepatitis may present some difficult problems. This has been greatly alleviated by the appearance of serological tests for hepatitis C and by an increased understanding of the nature of antimitochondrial antibodies. Nevertheless, individual biopsies and clinical situations may present significant challenges, since some cases of PBC show aggressive parenchymal damage and some cases of hepatitis C damage interlobular
ducts significantly (Figure 8-35). The use of methods for visualizing copper and copper binding proteins is particularly important here since the demonstration of significantly increased amounts of copper in periportal hepatocytes strongly favors PBC over chronic hepatitis (Figure 8-36).

**Primary Sclerosing Cholangitis**

Although in many ways primary sclerosing cholangitis (PSC) closely resembles PBC, there are important clinical, histologic, and prognostic differences. Just as we became aware of a disease with a striking predilection for attacking the biliary tree of middle aged women in the decades of the 50's and 60's, there has been a realization during the decades of the 70's and 80's of a disease with a distinct predilection for damaging the biliary tree of young to middle aged men. It is clear that the Deity believes in a certain balance in the universe, and keeps current with the rising consciousness of sexual equality!

In fact, the typical patient with PSC is a man under 45 years of age; the sexual predominance seen in PBC is not quite so striking, but some 60-70% of PSC patients are male. Patients with PSC are more likely to have a "cholangitic" presentation than patients with PBC, that is, they may have right upper quadrant pain or tenderness and are more likely to be jaundiced than a PBC patient. Nevertheless, there is usually the same striking dissociation between the alkaline phosphatase levels and the serum bilirubin. The alkaline phosphatase is usually fourfold or greater increased, often with a normal bilirubin level. The antimitochondrial antibody levels are negative except under extraordinary circumstances. Another antibody, the anti-neutrophil cytoplasmic antibody (ANCA), is positive in about two thirds of the cases. While ANCA levels have been shown to be elevated in a number of disease processes, particularly vasculitis (Wegener's) the pattern of positivity seen in PSC differs in being particularly perinuclear (p-ANCA) (Figure 8-37). Even a positive p-ANCA titer is not specific for PSC, since patients with ulcerative colitis (with or without PSC) frequently have positive titers. The p-ANCA titer is negative in PBC.

There is a striking association between the presence of PSC and inflammatory bowel disease. Ulcerative colitis will be found in over 70% of patients with PSC; uncommonly the underlying inflammatory bowel disease will prove to be Crohn's disease. Ordinarily PSC appears in a patient with known ulcerative colitis; the ulcerative colitis often appears particularly quiescent in these patients (Figure 8-38). However, PSC may precede the onset of typical UC by a year or more. Colectomy for colitis does not seem to alter the course of PSC. The exact incidence of PSC in ulcerative colitis is not entirely clear largely due to the controversy concerning the presence of PSC limited to the intrahepatic biliary tree (see below), but most estimates would put it at about 4%.

PSC clearly involves the extrahepatic biliary tree and the large ducts at the hilus of the liver (Figure 8-39); it is this latter area that is the main focus of attack in most cases. The multifocal segmental areas of inflammation and subsequent fibrosis result in areas of stricture alternating with areas of saccular dilatation. This gives the characteristic "beaded" appearance seen on cholangiography, and is in contrast to the "pruned" appearance seen radiologically in PBC. Cholangiogram, usually obtained via ERCP, remains the gold standard for the diagnosis of PSC. When specimens of the large bile ducts are available, multifocal areas of acute and chronic inflammation are present; there is usually a striking lymphocytic predominance, and lymphoid aggregates are commonly prominent (Figure 8-40). The gallbladder may be affected in a similar fashion (Figure 8-41 A&B); the presence of acalculous cholecystitis with prominent lymphoid aggregates in a young man should bring to mind the possibility of PSC.

The small bile ducts within the liver are clearly affected in PSC, at least secondarily. Most cases of PSC show abnormalities in both large and small ducts. The evidence is mounting that there exists a small duct PSC limited to the substance of the liver at least at the outset. There
are a number of well documented cases in which needle biopsies of livers show changes typical of combined large and small duct PSC, in whom cholangiograms are normal; some of these patients later develop typical PSC changes in their large ducts.

The livers from patients with PSC usually show typical gross changes of biliary cirrhosis when seen at autopsy or in explanted livers at the time of transplant. One notable difference is a more striking degree of variability of involvement than seen in cirrhosis secondary to duct obstruction by stones or even in PBC. At times one lobe will show full-fledged cirrhosis while the adjoining lobe will seem nearly spared.

As is true of PBC, the histologic changes are usually confined to the portal triads initially. Edema and inflammation in a normal sized triad is the earliest finding; the edema may not be particularly prominent despite a readily evident infiltrate of neutrophils which typically bear a close relationship to the external surface of the basement membrane of the interlobular bile ducts (Figure 8-42). As the disease progresses, the portal triads begin to enlarge. They tend to do so in a peculiar elongated fashion (Figure 8-43 A&B) in contrast to the more rounded triads characteristic of PBC. Within these elongated tracts it is not uncommon to see rather long relatively straight segments of interlobular bile ducts cut longitudinally and cuffed by neutrophils. Quite commonly the periductal basement membrane will be thickened, at times to a striking degree (Figure 8-44). While this finding is present in the minority of patients with PSC and may be seen rarely in a variety of other circumstances (diabetes, cirrhosis of several causes, etc.), its presence should always occasion careful consideration of the possibility of PSC. Proliferation of ducts and ductules may become conspicuous. The most characteristic lesion of PSC, fibrous-obliterrative cholangitis, may be present (Figure 8-45). This lesion is analogous to the florid duct lesion of PBC although it is not observed quite so commonly nor does it have the same degree of specificity. Nevertheless, a patient with prominent fibrous-obliterrative lesions should be considered to have PSC until proven otherwise, even if this necessitates cholangiographic visualization of the biliary tree. As biliary piecemeal necrosis progresses, fibrous septae begin to form (Figure 8-46). These septae are portal-portal. Fibrous-obliterrative lesions may give way to rounded scars (Figure 8-47), although active lesions will still be found. Variability is the rule; in some areas ducts are destroyed and round scars may be present, while in others striking ductal and ductular proliferation is taking place (Figure 8-48). The occasional normal triad may still be identified.

Finally the stage of biliary cirrhosis is reached, with its typical garlands and jigsaw puzzle pieces. It is important to remember that in a fashion similar to PBC, all stages of the disease process may coexist, and an early lesion may be found adjacent to a regenerative nodule.

Cholestasis may be present at any stage of PSC, and in contrast to large duct obstruction, it begins in zone 1 (periportal); it shares this peculiarity with PBC.

The chief differential histologically is from PBC and from chronic viral hepatitis. With regards to PBC, the key differences are in the presence of fibrous-obliterrative versus florid duct lesions, and the degree of neutrophilic infiltrate. With regard to chronic hepatitis, the relative paucity of lymphocytic infiltrate and prominent periportal copper deposition are the major clues to PSC. In both instances, the clinical scenario and the serological testing are usually clear-cut. In even more difficult cases, the final decision may rest on cholangiographic findings.

Special mention should be made of the dilemma of cholangiocarcinoma (see Chapter 11). This tumor may mimic the cholangiographic findings of PSC, and may present very subtle features histologically. The situation is further complicated by the fact that cholangiocarcinoma may complicate pre-existing PSC (in contrast to PBC, where hepatocellular carcinoma, though uncommon, is the most frequently encountered complicating neoplasm). At times this dilemma can be resolved only by continued sampling and the passage of time.

Miscellaneous Biliary Tree Diseases
Infantile obstructive cholangiopathy - this term has been used to refer to a related group of diseases sharing in common damage to the biliary tree. One grouping consists of extrahepatic biliary atresia, neonatal hepatitis, and choledochal cyst; changes are most prominent in the extrahepatic biliary tree, although smaller intrahepatic ducts are also affected secondarily. In another major grouping, it is the small ducts within the liver that are primarily targeted. This results in intrahepatic paucity of bile ducts, or ductopenia. This may be syndromatic (in association with other abnormalities in vessels, eyes, etc.) or non-syndromatic, seemingly occurring in isolation. These diseases will be discussed in more detail in Chapter 10.

Idiopathic ductopenia of adulthood refers to a situation where cholestatic liver disease and a diminution in intrahepatic ducts is recognized with normal cholangiographic findings, absence of florid duct lesions or antimitochondrial antibodies, and absence of the associated disease discussed at the end of this chapter. This process, recently recognized, appears to be quite uncommon, and is yet little understood.

Atlas of Liver Pathology, Chapter 8: Biliary Tree Disease
Miscellaneous Diseases with Significant Involvement of the Biliary Tree
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Finally there exists a number of diseases and clinical situations in which the laboratory and histological findings may mimic disease intrinsic to the large and small ducts if the clinical scenario is not recognized. As always, the importance of history for the proper interpretation of a biopsy specimen cannot be overemphasized. These processes will now be briefly discussed.

Infectious diseases can produce a cholestatic picture by their systemic effects as in sepsis, or by directly damaging the liver as part of the infectious process. The frequent occurrence of jaundice in patients with lobar pneumonia due to streptococcus pneumoniae has been known for well over a century, and pediatricians are only all too aware of the fact that the only manifestation of significant infection in the neonate may be jaundice. It is less well recognized that about half of all adults with positive blood cultures will have elevated bilirubin levels. While these elevations are usually mild, they can be striking, particularly in the critically ill patient. The bilirubin is predominantly direct reacting, and is elevated out of proportion to the relatively mild increases in alkaline phosphatase and the transaminases. Most commonly the liver biopsy specimen or autopsy liver will manifest this effect of sepsis by the appearance of bile in zone 3 canaliculi and hepatocytes. In other words, pure or bland cholestasis will be present; it may be engrafted on other diseases in the liver predisposing the patient to his or her critical illness. A less well recognized but very important pattern of injury has been referred to as bile ductular cholestasis or cholangitis lenta. The strikingly dilated duct structures at the periphery of the triads and the periductular neutrophilic infiltrate may trap the unwary into considering large duct obstruction (Figures 8-49 and 8-50).

With regards to specific infectious agents affecting the liver, the propensity for the duct damage in chronic hepatitis C to mimic PBC and PSC has already been mentioned (see figure 8-35). Less well recognized is that one of the variants of cytomegalovirus infection is the production of a cholestatic laboratory and histological picture that may resemble large duct obstruction (see Chapter 5). CMV inclusions may be lacking, and serological studies may provide the only clue (Figure 8-51). In the patient with AIDS, cryptosporidia may produce a clinical and cholangiographic picture identical to PSC except for the presence of organisms in the lumena of bile ducts (see Chapter 13).

An adverse reaction to drugs and toxins can clearly cause a cholestatic picture and damage or destruction of the small intrahepatic bile ducts. Isolated instances of such damage
have been reported with such drugs as benoxaprofen, chlorpromazine, haloperidol, imipramine, and others. Such reactions are further discussed in Chapter 7.

Damage to the vasculature of the biliary tree can also induce significant bile duct damage. Examples of this phenomenon are provided by the biliary tree damage sometimes seen complicating liver transplantation (Chapter 12) or following intra-arterial injection of chemotherapeutic agents.

Following organ transplantation, the bile ducts may become the target for the immunologic attack seen in graft versus host disease or in cellular rejection of the transplanted liver (see Chapter 12).

Fulminant hepatic necrosis of any cause can result in some attempts at regeneration in the periportal areas resulting in structures called neocholangioles (Figure 8-52). These structures share features of hepatocytes and ductal cells; again the unwary may be misled into considering biliary tree obstruction, only to be puzzled by the demonstrable patency of all duct structures at autopsy. A particularly florid and confusing example of this phenomenon is to be seen in cases of Wilson's disease (Figure 8-53), particularly those cases which undergo a fulminant course.

Total parenteral nutrition is well known to be capable of inducing a cholestatic state in both infants and adults. The typical histological picture includes centrilobular canalicular and hepatocellular cholestasis, often associated with some degree of fatty change (Figure 8-54). The triads may show a variable degree of ductal and ductular proliferation, and may even demonstrate edema and a neutrophilic infiltrate.

A described in Chapter 6, alcohol related liver disease may result in a confusing picture with striking ductular proliferation. Typical alcohol related changes in the surrounding parenchyma provide the critical clue.

A peculiar combination of duct and vascular damage can be seen in liver biopsy specimens taken from near large space occupying lesions (typically large deposits of metastatic tumor). Normal triads alternate with those resembling triads seen in duct obstruction (Figure 8-55 A and B), while central veins that are normal alternate with those showing ischemic damage (Figure 8-56). This pattern results from variable impingement on branches of the vascular and biliary trees by the underlying lesions.

Cystic fibrosis commonly affects the liver (see Chapter 10). The typical pattern of biliary cirrhosis may be seen; the peculiarity is that this pattern tends to be focal within the liver, and some of the ducts may contain thick inspissated secretions.

Sarcoidosis can present a particularly confusing histological picture, since there is a predilection for a portal location to the granulomas, in which case a florid duct lesion may be mimicked (see Chapter 2). The granulomas in sarcoid tend to be larger, more numerous, and more well formed than in PBC. Parenchymal granulomas are also more numerous than in PBC. In most cases associated clinical and serological findings allow for confident separation of the two processes.

**Conclusion**

As is true in many diseases affecting the liver, multiple factors may be operative. The individual diseases just discussed may be fairly difficult to recognize. A great deal of expertise is required to find the way through certain diagnostic mazes. The alcoholic with some complaints of diarrhea may have fibrosis secondary to alcohol related liver disease. This may predispose to gallstones, which in turn can lead to common bile duct obstruction. Such an obstructed duct can give rise to infection, with ascending cholangitis and sepsis. This may necessitate major abdominal surgery, and the critically ill patient may require total parenteral nutrition and several pharmaceutical agents. A biopsy from such a jaundiced patient is a true nightmare for the pathologist. Careful clinical correlation, and an understanding of each of the parts of the illness, can lead to useful information if the pathologist is patient and careful enough.
Figure 8-1: (A) Cross section of liver from patient with biliary cirrhosis due to sclerosing cholangitis. (B) Same section through liver after overnight fixation; note increased intensity of green color. Some inspissated material is present within dilated intrahepatic ducts.
Figure 8-2: (A) Canalicular cholestasis with several longitudinal and cross sectional cuts through dilated canaliculi (x250). (B) The green color of bile is ordinarily more apparent on frozen section; the amount of bile seen on the frozen section is more than on the corresponding permanent section (x100).
Figure 8.3: Several hepatocytes contain granules of bilirubin pigment; canalicular cholestasis is also evident (x250).

Figure 8.4: Both canalicular and hepatocyte cholestasis are more evident after specific staining for bile (Hall's stain, x250).
**Figure 8-5:** (A) With severe cholestasis it is not infrequent to find a variable amount of bilirubin in Kupffer cells in sinusoids (x250). (B) The PAS stain can be confusing, since, dependent on its composition, bile is variably PAS positive (PAS with diastase, x160).
Figure 8-6: Another phenomenon observed with cholestasis is the formation of a tubular or gland-like structure around a dilated canaliculus (x132).

Figure 8-7: (A) Lipid indents the nuclei of phagocytic cells within the sinusoids; xanthomatous cells such as this may appear from any chronic cholestatic condition (x160). (B) Pseudoxanthomatous change refers to a similar accumulation of foamy lipid within cells that may be hepatocytes (x132).
Figure 8-8: (A) Copper accumulation is regularly demonstrable in obstructive diseases of the biliary tree (Rhodanine, x100). (B) Copper may also be indirectly demonstrated by staining for the copper binding protein (Victoria blue, x100).
Figure 8-9: (A) As the portal triad enlarges, irregular extensions of fibrous tissue extend into the parenchyma (Klatskin, x40). (B) As biliary piecemeal necrosis progresses, the fibrous septae begin to distort hepatic architecture (PAS, x10).
<table>
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<th>Cholestasis identified in biopsy</th>
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**Figure 8-10:** Algorithm for cholestatic biopsy.

**Figure 8-12:** (A) Pure canicular cholestasis secondary to oral contraceptives; note the formation of tubules (particularly common with an adverse reaction to steroids) (x100). (B) Portal triad from the same patient; it is essentially normal (x100).
Figure 8-13: This unfortunate elderly woman presented with painless jaundice; presumed to have tumor, she was found to have this huge common bile duct stone at autopsy!
Figure 8-14: (A) The normal common bile duct has a somewhat irregular lumenal contour; little smooth muscle tissue is present except distally (x16). (B) This common bile duct was obtained many months after the repair of a surgical stricture; there is increased fibrosis of the wall with subsequent compromise of lumenal diameter (x4).

Figure 8-16: The central normal preexisting triad stains more densely than the edematous halo which contains ductular proliferation (Klatskin, x33).
Figure 8-17: This expanded portal triad was noted in a biopsy obtained several weeks after onset of obstructive jaundice; other triads in the biopsy had a similar appearance (x50).
Figure 8-18: (A) Edema and xanthoma cells are seen surrounding these branched proliferating interlobular ducts; inspissated material is present within one near the center of the enlarged triad (x100). (B) Striking edema is present around these abnormal ducts and ductules (Klatskin, x50). (C) Strikingly abnormal ductal structures in well established large duct obstruction (Masson trichrome, x80).

Figure 8-19: (A) Cholate stasis, here manifested by a number of swollen hepatocytes in the periportal area (x25). (B) Upon higher power, the reason for the pallor is seen to be feathery degeneration; note the bile, and the wisps of cytoplasm traversing the expanded cytoplasm (x100).
Figure 8-20: (A) A central area of bile infarct is surrounded by a collar of foamy macrophages (x33). (B) At higher power, these foamy cells show typical scalloping of the nuclei characteristic of xanthomatous cells (x200).
Figure 8-21: (A) The triad shows edema and duct proliferation; the collection of necrosed cells in the lobule represents a bile infarct (Klatskin, x33). (B) The same area at higher power shows loss of cellular detail within the hepatocytes and bile staining of the cytoplasm (x100).

Figure 8-22: This patient with large duct obstruction showed extravasation of a large amount of bile; xanthomatous cells ringed this bile lake (x25).
Figure 8-23: The smooth contoured interlocking regenerative nodules so characteristic of biliary cirrhosis; this has been likened to the pieces of a jigsaw puzzle or to a series of garlands (Masson trichrome, x10).

Figure 8-24: (A) This mass of neutrophils is forming a small microabscess; note the disrupted septal bile duct in its midst (x4). (B) Elsewhere in the same biopsy some of the smaller triads showed interlobular ducts with neutrophils in their lumena and traversing their walls; this feature is characteristic of ascending cholangitis (x160).
Figure 8-25: The cellular infiltrate with a mixture of lymphocytes, plasma cells, and eosinophils were the clue to PBC in this triad; there is minimal distortion of the interlobular duct (x100).

Figure 8-26: Note the loss of continuity of the basement membrane around this damaged interlobular duct (x66).
Figure 8.27: (A) There is an irregular lumen with slight papillary tufting to this damaged septal bile duct; note the cellular infiltrate and focal loss of basement membrane continuity (x50). (B) There is a significant cellular infiltrate, loss of basal polarity of the bile duct nuclei, and disruption of the basement membrane in this patient with PBC (x100).
Figure 8-28: (A) The portal inflammation in PBC is robust, but irregularly distributed; two florid duct lesions are present in this field (Klatskin, x10). (B) At higher power, the relationship of the granuloma to the interlobular bile duct is apparent (x25). (C) Another florid duct lesion, with a granuloma showing larger histiocytes than is usual (x100). (D) The relationship of this granuloma to the involved duct is all too apparent, the histiocytes are nearly totally symmetric in a concentric fashion (x40). (E) A more eccentric florid duct lesion, with the granuloma related to that portion of the septal bile duct which has been most severely damaged (x50). (F) There has been almost complete obliteration with only a linear scar left of the prior septal bile duct (Klatskin, x33).
Figure 8-29: (A) The striking portal inflammation should bring to mind the possibility of primary biliary cirrhosis (x10). (B) At higher power, the lymphoid infiltrate is seen to include a germinal center; the spatial relationship to the damaged bile duct is evident (x25).

Figure 8-30: A well formed hepatic arterial stands unaccompanied by an interlobular bile duct; several such triads were present in this biopsy from a patient with PBC (x66).
Figure 8.31: (A) Biliary piecemeal necrosis in a patient with PBC; although there is a striking lymphocytic infiltrate, it is confined to the triad and related to the ducts rather than being present diffusely throughout the fibrous connective tissue (PAS, x4). (B) As piecemeal necrosis progresses, fibrous septae are formed (Trichrome, x2.5).

Figure 8.32: The periportal hepatocytes contain abundant copper in this patient with moderately early PBC (Rhodanine, x33).
Almost all patients with PBC have increased numbers of Ito cells that tend to have prominent, large, fat vacuoles (x250).

Stage 1: Portal Stage
Normal sized triads; portal inflammation, subtle duct damage

Stage 2: Periportal Stage
Enlarged triads; periportal fibrosis and/or inflammation

Stage 3: Septal Stage
Active and/or passive fibrous septae

Stage 4: Biliary Cirrhosis
Nodules present; garland or jigsaw pattern

Staging of PBC and PSC.

This interlobular bile duct is showing a particularly severe lesion in a patient with typical clinical and serological hepatitis C (Trichrome, x250).
Figure 8-36: (A) Only a few sparse red-brown granules of copper are present in periportal hepatocytes; this constitutes mild or grade I deposition (Rhodanine, x66). (B) The red-brown granules make larger clusters in a moderate number of periportal hepatocytes; this constitutes moderate, or grade II copper deposition (Rhodanine, x50). (C) Many hepatocytes, even those outside the area of the limiting plate, contain large clusters of red-brown granules; this constitutes severe, or grade III copper deposition (Rhodanine, x50).
Figure 8.37: There is striking green immunofluorescence around the lobes of the neutrophils exposed to the serum of a patient with both ulcerative colitis and primary sclerosing cholangitis (ANCA immunofluorescence, x250).

Figure 8.38: The crypt branching, atrophy and mild inflammation are the histological hallmarks of quiescent ulcerative colitis; this patient presented with PSC one year before a bout of fulminant colitis (x40).

Figure 8.39: This liver showed significant narrowing and periductal fibrosis in the common hepatic ducts and in the common bile duct at the time of explant.
Figure 8-40: This cross section through an area of stricturing of a common bile duct in a patient with PSC corresponded to one of the areas of beading on cholangiogram (x4).
Figure 8-41: (A) The gallbladder from this child with sclerosing cholangitis showed prominent lymphoid aggregates with germinal centers; there was also an area of focal dense sclerosis in the wall (x10). (B) The cystic duct from the same child showed complete lumenal obliteration (x10). (C) Acute cholecystitis from an adult with ulcerative colitis and PSC; note the lymphoid aggregates (x13).

Figure 8-42: Typical relatively small triad in PSC; note the propensity for the inflammatory cells to hug the outer surface of the interlobular bile ducts (x160).
Figure 8-43: (A) In this patient with pre-cirrhotic PSC there is expansion of the portal triads with elongated fibrous septae containing segments of inflamed bile ducts and ductules (Klatskin, x25). (B) For reasons which are not clear, one often sees long segments of interlobular bile ducts that are relatively unscathed in the distorted triads in a patient with PSC (Klatskin, x50). (C) Even when the triads are more irregular in PSC, they still have a somewhat stretched out or attenuated appearance (Klatskin, x50).
Figure 8-44: (A) The eosinophilic basement membrane is thickened in a significant minority of patients with PSC (x160). (B) The PAS diastase stain helps one appreciate the morphology of the abnormal ducts in PSC; note the peculiar pattern of proliferation (PAS diastase, x66). (C) The thickening of the basement membrane is best appreciated on the PAS diastase stain; similar changes can be seen in diabetic patients with normal biliary trees (PAS diastase, x400).
Figure 8-45: (A) Fibrous oblitative cholangitis, here affecting a somewhat larger than usual interlobular bile duct; the concentric lamellar fibrosis is well formed (x40). (B) These septal bile ducts show irregular distortion of their lumina, periductal fibrosis, and inflammation (x16). (C) A single septal duct showing significant fibrous oblitative cholangitis; some ductular proliferation is present eccentrically (x25). (D) At a higher power, the duct seen in 8-45C reveals the inflammatory infiltrate to be mixture of lymphocytes and neutrophils; note the neutrophils between the bile duct epithelial cells (x80). (E) The nature of the concentric fibrosis and the ductular proliferation are more evident with the use of trichrome stains (Klatskin, x13). (F) The larger duct seen in 8-45E shows loss of continuity; there is a granulomatous response to the released bile. This can cause a dilemma when PBC is in the differential (x50).
Figure 8-46: Well established biliary piecemeal necrosis in PSC; numerous fibrous septae are present, and the stage of biliary cirrhosis is about to begin (Klatskin, x5).

Figure 8-47: The tombstone of the fibrous obliterative lesion is seen in this triad; note the bland, dense, rounded fibrous scar (x50).

Figure 8-48: There is a striking degree of variability within this low power field in a patient with PSC; some areas are active with septum formation, while nearby triads are essentially normal (Klatskin, x8).
Figure 8-49: The jaundice in sepsis may be manifested by striking dilated ductal structures containing bile at the periphery of the triads; this is in contrast to large duct obstruction, where such ducts are more centrally placed (x66).
Figure 8-50: (A) Bile ductular cholestasis or cholangitis lenta is a less common manifestation of sepsis; numerous neutrophils line the periductal basement membrane (x66). (B) The combination of such an inflamed portal triad with some centrilobular swelling of hepatocytes due to poor perfusion is a valuable clue to shock and sepsis (x25).

Figure 8-51: Portal inflammation with ductular proliferation and centrilobular cholestasis may mimic biliary tree disease in cytomegalovirus (Klatskin, x33).
Figure 8.52: (A) This patient with fulminant hepatic necrosis secondary to a viral infection showed little recognizable liver parenchyma; the periportal area showed striking duct-like structures (x40). (B) These duct-like structures, or neocholangioles are hybrids of ducts and liver cells; this patient had survived two weeks after the onset of hepatic failure (x160).

Figure 8.53: A peculiar proliferation of ductular structures can be seen focally in patients with Wilson’s disease; this can mimic biliary tree disease or even tumor. It probably reflects focal neocholangiolar proliferation (x50).
Figure 8-54: This infant on prolonged total parenteral nutrition shows striking central canalicular cholestasis with portal expansion, inflammation, and ductular proliferation; a small amount of fatty change is present (x40).

Figure 8-55: (A) This normal triad was in the minority in a needle biopsy of liver from a patient who died several days later with massive hepatic metastases; note the sinusoidal dilatation (Klatskin, x50). (B) The same patient, with a more typical appearance for the triad in the patient (Klatskin, x100).
Figure 8-56: