Hepatic neoplasms are relatively uncommon, except for those parts of the world where the high incidence of hepatitis B leads to a corresponding high incidence of hepatocellular carcinoma. Of those neoplasms causing clinical symptoms, malignant tumors far outnumber their benign counterparts. The majority of malignant tumors prove to be metastatic rather than primary. Neoplasms arising from within the liver, both benign and malignant, may have their origin in hepatocytes, biliary epithelium, neuroendocrine cells, or a variety of mesenchymal elements such as endothelium, smooth muscle, lymphoid tissue, etc. (Figure 1). Each of these tumors tends to produce a fairly characteristic clinical and pathologic picture.

Benign Tumors

Cysts:
The simple hepatic cyst is a unilocular lesion lined by a simple cuboidal epithelium. It is usually single, although rarely as many as ten cysts may be found. The surrounding liver is normal. They vary from millimeter size up to 20 cm in diameter, although smaller cysts are more common (Figure 3) (Figure 4). Clinically evident cysts are distinctly uncommon; however, a careful search at autopsy will reveal small cysts as a relatively frequent incidental finding. About 80% of patients with cysts are female. The cysts in polycystic liver disease are indistinguishable from simple hepatic cysts except for their larger numbers and association with changes in the surrounding liver. Typically, multiple bile duct hamartomas are found in the surrounding liver. When such hamartomas are numerous, there is a resemblance to congenital hepatic fibrosis (see below). The term hepatobiliary fibropolycystic disease has been used to refer to the spectrum of diseases including hepatic cysts, congenital hepatic fibrosis, Caroli's disease, and choledochal cysts (see Chapter 10). In adults, rather dramatic cysts of liver may exist and be totally asymptomatic. They are often found in association with polycystic kidney disease; some 29% of such patients have liver cysts. Patients with polycystic liver disease have a slight predisposition towards developing cholangiocarcinoma.

Hepatobiliary cystadenoma is an uncommon lesion which presents as a multilocular cyst which is usually large (7 to 25 cm). There may be a peculiar mesenchymal stroma, although this is focal in an otherwise bland to hyalinized fibrous wall. This peculiar stroma is found only in women, and bears a close resemblance to ovarian stroma. The usually smooth internal surface should be searched carefully for polypoid projections since there seems to be a relatively high percentage that undergo malignant change (4 of 17 patients in one series). On occasion, these lesions can form a polypoid intraductal mass that can cause jaundice.

Choledochal cysts are said to have a classic presentation with pain, a mass in the right upper quadrant, and jaundice. This is most common in children, and is often not present. Many cases are first discovered in adult life, where cholangitic symptoms may prevail. There is a striking female predominance. The cysts may be huge (Figure 8A) (Figure 8C) (Figure 8D). The wall is thick and fibrous, and may be quite inflamed. A columnar epithelium is usually present, but may be discon-
tinuous; rarely, squamous metaplasia occurs. There is a predisposition to adenocarcinoma which is age related, reaching 14% in adult life.

Mesenchymal Tumors
Frank A. Mitros, M.D.

The mesenchymal hamartoma is an uncommon lesion of childhood, usually diagnosed in the first two years of life. There is progressive painless abdominal enlargement; radiographic studies reveal a large mass with multiple cysts. There is a striking male predominance. The tumor is large (up to 21 cm) and solitary. It is composed of a gelatinous mesenchyme and cysts or poorly formed cystic spaces filled with clear fluid (Figure 9) (Figure 10) (Figure 11). A loose mesenchyme with stellate cells may contain scattered bile ducts and hepatocytes, although the latter appear to be entrapped (Figure 12) (Figure 13).

Infantile hemangioendothelioma is one of the more common childhood hepatic tumors. Despite its rather dramatic appearance (Figure 14), these tumors almost always follow a benign course and usually spontaneously involute. Most are discovered within the first six months of life. In addition to liver, other organs such as skin, lung, lymph nodes, and bone may be involved. Massive hemateomegaly may bring the child to attention, although some infants present with congestive heart failure or thrombocytopenia as secondary effects of these vascular neoplasms. Most are multinodular and involve both hepatic lobes, though rare cases present as solitary right lobe lesions. Typical nodules are from 0.5 to 3 cm in diameter. The nodules are sharply defined and firm; they vary from white to red brown (Figure 15). There are two histologic types. Most are type I, with multiple small histologically bland vascular channels. Bile ducts may be scattered throughout. The rare type II has more pleomorphic endothelial cells; rare examples of this type have metastasized.

Hemangiomas of liver are reasonably common incidental findings, being present in over 1% of autopsies. Most are totally asymptomatic. The 15% of individuals with these lesions who have symptoms present with the effects of a mass compressing adjacent structures. Almost all of these patients have giant hemangiomas, defined as being more than 10 cm in diameter; these lesions are characteristic radiographically. Clinically apparent hemangiomas are more common in women. These lesions range up to 20 cm in diameter; some 10% are multiple (Figure 17). They are usually evident on examining the capsular surface (Figure 18). Most are well circumscribed grossly, and have a readily evident vascular nature (Figure 19A). Fibrosis commonly occurs in larger lesions (Figure 19B); sometimes lesions sclerose entirely, leaving only a round fibrous scar. Microscopically the blood filled spaces vary in size and contour; a bland endothelial lining is readily evident. Fibrosis, calcification, and even ossification may be seen.

Peliosis hepatis is a tumor-like condition affecting liver that must be considered when evaluating vascular lesions. It consists of multiple, small, blood filled cystic spaces throughout the liver (Figure 21), most often appearing as an unexpected finding at autopsy. The spaces lack an endothelial lining (Figure 22), but can be seen to communicate with sinusoidal spaces, which may be dilated or thrombosed (Figure 23). It was originally described as complicating advanced tuberculosis or carcinomatosis, but the ever growing list of associations now includes: androgen/anabolic steroid use, renal transplantation, vinyl chloride exposure, Thorotrast exposure, and AIDS. Rarely intraperitoneal hemorrhage and death may occur.

Lipomas occur rarely in the liver and are usually incidental findings. They may be composed purely of mature adipocytes, or of brown fat (hibernomas), or of adipocytes in combination with mature smooth muscle and vascular elements (angiomyolipoma). These latter tumors may be large and clinically evident; in fact, they can be mistaken for malignancy (Figure 24). The smooth muscle elements usually predominate. Vessels consist of tortuous arteries and veins. Mature adipocytes constitute some 5 to 90% of the lesion (Figure 25). Despite their resemblance to their namesake in the kidney, they are not associated with tuberous sclerosis. Lipomas of liver must be distinguished from focal fatty change, which can grossly mimic lipoma; the presence of fat vacuoles in hepatocytes rather than adipocytes is the key to recognition.
**Inflammatory pseudotumor** of liver, also known as inflammatory myofibroblastic tumor, is a tumor-like mass lesion composed of a mixture of lymphocytes, plasma cells, macrophages, foam cells, and spindled cells (fibroblasts or myofibroblasts) (Figure 26). It may be quite large; lesions in excess of 20 cm have been reported. If there is a known cause, such as healing abscess or trauma, the term is not used, although the histological features may be identical. The mass is usually hilar; it is usually well circumscribed and may have distinctly yellow areas. It is probably heterogenous in etiology.

**Miscellaneous** benign tumors include lymphangiomas, leiomyomas, fibromas, and myxomas. All are quite rare, and are recognized by their resemblance to similar tumor types arising in other organs. A variety of heterotopic tissues, not all mesenchymal, can be found in liver. The adrenal rest tumor consists of adrenocortical cells in liver capsule; with the utmost rarity such nests are functional. Primary hepatic pheochromocytomas can occur. Heterotopic pancreatic tissue has been reported in liver from 0.6 to 5.6% of autopsies; patients are usually adult males (Figure 27).

**Epithelial Tumors**

Frank A. Mitros, M.D.

Peer Review Status: Internally Peer Reviewed

The **bile duct hamartoma**, also known as the von Meyenberg complex, is a common incidental finding. They are reported to be present in just under 1% of all autopsies, but are probably more common than that, since their small size (less than 0.5 cm) makes them easy to miss. They vary from grey-white to green depending on their bile content (Figure 28A) (Figure 28B). Since they often are located in a subcapsular position, they may be biopsied during a laparotomy, providing a potential pitfall for the unwary surgical pathologist. They can usually be seen to emanate from a pre-existing portal triad, and may have a broad base along the capsule (Figure 29). The bland nature of the biliary type epithelium lining the peculiarly contoured lumena makes for ready identification if one is aware of this entity (Figure 30). They form part of the spectrum of hepatobiliary fibropolycystic disease (Figure 31); indeed, congenital hepatic fibrosis has the appearance of innumerable bile duct hamartomas in continuity.

**Bile duct adenomas** are distinctly less common than their cousins, the hamartomas. They are almost always single, and make a larger more rounded nodule, typically ranging in size from 0.5 to 1.0 cm (Figure 32A) (Figure 32B). They are almost always incidental findings. The ducts composing them much more closely resemble interlobular bile ducts than do the dilated ducts of hamartomas (Figure 33A) (Figure 33B) in a uniform fashion, in contrast to cholangiocarcinoma. There may be prominent basement membrane material around ducts (Figure 34A) (Figure 34B) and there is often a significant lymphatic or neutrophilic infiltrate in the stroma. Rarely lesions that are difficult to distinguish from biliary hamartoma are encountered (Figure 35). Distinction from cholangiocarcinoma is based on the small size, solitary nature, and lack of pleomorphism in the adenoma.

**Hepatic adenomas** are benign tumors composed entirely of hepatocytes and the appropriate supporting connective tissue framework. The most common setting for their appearance is related to estrogen exposure, particularly with the use of birth control pills in women. Anabolic steroids can produce peculiar adenomas that may be multiple. Glycogen storage disease type I and tyrosinemia may also be complicated by the appearance of adenomas. Rarely apparently sporadic adenomas may arise. In the absence of anabolic steroid exposure, these tumors are virtually exclusively found in females. Adenomas may present as an asymptomatic mass, or may produce right upper quadrant pain, or may rupture producing life threatening intra-abdominal hemorrhage. Hepatic adenomas tend to be large, usually measuring over 10 cm in diameter. Except for those related to anabolic steroids, most are single. The surface is variegated and bulging. Color will vary depending on the amount of fat and glycogen, which may differ from that of the surrounding liver, and the amount of and age of hemorrhage, which is common (Figure 36). The tumor is usually visible from the capsular surface and may even be pedunculated. Histologically the tumor cells closely resemble normal hepatocytes, although the cytoplasm may be more acidophilic or hydropic than in those cells in the surrounding liver. Fat droplets, cholestasis, or alcoholic hyaline may on occasion appear within
cells of the adenoma. Hepatocyte giant cells may be present. The cells usually grow in thin cords resembling those of normal liver, but these may be so closely approximated that the neoplasm appears to be composed of solid sheets of hepatocytes. Thick trabeculae do not occur; the presence of such structures is evidence for the transformation to hepatocellular carcinoma. A peliosis like change may be prominent, perhaps accounting for the tendency of these neoplasms to rupture (Figure 37). The arteries and veins present in the adenoma occur in close proximity to each other, and are devoid of the usual connective tissue framework of the portal triads in which they usually are located. These "free floating" vessels often provide a useful diagnostic clue (Figure 38). Adenomas related to anabolic steroids differ from the others in their male predominance, their tendency to multiplicity, and their marked histologic variability. This latter includes prominent acinar formations (Figure 39) and giant cells. Hepatic adenomas can become so large as to be life-threatening (Figure 40). Most are steroid related, and there is evidence that regression occurs if steroid use is discontinued. There have been reports that hepatocellular carcinomas may arise from pre-existing adenomas, but such occurrences are quite rare.

**Focal nodular hyperplasia** is a lesion which has frequently been confused with hepatic adenoma. It consists of a mass, usually solitary, ranging in size from 1 to 15 cm, with a characteristic central stellate scar (Figure 41). Unlike the adenoma, it contains bile ductular structures; these are usually arrayed in and around bands of fibrous tissue criss-crossing the lesion. Their appearance led to the old name of focal cirrhosis; in fact, a biopsy of this lesion can readily be confused with cirrhosis if one is not aware that the biopsy came from a localized lesion in an otherwise normal liver (Figure 42). It also differs from the adenoma in that there is no capsule. Although there is a moderate female predominance, this is not so striking as with adenomas, nor is there the same clear relationship to estrogen usage. Many of these lesions are thought to develop as a result of an anomalous arterial branches.

In **nodular regenerative hyperplasia** there is a diffuse nodularity of the liver which is not associated with fibrosis. Although it is often an incidental finding, it can produce portal hypertension and present with its consequences. It is thought that the process may result from damage to branches of the intrahepatic portal vein. In most of the diseases associated with nodular regenerative hyperplasia there is a potential for vascular damage. This list includes: rheumatoid arthritis, Felty's syndrome, polycythemia vera, hereditary hemorrhagic telangiectasia, lupus, toxic oil syndrome, myelofibrosis, and myeloma. The bulging nodules are evident grossly, ranging up to 1 cm in diameter (Figure 44). The nodules are often roughly the size of a hepatic lobe (Figure 45A); in contrast to cirrhosis, there are no fibrous bands separating the nodules (Figure 45B). The hepatocytes within the nodules are unremarkable. Between the nodules there is compression of hepatocytes (Figure 46). A related lesion is partial nodular transformation, in which similar nodules are confined to the perihilar area. Portal hypertension is usually prominent in this exceedingly rare condition.

**Hepatocellular carcinoma** is far and away the most common primary tumor of liver, even in those parts of the world where its incidence is low. In nations where the prevalence of hepatitis B infection is high, it is a very common neoplasm and one of the leading causes of death. Hepatocellular carcinoma arises from hepatocytes in a liver which is almost always chronically diseased, and often cirrhotic. Worldwide, hepatitis B is the most common setting, but hepatocellular carcinoma can arise in cirrhosis of virtually any etiology. Cirrhosis due to hepatitis B or hemochromatosis seem particularly prone to give rise to hepatocellular carcinoma; malignant degeneration is much less common in cirrhosis due to Wilson's disease or primary biliary cirrhosis. In any given geographic location, the relationship to cirrhosis probably best reflects the local epidemiology for cirrhosis. For example, in those parts of the world where alcohol is the most common cause of cirrhosis, most hepatocellular carcinomas will arise in patient with alcohol related liver disease. In the United States, as many as 80% of hepatocellular carcinomas arise in cirrhotic livers, with alcohol as the most common underlying disease, followed by hepatitis B infection.

Patients present with abdominal pain or fullness and often have a palpable mass; jaundice, weight loss, and fever are often present. The serum alpha-fetoprotein is elevated in over 80% of patients, with massive elevations in about 60%. Serum carcinoembryonic antigen is also frequently elevated.
With the evolution of modern radiographic techniques, hepatocellular carcinomas less than 2 cm in diameter can be identified. Data from such screening studies, and the frequent presence of small incidental hepatocellular carcinomas in chronically diseased livers at the time of transplant, provide evidence that there is a variable and sometimes prolonged subclinical period in the lifespan of these tumors.

The gross appearance of hepatocellular carcinoma is extremely variable. An important point to remember is that multiple areas of involvement are quite common, and there may not be a single dominant mass (Figure 47). Failure to appreciate this point may lead to confusion with metastases. If the liver is cirrhotic, the probability of metastasis is very small. There may be a single dominant mass, with or without multiple distinct nodules, or the tumor may spread diffusely being barely distinguishable from the surrounding damaged liver. The presence of multifocal discrete nodules appears to be particularly likely to occur in hemochromatosis. The tumor with its variable gross configurations has equally varied colors and texture. A green hue due to production of bile by the tumor cells is particularly helpful (Figure 49). Golden yellow colors reflecting the presence of some fat and variable degrees of glycogen compared to the surrounding liver are particularly common (Figure 50). Hemorrhage is frequent, and may produce a red to black color. Grey indicates collagenization, or may suggest a component of cholangiocarcinoma. Tumors with a granular friable cut surface usually have prominent trabecular histologically, while soft smooth tumors tend to show a solid growth pattern. Pedunculated tumors may occur. There is also an intrabiliary growth pattern, which usually presents with hemobilia in patients with cirrhotic livers. Fibrolamellar hepatocellular carcinoma usually arises in a normal liver, commonly in the left lobe, and has a gross appearance that mimics focal nodular hyperplasia, including the presence of a central depressed stellate scar (Figure 52). It also may be pedunculated on occasion.

The histologic appearances are at least as varied as are the gross appearances. There may be striking variability within a given tumor, and thorough sampling (1 block per cm of greatest tumor diameter) should be the rule. The most characteristic pattern, present in most tumors, is the presence of trabecular architecture. There are microtrabecular (Figure 53) and macrotrabecular patterns. In the latter the trabeculae are eight or more cells thick; it is virtually diagnostic of hepatocellular carcinoma, and is particularly useful in differentiating carcinomas from adenomas (Figure 54A) (Figures 54B). Hepatocellular carcinomas are usually richly vascular. The trabeculae are covered by an endothelial lining, and the space between adjacent trabeculae is analogous to the sinusoids (Figure 54A). The next most common pattern is the presence of acinar structures, which can mistakenly be interpreted as evidence of ductal origin (Figure 55). The cells lining the acini have the abundant eosinophilic cytoplasm characteristic of hepatocytes. Bile is often present, both in lumen and tumor cell cytoplasm. This helps identify the cell of origin as hepatocyte. It is the hepatocyte that is the bile maker; bile duct cells merely form passive conduits for bile flow. Often there are combinations of trabecular and acinar architecture (Figure 56). The next most common pattern is the formation of solid sheets of cells (Figure 57). Significant collagen deposition is uncommon except in the fibrolamellar variant. What collagen is present is usually found associated with the acinar pattern. On occasion, bizarre hepatocyte giant cells may be present (Figure 58).

Fat and glycogen are frequently present in tumor cytoplasm; while this suggests hepatocyte origin, it does not provide positive proof for such origin. Likewise pale, round, eosinophilic cytoplasmic inclusions, usually PAS positive, are frequent, but not specific for hepatocellular carcinoma (Figure 59A) (Figures 59B). They have been shown on occasion to represent accumulations of alpha-1-antitrypsin or fibrinogen. Intranuclear cytoplasmic invaginations, similar to that seen in non-neoplastic hepatocytes (or in metastatic melanoma) are also frequent (Figure 60). Vascular invasion into portal vein or terminal hepatic vein can frequently be demonstrated, but is not specific (Figure 61). Proof positive of hepatocellular origin is provided by the presence within tumor cell cytoplasm of bile (Figure 56), alcoholic hyaline (Figure 62) or ground glass material (Figure 57).

Hepatocellular carcinoma is amenable to biopsy by percutaneous needle biopsy of liver (Figures 63A) (Figures 63B). Laparoscopically directed biopsies increase the yield. Fine needle aspirations often yield "micro-biopsies" rich in the friable trabecular material.
There are a number of variants of hepatocellular carcinomas that have been described. The most important of these is fibrolamellar hepatocellular carcinoma. These usually occur in otherwise normal liver, and occur in a strikingly younger age group than typical hepatocellular carcinoma, the average age of affected individuals being in the mid-twenties. Serum alpha-fetoprotein is usually normal. The distinctive gross appearance has already been described. Histologically, the tumor cells are large with abundant eosinophilic ("oncocytic") cytoplasm. Clear areas of cytoplasm referred to as pale bodies are frequent; dense PAS positive cytoplasmic inclusions may also be present. Copper is demonstrable in most tumors. Another characteristic feature is the presence of abundant connective tissue, occurring in the form of lamellations of dense collagen strands (Figure 52B). The survival rate is far better than that of typical hepatocellular carcinoma, particularly if resection with a clean margin can be accomplished.

Other variants included the so-called spindle cell carcinoma (which mimics sarcoma), clear cell variant (due to large quantities of glycogen or fat), giant cell carcinoma, and sclerosing cholangiocarcinoma. None of these share the good prognosis of the fibrolamellar variant. Finally, there are descriptions of combined hepatocellular carcinoma and cholangiocarcinoma. Care must be taken to avoid overenthusiastic interpretation of acinar areas as being of bile duct origin. Tumors with clearly identifiable hepatocellular and cholangiocarcinomatous areas are quite uncommon. Liver cell dysplasia occurs most commonly in the setting of hepatitis B. It is best recognized in cirrhotic livers, where entire nodules may be comprised of hepatocytes with significant nuclear enlargement and hyperchromatism (Figure 64A) (Figure 64B). Individual nuclei in these dysplastic foci can be indistinguishable from the striking anisonucleosis so common in the elderly, and the term dysplasia is misleading in such individuals.

**Cholangiocarcinoma** is a malignancy arising from bile duct epithelium. It is much less common than hepatocellular carcinoma, accounting for less than 10% of primary hepatic malignancies. Cirrhosis is usually not present, and predisposing factors are identified less commonly than in hepatocellular carcinoma. Such factors are present in about 20% of cases and include the following: Primary sclerosing cholangitis, ulcerative colitis, parasitic infection (Clonorchis sinensis or Opisthorchis viverrini), hepatobiliary fibropolycystic disease, Thorotrast exposure, and intrahepatic calculi. There are two broad categories of cholangiocarcinoma, peripheral and hilar. Peripheral cholangiocarcinomas are the most common, and are thought to arise from interlobular bile duct branches within the portal triads. There may be a single large mass, or multiple masses with a dominant primary focus (Figure 65A) (Figure 65B). Less commonly there is diffuse involvement of individual portal areas. The hilar tumors arise as discrete masses in the large ducts in and around the hilum (Figure 66A) (Figure 66B) (Figure 66C). A peculiar variant described by Klatskin appears as a mass at first relatively small and confined to the right or left hepatic duct. Patients with these "Klatskin tumors" may present with some combination of pruritis, fever, and jaundice (Figure 67A) (Figure 67B).

The histology of cholangiocarcinomas is that of small glandular structures which often appear deceptively bland (Figure 68). The nuclei are often quite oval and vesicular. There is characteristically a dense sparsely cellular fibrous stroma (Figure 69). There may be a papillary configuration (Figure 20). Mucin production is frequently demonstrable, and, when present, clearly excludes hepatocellular carcinoma (Figure 71). Another valuable clue to ductal origin is the presence of nuclear atypia in surrounding triads (Figure 72A). There has been much recent interest centering on immunoperoxidase methods for identifying cholangio-carcinoma. Markers such as CA 19-9 and CA-50 are said to be consistently positive in cholangiocarcinoma and negative in hepatocellular carcinoma. A polyclonal CEA tends to stain canalici; if present, this pattern is specific for hepatocellular carcinoma. Keratin staining with AE-1 is highly suggestive of bile duct rather than hepatocyte origin. Once hepatocellular carcinoma is excluded, the problem of excluding metastatic adenocarcinoma remains. This can be done in a rigorous fashion only after an autopsy has been performed. However, the diagnosis of cholangiocarcinoma can usually be made reasonably reliably based on the clinical information and characteristic histology; it is virtually certain when one of the predisposing conditions listed earlier is present (Figure 72B).
Hepatoblastoma is the most common primary malignant hepatic tumor in children. It occurs in the younger age group, being virtually unheard of after the age of three years; most occur between the age of one and two years. This helps in differentiation from hepatocellular carcinoma of childhood which occurs in an older group (average age nine years), and is usually seen in association with some metabolic abnormality such as tyrosinemia or glycogen storage disease type I. The serum alpha-fetoprotein is elevated in most cases. Such metabolic effects as osteopenia, hypoglycemia, iso-sexual precocity, and left hemihypertrophy has occurred in children with hepatoblastoma; various congenital anomalies are also common. The appearances are distinctive. The tumors are usually quite large, often up to 20 cm in diameter. The surface is quite variegated (Figure 74A) (Figures 74B). A solitary mass in a non-cirrhotic liver is most common, but multiple nodules are not unheard of. The right lobe is slightly more commonly affected. Histologically the tumors may be pure epithelial, or, less commonly, mixed (with mesenchymal elements). There are two basic epithelial subtypes (Figure 75). These are the fetal, characterized by abundant eosinophilic cytoplasm and a tendency to mimic the growth pattern of hepatocellular carcinoma with endothelial invested trabeculae. The other type is the embryonal, with basophilic cytoplasm and a higher nuclear to cytoplasmic ratio. The mesenchymal element is usually osteoid or chondroid, with the former being the most common (Figure 76). At times the mesenchyme is represented by spindled cells with no definite differentiation. Extramedullary hematopoiesis is frequent, and is usually found juxtaposed to tumor with the fetal cell type.

Undifferentiated sarcoma, also known as embryonal sarcoma or mesenchymal sarcoma, is one of the more frequent primary malignant hepatic neoplasms in childhood. Most children are between six and ten years of age when diagnosed. Rarely the tumor arises in older children and even adults. By definition, there is no overt differentiation towards any specific mesenchymal element. Tumors are huge and solitary, usually occurring in an otherwise normal liver (Figure 77). Hemorrhage and cyst formation is common. There is often a thick fibrous pseudocapsule. The myxoid stroma may contain widely scattered nests of bile ducts and even hepatocytes. The more densely cellular stromal areas usually contain mesenchymal cells that exhibit significant nuclear hyperchromatism (Figure 78). Scattered large pleomorphic neoplastic cells are present. A highly characteristic feature is the presence of eosinophilic spherical PAS positive inclusions (Figure 79). A relationship to mesenchymal hamartoma has been suggested but remains unproven.

Angiosarcoma is relatively uncommon, but remains the most common primary malignant mesenchymal tumor of liver. There is a distinct male predominance. There is often a history of chemical or radiation exposure, with Thorotrast, vinyl chloride and arsenicals being commonly reported. Rarely these tumors complicate hemochromatosis. There is usually a diffuse distribution of multiple nodular areas throughout the liver. There may be an obvious vascular (cavernous) character on the capsular (Figure 80A) or cut surface (Figure 80B). The histology varies from solid to cavernous areas. The most recognizable feature is the presence of highly pleomorphic endothelial cells lining the sinusoids at the periphery of the more solid areas. Vascular invasion is common. Cirrhosis may co-exist. The prognosis is exceedingly bleak. Epithelioid hemangioendothelioma is a clearly malignant lesion despite its innocuous name. It closely resembles its namesake in soft tissue and lung; its prognosis is intermediate between the two. There is a distinct female predominance, and there is some evidence to support a relationship to oral contraceptive usage. There is also some suggestion that the lesion may be related to exposure to vinyl chloride or arsenicals. The usual appearance is that of a dense pale fibrotic mass (Figure 82); satellite nodules may be present. Calcification is frequent. Early lesions may be deceptively bland (Figure 83). Densely fibrotic areas may contain remnants of portal areas. These fibrotic areas are sparsely cellular but contain scattered elongated cells with vacuolated cytoplasm (Figure 84). At the periphery of these dense areas the sinusoids may contain pleomorphic endothelial cells in a fashion reminiscent of angiosarcoma (Figure 85). Because of the sinusoidal involvement, residual hepatocyte cords atrophy and become surrounded by fibrous tissue (Figure 86). Larger vessels are frequently invaded by the pleomorphic cells (Figure 87). Many of these lesions have been previously misdiagnosed as sclerosing cholangiocarcinoma.
Attention to clinical and histological details should avoid this pitfall; in difficult cases, reactivity of these tumor cells with antibody to Factor VIII is helpful.

**Kaposi’s sarcoma** not infrequently involves the liver in patients with AIDS. It is uncertain whether these lesions represent metastases or multicentric primaries. Multiple small nodules, usually but not necessarily hemorrhagic, are present. The histology is similar to that of Kaposi’s elsewhere (Figure 88) (Figure 89).

**Miscellaneous** malignant tumors of a wide variety have been reported to arise in liver. They are all exceedingly rare. Carcinoids apparently primary in liver are thought to arise from the widely scattered neuroendocrine cells normally present. They must be distinguished from the occasional hepaticocellular carcinoma which may have focal areas exhibiting neuroendocrine differentiation. One must exclude metastases from carcinoids of more typical sites of origin. These bulky tumors appear in non-cirrhotic livers. The histology is similar to that of carcinoids from other sites. Teratomas occasionally arise in liver; this typically occurs in the first year of life. Likewise, the occasional yolk sac tumor arising in liver has been reported in childhood. Young women may very rarely develop a malignant trophoblastic tumor, presumably derived from ectopic germ cell tissue. A variety of sarcomas similar to those seen in other sites may originate in liver; this includes leiomyosarcomas, fibrosarcomas, liposarcomas, malignant fibrous histiocytomas, osteosarcomas, rhabdomyosarcomas, malignant Schwannomas, and primary lymphomas. The most commonly encountered of these are leiomyosarcomas (Figure 90).

**Metastasis** is far and away the most common malignancy involving the liver. Metastatic tumors outnumber primary tumors by 15-20 to one in most series. Virtually any tumor can metastasize to liver. The frequency of given primary sites will vary from one geographic locale to another, reflecting the differences in regional cancer epidemiology (Figure 91). Colon, lung, pancreas, and breast are the most common primaries encountered in clinically obtained liver biopsies in most areas of the United States. The access to the portal venous system is an important factor in determining the frequency of metastasis. For this reason, a much higher percentage of neoplasms of colon, pancreas, and gallbladder metastasize to liver than is true of neoplasms from other primary sites. Neoplasms without direct access to the portal venous system that seem to have a particular propensity for metastasizing to liver include: breast, melanoma (particularly ocular), testis, and lymph nodes. Sampling is key, and two passes should be made if percutaneous biopsies are employed. Laparoscopically directed biopsies will increase the yield.

Patients with metastases may have no clinical symptoms. Hepatomegaly can be massive, but is not always present. Except for tumors involving the biliary tree directly, jaundice is a late occurrence. Usually 60% or more of the liver is replaced in jaundiced patients. An exception to this is the patient with Hodgkin’s disease, who may develop jaundice in the absence of biliary tree and hepatic involvement by tumor.

Typically, metastases present as multiple variably sized masses in the liver; peripheral hyperemia and central umbilication are characteristic of these masses (Figure 92). Colon carcinoma will frequently produce a single large mass amenable to resection (Figure 93); unfortunately, all too often, careful examination reveals small satellite nodules. Hemorrhage may be prominent, particularly in renal carcinoma, thyroid carcinoma, chorionicarcinoma, melanoma, angiosarcoma, and Kaposi’s sarcoma.

The histology varies greatly depending on the primary site. The pathologist cannot usually identify the primary with certainty from the histologic appearance. The statement as to whether or not a given metastasis is consistent with a presumed clinical primary can usually be made. In the absence of a known primary, the experienced surgical pathologist can and should significantly narrow the differential diagnosis. A primary site can often be suggested with a high degree of accuracy. A variety of histological clues help in this process (Figure 94) (Figure 95) (Figure 96) (Figure 97) (Figure 98) (Figure 99) (Figure 100). Mucin production is expected to be prominent with colon primaries. Small cell undifferentiated carcinomas and melanomas infiltrate sinusoids and may be inapparent; melanin pigment and HMB-45 positivity help to identify the latter. Desmoplasia is usually prominent with pancreatic, biliary tree, and gastric primaries.
At times, the tumor is missed when the biopsy is obtained. The liver near large masses of tumor shows characteristic changes. There is variability from one triad to the next, with some triads showing duct proliferation, edema, and inflammation in a pattern similar to that seen in biliary obstruction. Adjacent triads may be normal. Likewise, the central veins present a variable picture, with some appearing to show evidence of outflow obstruction and their neighbors being normal. This probably reflects the variable impingement by tumor on intrahepatic branches of the biliary and vascular systems.

A final important practical note deals with the fact that metastases go to cirrhotic livers with the utmost rarity. A neoplasm in a cirrhotic liver should be considered to be primary in liver until clearly proven otherwise.

## Table 1: Benign Tumors and Tumor-like Conditions of Liver

Frank A. Mitros, M.D.
Peer Review Status: Internally Peer Reviewed

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Atlas of Liver Pathology: Chapter 11: Tumors of Liver
Figure 2: Multiple cysts are visible on cut surface of liver; the cyst walls are thin, translucent, and grey. This is from a case with polycystic disease; note the small green bile duct hamartomas in the surrounding liver (photograph courtesy of Chris Reuter, M.D.).

Figure 3: The wall of this simple cyst is composed of a thin layer of fibrous connective tissue; the surrounding liver is unremarkable (X10).
Figure 4: The typical cuboidal lining of a simple cyst bears only slight resemblance to biliary epithelium; rarely the lining may be columnar or even squamous (X80).

Figure 5: Polycystic liver and kidney disease at autopsy; the liver was completely normal functionally (photograph courtesy of Chris Reuter, M.D.).

Figure 6: One of the locules of a hepatobiliary cystadenoma with mesenchymal stroma; the smooth lining must be searched carefully for nodules.
Figure 7: The typical columnar lining overlying the ovarian-like mesenchymal stroma (X33).

Figure 8A: This huge choledochal cyst in a young adult affected much of the extrahepatic biliary tree.

Figure 8B: The interior of the cyst was roughened due to inflammation; the intact areas were lined by biliary epithelium.
Figure 8C: The wall of the cyst is bland fibrous tissue with widely scattered smooth muscle cells (X10).

Figure 8D: The columnar lining of the choledochal cyst is biliary in character (X100).

Figure 9A: The large size of the liver and cystic nature of the mesenchymal hamartoma are readily evident in this lesion discovered at autopsy (photograph courtesy of C.E. Foucar, M.D.).
Figure 9B: Cut surface of the tumor emphasizes its cystic nature (photograph courtesy of C.E. Foucar, M.D.).

Figure 10: Highly characteristic histology of a mesenchymal hamartoma with sparse cellularity, edema, and poorly defined cystic spaces (X2.5).

Figure 11: A 25 cm mesenchymal hamartoma from a 3 year old; cystic change is less pronounced than usual. The patient recovered uneventfully after lobectomy (photograph courtesy of T.H. Kent, M.D.).
Figure 12A: The junction with the surrounding liver is not sharp (X2.5).

Figure 12B: Small branching duct-like structures are present at the periphery of the lesion; scattered stellate cells are present in the mesenchymal matrix (X20).

Figure 13: Scattered islands of ducts and hepatocytes in the mesenchymal matrix (X10).
Figure 14: Massive hepatomegaly was noted by the mother in this 3 month old; despite this appearance on scan, the child has done well with conservative management.

Figure 15: The vascular nature of this hemangioendothelioma was not immediately apparent; closer examination reveals a subtle "spongy" appearance.
**Figure 16A:** There is a sharp demarcation with the surrounding liver; scattered ducts are mixed with the vascular channels (Klatskin, X4).

**Figure 16B:** Scattered larger vascular spaces, some more cavernous in appearance, may be present, particularly near the center of the lesion (X10).

**Figure 16C:** The endothelial lining of the vascular spaces is quite bland in this Type I lesion (X100).
Figure 17: Multiple cavernous hemangiomas in a young woman with episodic abdominal pain; white tissue in the largest lesion represents fibrosis indicating some degree of involution.

Figure 18: The honeycomb appearance and vascular nature of this giant cavernous hemangioma are readily apparent from the capsular surface.

Figure 19A: Hemangioma showing characteristic sharp demarcation from the surrounding liver and "spongy" texture.
Figure 19B: The cut surface of this hemangioma varies from honeycomb to spongy to fibrotic (photograph courtesy of S. Goetz, M.D.).

Figure 20: A: Large cavernous vascular spaces are readily evident (Klatskin, X10). B: The endothelial lining is flat; endothelial nuclei are inapparent. The boundary with surrounding parenchyma is sharp (X50).
**Figure 21:** The characteristic appearance of peliosis: multiple variably sized blood filled spaces at autopsy.

**Figure 22:** Recent hemorrhage seems to have formed these blood filled spaces which lack a lining (X8).

**Figure 23:** Sinusoidal dilatation and thrombosis in a case of peliosis; some feel that the primary deficit is a weakening of the sinusoidal lining (X100).
Figure 24: The spongy vascular component predominates over the yellow adipose component in this angiomyolipoma.

Figure 25: Characteristic admixture of the mature elements in a hepatic angiomyolipoma (X10).
Figure 26: A: The inflammatory mass compromising this pseudotumor is fairly well demarcated from the adjacent normal liver (X2.5). B: Plasma cells, lymphocytes, and spindled fibroblasts in a typical array in this pseudotumor (X100).

Figure 27: Benign pancreatic acinar tissue in the connective tissue allows for ready identification of this pancreatic nest (X25).

Media By Chapter: Epithelial Tumors
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Figure 28A: Multiple bile stained bile duct hamartomas are visible through Glisson's capsule.
Figure 28B: Multiple bile stained bile duct hamartomas are visible through Glisson’s capsule.

Figure 29: Classic von Meyenberg complex was biopsied during a colectomy for colon carcinoma; note residual portal triad structure deeper in the liver (X25).

Figure 30: The epithelial lining is benign and clearly biliary; note the unusual "animal-like" contours (X40).
Figure 31: One of several biliary hamartomas found incidentally. The degree of dilatation of one of the spaces is striking giving a hint of evolution towards becoming a simple cyst (X12).

Figure 32A: Typical bile duct adenoma, some 0.7 cm in diameter, is sharply demarcated from the surrounding parenchyma (X4).

Figure 32B: The demarcation is accentuated by the trichrome stain; several triads can be seen in the background within the adenoma (Klatskin, X5).
Figure 33A: The uniform dispersion of ducts in the stroma is evident (X16).

Figure 33B: The resemblance to interlobular bile ducts is striking in this adenoma, in contrast to the dilated structures seen in hamartoma. The bland fibrous stroma is infiltrated by mature lymphocytes and plasma cells (X100).

Figure 34A: The mature collagen in the stroma and the thickened basement membrane around the ducts are usually present (A-Klatskin, X100; B-PAS with diastase, X40).
**Figure 34B:** The mature collagen in the stroma and the thickened basement membrane around the ducts are usually present (A-Klatskin, X100; B-PAS with diastase, X40).

**Figure 35:** Hybrid lesion of bile duct adenoma and hamartoma; a large solitary circumscribed nodule, but with dilated ducts (X4).

**Figure 36:** Sharply demarcated hepatic adenoma, which is somewhat paler than the surrounding liver; there is an area of fresh hemorrhage, as well as some fibrosis from earlier episode of hemorrhage.
Figure 37: The hemorrhagic area represents the peliosis like change commonly seen in estrogen related adenomas (X3.3).

Figure 38: A cordal architecture is evident in the bland hepatocytes of this adenoma; note the "free-floating" arterial vessel (X60).

Figure 39: The prominent acini throughout characterize this adenoma in a patient with Fanconi’s anemia treated with anabolic steroids (X100).
Figure 40: This estrogen related adenoma, benign histologically, replaced much of the liver, leading to the patient’s demise.

Figure 41: A classic focal nodular hyperplasia, paler than the surrounding liver, and with a distinct central stellate scar.

Figure 42A: The bands of fibrosis impart an appearance mimicking that of macronodular cirrhosis (Klatskin, X5).
Figure 42B: Note the large thick walled artery at the edge of the stellate scar (Klatskin, X10).

Figure 43A: Hepatocytes in the lesion resemble those of normal liver, but there is architectural disorganization mimicking cirrhosis (X8).

Figure 43B: Some duct-like structures are present adjacent to the fibrous tissue (PAS-d, X33).
Figure 44: The pale tan discrete nodules of nodular regenerative hyperplasia have been mistaken for cirrhosis or even metastatic carcinoma.

Figure 45A: Several nodules are evident; the hepatocytes within the nodules are paler than the compressed hepatocytes between the nodules (X10).

Figure 45B: There are no fibrous bands between nodules, and normal triads and central veins are recognizable (Klatskin, X10).
Figure 46: Compression of hepatocytes between adjacent nodules is readily recognizable (X40).

- Hepatocellular carcinoma
- Cholangiocarcinoma
- Hepatoblastoma
- Sarcomas
  - Undifferentiated (Embryonal)
  - Angiosarcoma
  - Epithelioid hemangioendothelioma
  - Kaposi's
- Miscellaneous
- Metastases

Figure 47: Table 2: Classification of Malignant Tumors of Liver

Figure 48: Multiple irregular green areas of hepatocellular carcinomas are present throughout this cirrhotic liver.
Figure 49: A 2.0 cm hepatocellular carcinoma arising in a chronic viral hepatitis; the tumor, which had a predominant acinar architecture, produced abundant bile.

Figure 50: Nodule of hepatocellular carcinoma in chronic hepatitis C; the pale golden yellow color is common.

Figure 51: This hemorrhagic red hepatocellular carcinoma expanded the biliary tree.
Figure 52A: Well demarcated fibrolamellar carcinoma with central scar; the surrounding liver is normal.

Figure 52B: Coarse lamellar fibrosis is characteristic histologically; note the pale body in the large eosinophilic malignant hepatocyte (X40).

Figure 53: A well differentiated hepatocellular carcinoma secondary to hepatitis B with a prominent microtrabecular pattern (X25).
**Figure 54A:** Broad macrotrabeculae cut longitudinally; note the endothelial lining ensheathing the trabeculae (X40).

**Figure 55:** Prominent large acinar structures lined by malignant hepatocytes; bile is present within the lumen. Some macrotrabeculae are present (1 X100).

**Figure 56:** The pattern of small acini and microtrabeculae merge imperceptibly; note the prominent bile formation (X66).
Figure 57: The solid or compact pattern of hepatocellular carcinoma; note the presence of ground glass material in a number of the tumor cells (X50).

Figure 58: Bizarre tumor giant cell in a hepatocellular carcinoma; the character of the cytoplasm resembles that of the hepatocyte (X160).

Figure 59A: Eosinophilic round cytoplasmic inclusions are seen frequently in hepatocellular carcinomas (X100).
**Figure 59B:** The inclusions, which may represent a number of different proteins, are best recognized on PAS staining with diastase digestion (PAS-d, X100).

**Figure 60:** Prominent sharply demarcated nucleoli, cytoplasmic intranuclear invagination, and granular eosinophilic cytoplasm are highly characteristic (but not diagnostic) for hepatocellular carcinoma (X100).

**Figure 61:** The portal triads and central veins from this case of hepatocellular carcinoma were riddled with tumor showing a microtrabecular pattern (Klatskin, X40).
Figure 62: Alcoholic hyaline is present in tumor cells in from 4% up to 20% of hepatocellular carcinomas; it may occur in the absence of alcohol related liver disease (X160).

Figure 63A: The architectural distortion due to cirrhosis is evident; at one end the tissue appears quite fragmented (X8).

Figure 63B: The presence of macrotrebecular architecture in this fragmented area allowed for establishing the diagnosis of hepatocellular carcinoma (X40).
Figure 64A: Dysplasia characterized by large groups of abnormal cells (X10).

Figure 64B: Nuclear atypia is evident in the dysplastic focus to the left (X25).

Figure 65A: Peripheral cholangiocarcinoma secondary to remote Thorotrast exposure; a dominant mass replaces the entire left lobe, while the multiple secondary nodules in the right lobe mimic metastasis.
Figure 65B: The plain film of the abdomen still reveals residual Thorotrast in the spleen and peripancreatic lymph nodes.

Figure 66A: This hilar cholangiocarcinoma presented with jaundice in a young man.
Figure 66B: The polypoid lesion within the hepatic duct was bosselated; minimal invasion was present at the point of attachment to the duct.

Figure 66C: Several larger triads within the liver were expanded and fibrotic; tumor was present within the ductal system, but was not invasive.

Figure 67A: Tumors of the hilar region can mimic benign diseases such as primary sclerosing cholangitis; the stent in this patient was to no avail (photograph courtesy of Tim Greiner, M.D.).
Figure 67B: A malignant stricture caused by tumor encasing the hepatic ducts as they ramify through the liver (photograph courtesy of Mike Laszewski, M.D.)

Figure 68: Needle biopsy of cholangiocarcinoma, with normal liver adjacent to malignant glands; at this point, it would be impossible to exclude metastatic adenocarcinoma (X16).

Figure 69: The dense stroma in response to a glandular tumor with relatively little pleomorphism is a clue to the diagnosis of cholangiocarcinoma (X40).
Figure 70: The cholangiocarcinoma seen in Figure 66; note the papillary areas and vesicular nuclei (X50).

Figure 71: The mucin positivity in this hilar cholangiocarcinoma reflects the mucin production by the non-neoplastic duct epithelium from which the tumor arose (Mucicarmine, X50).

Figure 72A: Interlobular bile duct with atypia in a Thorotrast related peripheral cholangiocarcinoma (X160).
Figure 72B: Autoradiograph demonstrating continued emission from Thorotrast deposited many years earlier in the connective tissue of this triad (X160).

Figure 73: Clonorchis sinensis ensconced in a duct near the hepatic hilus; note the adjacent duct proliferation, a probable precursor to cholangiocarcinoma (X4).

Figure 74A: This mixed hepatoblastoma presented with massive hepatomegaly due to the huge size of the tumor occurring in this otherwise normal liver.
Figure 74B: The marked variability of the cut surface with areas of hemorrhage is particularly likely to be seen in the mixed forms.

Figure 75: The fetal and embryonal cell types are closely admixed here; the former is making some microtrabeculae (X25) (photograph courtesy of Bill Walker, M.D.).

Figure 76: Osteoid, embryonal, and fetal cell types are all present in this mixed hepatoblastoma (X16).

Figure 77: Multiple areas of hemorrhage, a slimy myxoid texture, and a thick pseudocapsule characterize this undifferentiated sarcoma.
**Figure 78:** Striking pleomorphism in undifferentiated mesenchymal cells in a loose myxoid stroma (X160).

**Figure 79:** Multiple spherical PAS positive inclusions associated with a pleomorphic giant cell (X100).

**Figure 80A:** Bulging purple nodules of angiosarcoma are visible through Glisson’s capsule.
Figure 80B: Cut surface reveals multiple indistinct foci of tumor, some with a “cavernous” appearance; the surrounding liver is cirrhotic.

Figure 81: The pleomorphism of the sinusoidal endothelial cells is striking; these, and tumor cells in more solid areas, marks well with the usual histological markers for endothelium (X100).

Figure 82: Typical epithelioid hemangioendothelioma in an explanted liver; the patient is alive 15 years after transplant despite the presence of pulmonary and duodenal metastases discovered at the time of transplant.
Figure 83: A confident diagnosis of malignancy could not be made on this sparsely cellular nodule. This is the patient whose liver is seen in Figure 82; the biopsy was obtained five years prior to the transplant (X3).

Figure 84: The densely cellular areas contained scattered vacuolated cells; the vacuoles are a clue to the vascular nature. Nuclear pleomorphism is minimal; nucleoli tend to be prominent (X500).

Figure 85: Pleomorphism is evident in many of the sinusoids; a loose connective tissue proliferation is associated with the tumor cells (X100).
**Figure 86:** Only a few hepatocyte cords remain intact; the diffuse nature of the process may mislead one into considering hepatic parenchymal disease rather than neoplasm (X13).

**Figure 87:** Tumor cells are forming small clusters in sinusoids and in the central vein (X50).

**Figure 88:** Hemorrhagic nodules of Kaposi’s sarcoma are frequently found related to portal triads (X2.5).
Figure 89: The slit like spaces between bland spindled neoplastic cells and the extravasated red blood cells are characteristic for Kaposi’s; note the residual bile ducts (X50).

Figure 90: Leiomyosarcomas can arise in liver, and present as bulky tumors. Appearances resemble leiomyosarcomas elsewhere, as seen in this well differentiated lesion. Metastases must be carefully excluded (X33).

- Colon
- Lung
- Pancreas
- Breast
- Gastric
- Gallbladder
- Prostate
- Melanoma

Figure 91: Table 3 - Sources of hepatic metastases.
Figure 92: Multiple confluent nodules with central umbilication and peripheral hyperemia are classic for metastasis to liver; the primary here was a breast carcinoma.

Figure 93: This large solitary metastatic nodule was from a colon primary; the glairy cut surface represents a high mucin content.

Figure 94: Classic histology of metastatic colon carcinoma: garlands of cribriform mucin producing glands with central necrosis (X20).
Figure 95: The presence of significant cellular atypia in structures that suggest pre-existing interlobular bile ducts is a valuable clue that the primary is in the pancreatico-biliary tree. Note the desmoplasia (X100).

Figure 96A: Small cell undifferentiated carcinoma of lung usually presents with massive deposits of tumor on needle biopsy (X5).

Figure 96B: The characteristic histology with prominent crush artifact and a tendency to fill the sinusoids are characteristic for small cell undifferentiated carcinoma (X100).
**Figure 97:** Melanoma also tends to fill sinusoids and hide among liver cells. The abundant cytoplasm and prominent nucleoli may mimic hepatocellular carcinoma. If the primary is ocular, the history may not be evident, since there is often a five to ten year interval from original surgery to metastasis (X50).

**Figure 98A:** Carcinoids also elicit a desmoplastic response; the pseudoglandular architecture may result in misdiagnosis as bile duct adenoma or adenocarcinoma (X10).

**Figure 98B:** An argyrophil stain readily reveals the true neuroendocrine nature of metastatic carcinoid tumors (Grimelius, X100).
**Figure 99A:** The liver in chronic lymphocytic leukemia and well differentiated lymphocytic lymphoma shows almost exclusively portal involvement (X10).

**Figure 99B:** The involvement in CLL is more robust and symmetric than the lymphoid infiltrate in chronic persistent hepatitis (X40).

**Figure 100A:** Both triads and lobules are involved in the non-lymphocytic leukemia (X10).
Figure 100B: Immature myeloid cells are seen to permeate the sinusoids at higher power (X100).

Figure 101: Patients with Hodgkin's disease may have nonspecific portal infiltrates; the diagnosis of liver involvement cannot be made until a Reed-Sternberg cell is identified (X100).