Fifth Edition

First Principles of Gastroenterology

The Basis of Disease and an Approach to Management

JANSSEN-ORTHO

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The Biliary System

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1. GALLSTONE DISEASE

Gallstones (cholelithiasis) are the most common cause of biliary tract disease in adults, afflicting 20-30 million persons in North America. Approximately one-fifth of men and one-third of women will eventually develop cholelithiasis. In Canada, calculous disease of the biliary tract is also a major health hazard, accounting for about 130,000 admissions to hospital and 80,000 cholecystectomies annually. Cholecystectomy is the second most common operation in Canada and the United States, where it is performed six to seven times as often as in the United Kingdom or France. Although the frequency of gallstone disease does vary between countries and regions, it is high in both Western Europe and North America (Table 1). Laparoscopic cholecystectomy has further increased the use of surgery. Such variance suggests overuse of our health-care system, particularly as few (20%) individuals with cholelithiasis ever become symptomatic.

1.1 Classification of Gallbladder and Bile Duct Stones

Two major types of gallstones exist (Table 2).

1. *Cholesterol stones* are hard, crystalline stones that contain more than 50% cholesterol plus varying amounts of protein and calcium salts. They predominate (> 85%) in the Western world.
2. *Pigment stones* consist of several insoluble calcium salts that are not normal constituents of bile.

TABLE 1. Frequency of gallstone disease in different countries

Very common (30–70%)	*Common (10–30%)*	*Intermediate (< 10%)*	*Rare (< 0%)*
American Indians	United States (whites)	United States (blacks)	East Africa
Sweden	Canada (whites)	Japan	Canada (Inuit)
Chile	Russia	Southeast Asia	Indonesia
Czechoslovakia	United Kingdom	Northern India	West Africa
United States (Hispanics)	Australia	Greece	Southern India
	Italy	Portugal	
	Germany		

TABLE 2. Classification of gallstones

		Pigment	
Characteristic	*Cholesterol*	*Black*	*Brown*
Composition	Cholesterol	Pigment polymer Calcium salts (phosphates, carbonates)	Calcium bilirubinate Calcium soaps (palmitate, stearate)
Consistency	Crystalline	Hard	Soft, greasy
Location	Gallbladder +/– common duct	Gallbladder Bile ducts	Common duct
Radiodensity	Lucent (85%)	Opaque (50%)	Lucent (100%)
Clinical associations	Metabolic Cirrhosis	Hemolysis	Infection Inflammation Infestation

1.2 Basis for Gallstone Formation

1.2.1 CHOLESTEROL STONES

Cholesterol gallstones form in three stages (Figure 1).

1.2.1.1 Chemical stage (Supersaturation of bile with cholesterol)
Bile, though mainly water, is secreted by the liver but can become supersaturated with cholesterol, a lipid that is virtually water insoluble. The bile that initially forms in the canaliculus contains unilamellar vesicles of lecithin and cholesterol. Bile salts meanwhile self-aggregate, forming simple micelles in the canaliculus. As bile flows along the biliary system and becomes more concentrated, these bile salts begin to solubilize the lecithin, from the vesicles forming mixed micelles. The lecithin, so incorporated, expands the solubiliz-

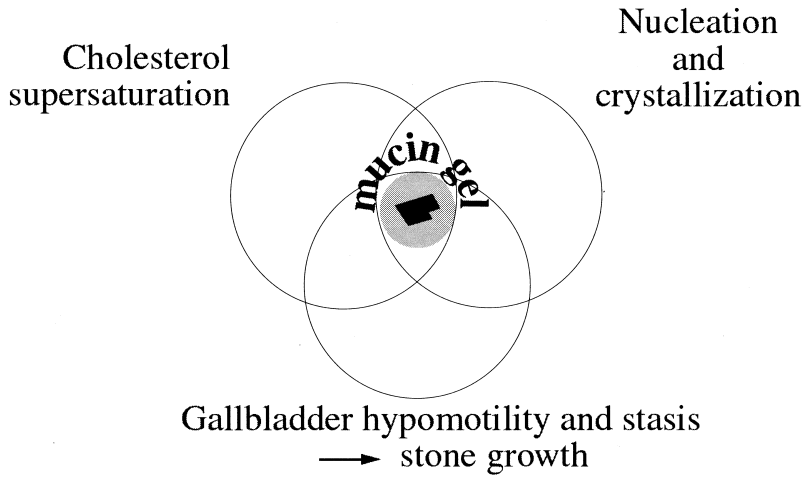

FIGURE 1. Key events in cholesterol gallstone formation, expressed as a Venn diagram. Excess cholesterol secretion causes bile to become supersaturated. This results in the production of pronucleating proteins (including mucins), which precipitate cholesterol microcrystals (shown as a notched rhomboid). Excessive bile cholesterol also becomes incorporated into the sarcolemma of smooth muscle cells, lessening gallbladder contractility. The resultant stasis traps the microcrystals of cholesterol in a mucin gel, allowing them to agglomerate, attract other insoluble components of bile (such as bile pigment and calcium), become biliary sludge and grow into overt gallstones.

ing capacity of the bile salt micelles (now termed mixed micelles) and incorporates cholesterol. The unilamellar vesicles take on more cholesterol, forming large multilamellar vesicles. Such abnormal bile thus contains an excess of cholesterol relative to the solubilizing agents, bile salts and the phospholipid lecithin. In cholesterol gallstone disease, with excess cholesterol the solubilizing capacity of vesicles and micelles becomes overwhelmed. Cholesterol then can precipitate from the multilamellar vesicles.

The cholesterol content of bile depends upon: 1. The flux of bile salts across the hepatocyte into bile (its secretion rate); 2. The detergent property of the bile salt type – highly detergent bile salts like deoxycholic acid extract more cholesterol from the canalicular membrane and unilamellar vesicles, and 3. The cholesterol, contained in the canalicular membrane, is derived predominantly from HDL cholesterol ester. The uptake of cholesterol by the hepatocytes also contributes to the free intrahepatic cholesterol pool. This provides the source of cholesterol, which is destined for secretion into bile.

This stage, in which bile becomes supersaturated with cholesterol, may develop as early as puberty and is often associated with obesity. Supersaturated bile results from excessive cholesterol secretion (as in diabetes or obesity), a decrease in bile salt secretion (e.g., ileal disease or loss) or in export of lecithin (e.g., a mutation of the MDR3 gene responsible for lecithin transport) (see Chapter 13: The Liver: Liver Structure and Function). This gene mutation causes a form of progressive familial intrahepatic cholestasis (PFIC-3) and cholesterol gallstone formation. The heterogeneous mutation presents in adulthood with stones and intrahepatic cholestasis of pregnancy.

1.2.1.2 Physical stage

This physical stage (nucleation) involves the excess cholesterol precipitating out of solution as solid microcrystals. The source is phospholipid vesicles that have become highly enriched with cholesterol and thermodynamically unstable, forming multilamellar vesicles. A nucleating factor (e.g., mucin, fibronectin, α1-globulin) secreted in bile hastens this relatively rapid precipitation. Conversely, there may be a deficiency of antinucleating factors (such as apolipoproteins A-I or A-II).

1.2.1.3 Gallstone growth

In this final stage, the cholesterol microcrystals precipitated from bile in the gallbladder are retained and aggregate and grow into macroscopic stones. Retention occurs in the gallbladder because the epithelium in stone-formers secretes excess mucus (consisting of mucin, a glycoprotein). This mucus gel also forms a colloidal mesh that entraps cholesterol microcrystals, preventing them from being ejected from the gallbladder. Mucin also creates a scaffold for the addition of more crystals. Furthermore, the excess cholesterol in bile accumulates in the sarcolemma and causes a defect in signal-transduction, impairing the contractile function of the gallbladder smooth muscle and resulting in its failure to properly evacuate the solid material. Another motility defect is slowed intestinal transit. This allows the bacterial transformation of cholic acid to the secondary bile acid, deoxycholic acid, a hydrophobic bile acid that enhances cholesterol secretion and may help trigger crystal precipitation.

"Biliary sludge" consists of calcium bilirubinate (formed from bilirubin), cholesterol microcrystals and mucin. On abdominal ultrasound, biliary sludge is echogenic material that layers but does not cast an acoustic shadow (unlike gallstones). Sludge develops in association with conditions causing gallbladder stasis, such as during pregnancy or total parenteral nutrition. Though frequently asymptomatic and prone to disappear, sludge in the gallbladder can produce biliary-type pain (or even pancreatitis) and progress to overt gallstones.

TABLE 3. Risk factors for gallstone formation

Factor	*Pigment stone*	*Cholesterol stone*
Demography		
Race	Asian	American Indian
Female sex	?	++
Age	+	++
Familial	Hemoglobinopathies	++
Diet	+	Obesity (high calorie) Weight reduction High animal fats Low fiber
Gallbladder stasis	+ Total parenteral nutrition	++ Reduced meal frequency Vagotomy Pregnancy
Female sex hormones		
Parity/fertility	—	Early menarche
Oral contraceptives	—	+
Estrogens	—	+
Associated disease	Cirrhosis Hemolytic anemia Biliary infections	Cystic fibrosis Ileal disease or loss Diabetes mellitus
Drugs	Clofibrate	

++ = definite; + = probable; ? = questionable; — = unknown

1.2.2 PIGMENT STONES

In North America, black pigment stones constitute about 15% of gallstones found at surgery (cholecystectomy). They are frequently associated with hemolysis or alcoholic cirrhosis (Table 3). These small, hard gallstones are composed of calcium bilirubinate as a polymer plus inorganic calcium salts (e.g., $CaCO_3$, $CaPO_4$). The basis for their formation is excessive (or abnormal) bilirubin excretion in bile. They tend to form in alcoholic patients, chronic haemolytic states and with old age. Curiously, this also occurs with bile salt malabsorption. When ileal disease or loss causes bile salts to escape into the colon (especially the caecum) in large quantities, this biological detergent can then solubilize bilirubin pigment and return it via the portal vein to the liver. This creates an enterohepatic circulation for pigment material whose excessive secretion into bile can then cause black pigment stones.

Brown pigment stones, soft and greasy, are composed of bilirubinate and fatty acids (calcium palmitate or stearate). The greasy texture comes from bacterial production of fatty acids from palmitic and stearic acid. These brown stones form in bile ducts in association with stagnation, inflammation, infection (often from a stricture or tumor) or parasitic infestation (e.g., liver flukes) of the biliary tract. Such conditions predispose to chronic cholangitis and eventually cholangiocarcinoma. Infection and inflammation increase ß-glucuronidase, an enzyme that deconjugates bilirubin; the resultant free bilirubin then polymerizes and complexes with calcium, forming calcium bilirubinate in the bile duct system.

1.3 Natural History of Gallstone Disease

Gallstones grow at about 1-2 mm per year over a five- to 20-year period before symptoms develop. They frequently are clinically "silent," being incidentally detected on routine ultrasound performed for another purpose. Most people (80%) with gallstones never develop symptoms. Problems, if they do occur, usually arise in the form of biliary pain during the first five to 10 years. Complications are from stones in the gallbladder:

1. Obstructing the cystic duct, leading to cholecystitis: this begins as a chemical inflammation and later may become complicated by bacterial invasion; or
2. Passing out of the gallbladder into the common duct, causing biliary obstruction (cholestasis), sometimes accompanied by bacterial infection in the ductal system (cholangitis) (Figure 2).

1.4 Clinical Features

Biliary colic pain ensues when an obstructing stone causes sudden distension of the gallbladder and/or the biliary tract. "Colic" is a poor term, as biliary pain typically does not increase and decrease spasmodically. Rather, the right upper quadrant or epigastric pain begins rather suddenly, quickly becomes intense, remains steady for 15 minutes to some six hours and then gradually disappears over 30 to 90 minutes, leaving a vague ache. Its duration is seldom shorter than 15 minutes and is often sufficiently severe for most to seek medical attention and may require narcotics for relief. Although biliary-type pain can follow a large meal, the old adage, "fatty food intolerance," is not specific for biliary tract disease. Mediated by splanchnic nerves, biliary pain may radiate like angina to the back, right scapula or shoulder tip, down the arm or into the neck. The pain may also, rarely, be confined to the back. Analgesics are usually required for relief. Episodes of pain occur irregularly, separated by pain-free periods lasting from days to years. The severity of pain also varies.

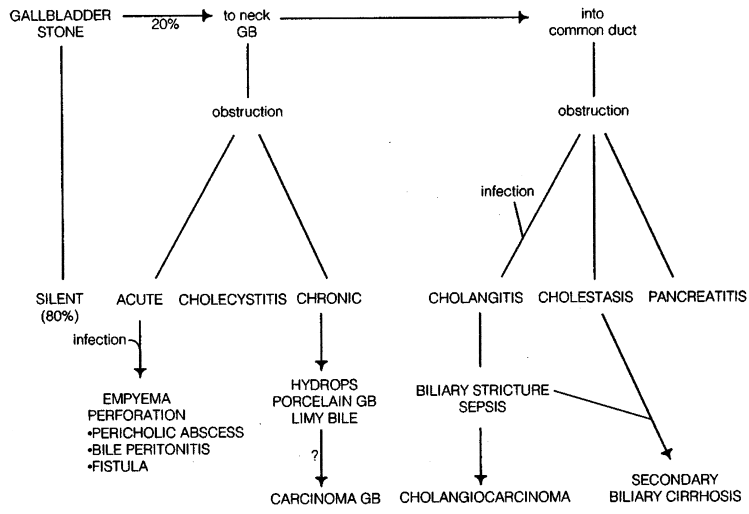

FIGURE 2. Potential complications of cholelithiasis. Migration of the stone in the gallbladder to impact in the neck of the gallbladder or the bile duct can cause obstruction and result in complications. Cystic duct obstruction results in cholecystitis. Chronic calculous cholecystitis may be associated with carcinoma of the gallbladder, but causality is unproven. Common duct obstruction leads to cholangitis, cholestatic jaundice and/or pancreatitis. Chronic cholestasis results in malabsorption. Stricture formation and recurrent cholangitis on occasion can lead to secondary biliary cirrhosis. Chronic duct obstruction and injury may lead to cholangiocarcinoma.

A visceral pain, biliary colic is not aggravated by movement but is deep-seated. The patient is usually restless and may exhibit vasomotor features such as sweating and pallor. Nausea and vomiting often accompany a severe attack. Fever and rigors are absent unless infection supervenes.

Findings consist of right upper quadrant or epigastric tenderness, perhaps with some guarding. During an attack or often soon after one, the pain disappears. There are no peritoneal signs. Often the examination is completely normal. Laboratory tests are usually normal, unless there is a concomitant bile duct stone (15%), liver bed inflammation due to cholecystitis, or compression of the bile duct from a distended gallbladder (Mirizzi's Syndrome).

Between attacks the patient feels well. Liver biochemistry is normal. Over long periods, the activity of the disease remains fairly constant. If having frequent episodes of biliary pain, the patient will probably continue to experience this pattern. Pain lasting more than six to 12 hours, especially if accompanied by persistent vomiting or fever, suggests another process such as

TABLE 4. Comparison of biliary colic to acute cholecystitis

	Biliary colic	*Acute cholecystitis*
Pain	Constant	Constant
Duration	Hours	Hours to days
Vomiting	Yes	Yes
Onset	Rapid	Variable
Jaundice	No	Later (20%)
Tenderness	RUQ	RUQ
Fever	No	Yes
Leukocytosis	Minimal	Marked
Resolution	Spontaneous	Spontaneous (< 66%)

cholecystitis or pancreatitis (Table 4). Conversely, abdominal pain, a history of bloating and altered bowel motions, relieved by defecation, suggests the irritable bowel syndrome.

Although most biliary colic resolves spontaneously, pain eventually recurs in 20-40% per year, while complications such as cholecystitis, choledocholithiasis, cholangitis or gallstone pancreatitis develop in 1-2% per year. Because of these increased risks, gallbladder removal (cholecystectomy) is indicated.

1.5 Diagnosis

Diagnosis of the gallstones (but not symptomatic disease) is radiological. Plain abdominal x-ray will only identify the 10-15% with a high calcium content as radiopaque densities in the right upper quadrant. Ultrasonography is the most sensitive and specific method for detecting gallstones (appearing as echogenic objects that cast an acoustic shadow) or a thickened gallbladder wall (indicating inflammation) (Figure 3). In suspected cases of acute cholecystitis, cholescintigraphy can assist the diagnosis by failing to fill the gallbladder with radionucleotide because of a stone obstructing the cystic duct.

1.6 Management

Most patients who do not have symptoms will remain asymptomatic. Once symptoms develop (e.g., biliary colic), it is likely that symptoms will recur. Although most biliary colic resolves spontaneously, pain eventually recurs in 20-40% per year leading to elective gallbladder removal (cholecystectomy). Furthermore, complications such as cholecystitis, choledocholithiasis, cholangitis or gallstone pancreatitis develop in 1-2% per year often necessitating emergency cholecystectomy. Because of these increased risks, cholecystectomy is indicated. Therefore, once gallstones become symptomatic, some form of treatment is recommended.

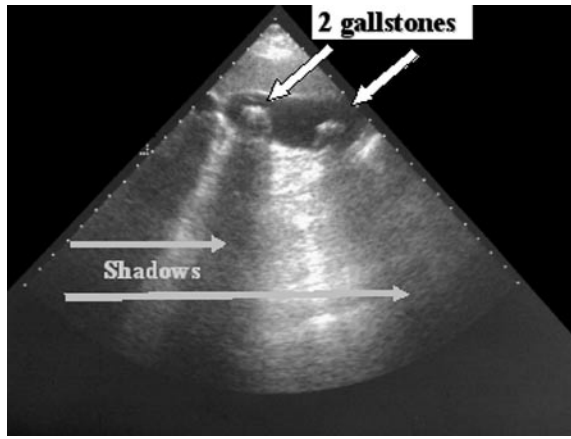

FIGURE 3. Abdominal ultrasound of two gallstones. In addition to each being echogenic, they each cast an acoustic shadow. Results in malabsorption. Stricture formation and recurrent cholangitis on occasion can lead to secondary biliary cirrhosis. Chronic duct obstruction and injury may lead to cholangiocarcinoma.

1.6.1 Medical Therapy

Bile Salt Dissolution

Administered orally, bile acids can dissolve cholesterol gallstones. Two bile acids, chenodeoxycholic acid and ursodeoxycholic acid, reduce cholesterol saturation of bile. The stones must be radiolucent and hence presumably composed of cholesterol, and the gallbladder must function (i.e., fill and empty through a patent cystic duct) for the unsaturated bile to bathe the stones. Gallbladder function can be assessed by visualization on either oral cholecystography (now rarely used or available) or cholescintigraphy, or by change in gallbladder size on fatty meal ultrasonography. Gallstone size largely determines the success rate. Stones must be less than 1.0 cm in diameter. Small stones with a relatively large surface area have the best result. Ideal cases have tiny (< 0.5 cm) gallstones that float on oral cholecystography (floating indicates a low calcium content); here, dissolution has a success rate greater than 80%. Large stones in obese individuals have less favorable results.

The reported success rate for complete dissolution varies from 13-80% with over one to two years of therapy. Medical therapy also reduces the frequency of episodes of biliary colic.

Chenodeoxycholic acid (15 mg/kg/day) originally was the cheaper agent, but soon proved to have marked side effects, specifically dose-related diarrhea (20-40%) and more importantly, liver damage, all because of its more

hydrophobic nature than ursodeoxycholic acid. It also increased serum cholesterol by 10%. Ursodeoxycholic acid (8-10 mg/kg/day), in contrast, is more hydrophilic and therefore has less detergent properties. It generally does not cause diarrhea and is not associated with liver toxicity. In fact, ursodeoxycholic acid is used in treating certain cholestatic liver diseases (see section on Primary Biliary Cirrhosis). This bile acid does not cause diarrhea or affect serum cholesterol. It is therefore the only one used therapeutically.

Prevention of gallstone formation is possible either following bariatric surgery in the very obese or while on a very restrictive diet to rapidly lose weight. Only 15-20% of patients with gallstones however are candidates for such dissolution therapy. Expense and the frequency of recurrence (50% at 5 years) have severely limited its use.

1.6.2 CHOLECYSTECTOMY

1.6.2.1 Open cholecystectomy

The term "open" connotes the need for an incision to open the abdominal cavity for direct visualization and operation. In contrast, the laparoscopic technique uses a scope and tiny incisions. The operation is relatively safe, with mortality less than 0.5% when electively performed for biliary colic. Mortality reaches 3% for emergency surgery in acute cholecystitis or for common duct procedures, and is higher in the elderly.

1.6.2.2 Laparoscopic cholecystectomy

This technique views the abdominal contents through a laparoscope (with the peritoneal cavity insufflated with gas) and uses instruments inserted through trocars into the abdominal wall to perform surgical manipulation. In 5% of cases the procedure must be converted to an open cholecystectomy because of technical problems. The patient has less postoperative pain, can be discharged from hospital after only one to two days (sometimes as an outpatient) and can return to work early. Its cosmetic appeal leaves only tiny scars. The disadvantages include a somewhat higher complication rate, particularly from common duct injury and retained common duct stones, plus the potential for overuse. Laparoscopic cholecystectomy is now the standard for elective surgery and for most cases of acute cholecystitis. It has eliminated any value for medical dissolution.

Surgery is indicated in those with significant symptoms (e.g., repeated visits to the emergency room for narcotic relief) or with complications. Prophylactic cholecystectomy is not warranted except for rare cases suspected of developing/harboring carcinoma of the gallbladder (e.g., very large stones > 3 cm or a calcified gallbladder wall). It generally should not be done on asymptomatic people with gallstones.

2. CHOLECYSTITIS

2.1 Chronic Calculous Cholecystitis

Chronic inflammation of the gallbladder is the most common pathologic process in this organ. Some degree of chronic inflammation inevitably accompanies gallstones, but the stones will have developed first. Even transient obstruction of the cystic duct can produce biliary colic and some degree of inflammation. There is little correlation between the severity and frequency of such biliary episodes and the degree of inflammatory or fibrotic pathology found in the gallbladder and therefore the term chronic cholecystitis is generally avoided. The most common histologic changes observed are mild fibrosis of the gallbladder wall with a round cell infiltration and an intact mucosa. Prolonged obstruction can lead to acute cholecystitis (Figure 2). The inflammatory process is chemical in origin. Chronic inflammation may follow the resolution of acute cholecystitis or evolve insidiously.

2.1.1 CLINICAL FEATURES

The clinical features are those of either biliary colic or a previous episode of acute cholecystitis that has resolved leaving the gallbladder chronically inflamed. The pain characteristically is a constant dull ache in the right upper quadrant and epigastrium, and sometimes also in the right shoulder or back. Nausea is frequent. Flatulence, fatty food intolerance and dyspepsia occur, but are equally frequent in patients without gallstone disease. Fever or leukocytosis suggests acute cholecystitis or another entity. There may be local tenderness in the right upper quadrant of the abdomen.

2.1.2 DIAGNOSIS

Diagnosis largely depends upon detecting gallstones by plain film of the abdomen (10-15% are calcified) or abdominal ultrasound (95% accurate). Oral cholecystography, though quite accurate is rarely used. If the gallbladder is fibrotic and shrunken, visualization may be difficult. Cholescintigraphy with failure of the gallbladder to fill is much less sensitive in diagnosing chronic cholecystitis, because there are too many false positive and negative tests.

2.1.3 MANAGEMENT

Once symptoms begin, they are likely to recur (70%), whereas asymptomatic stones, or stones associated with dyspepsia without biliary colic, are generally treated expectantly. Medical management depends upon gallstone size, gallbladder function and any co-morbid conditions (e.g., age, obesity, diabetes). Cholecystectomy provides definitive treatment, removing the stones and the gallbladder, if one can be secure that true biliary pain exists.

2.2 Acute Cholecystitis

Here the gallbladder becomes acutely inflamed. In most, a stone has obstructed the cystic duct for a prolonged period, resulting in a vicious cycle of increased secretion of fluid, causing distension, mucosal damage and the release of chemical mediators of the inflammatory process. Inflammatory damage results from agents such as lysolecithin, derived from the hydrolysis of lecithin by phospholipase, and prostaglandins whose synthesis increases. Any role that bile salts and regurgitated pancreatic enzymes may have is unclear. Bacterial infection is a late complication.

Obstruction of the cystic duct results in the gallbladder becoming distended with bile, an inflammatory exudate or even pus. The gallbladder wall can go on to necrosis and perforation. If resolution occurs, the mucosal surface heals and the wall becomes scarred, but the gallbladder may not function – e.g., fill on cholescintigraphy or oral cholecystography.

2.2.1 CLINICAL FEATURES

Acute cholecystitis begins like biliary colic (Table 4). The abdominal pain rises to a plateau and remains constant. Its location is usually the right upper quadrant or epigastrium, sometimes radiating to the back or the right shoulder. There may be a previous history of biliary pain. Pain in acute cholecystitis, unlike biliary colic, persists for more than six to 12 hours. As the gallbladder becomes inflamed, the visceral pain is replaced by parietal pain, which is better localized and is aggravated by movement. Anorexia and vomiting are common. Fever is usually low-grade. If rigors occur, suspect bacterial invasion.

Abdominal examination characteristically shows tenderness in the right upper quadrant. During palpation of the right upper quadrant, a deep breath during the inspiratory effort worsens the pain and inspiration suddenly ceases (Murphy's sign). Severe cases exhibit peritoneal signs: guarding and local rebound tenderness. A reflex paralytic ileus may be present. Patients appear unwell and are reluctant to move with such parietal pain. An enlarged gallbladder is sometimes palpable, particularly with the first attack.

2.2.2 DIAGNOSIS

Jaundice with mild hyperbilirubinemia and elevated liver enzymes occur in about 20% of cases, even in the absence of common duct stones. The higher the bilirubin level, the more likely is a common duct stone. High levels of aminotransferase or alkaline phosphatase, and of amylase or lipase suggest a common duct stone. Leukocytosis is common. If the patient is febrile, blood cultures may be positive.

Diagnosis is best confirmed by ultrasound, which detects the stone(s) and a thickened gallbladder wall. In doing the procedure, the physician may elicit

tenderness ultrasonographically when pressing over the gallbladder (the ultrasonographic Murphy's sign). A plain film may reveal calcification of the stone(s). Cholescintigraphy, one hour after injecting the radiopharmaceutical, typically fails to visualize the gallbladder, a feature quite sensitive and specific for acute cholecystitis. Late visualization (after one hour) sometimes occurs in chronic cholecystitis.

2.2.3 MANAGEMENT

Treatment is surgical and is performed in hospital. General measures include rehydration, observation, analgesia and antibiotics. Parenteral nonsteroidal anti-inflammatories (NSAIDs) can relieve acute biliary pain and may decrease the risk of progression to cholecystitis. In mild cases of acute cholecystitis that resolve, cholecystectomy can be delayed for up to six weeks. Because of the risk of recurrent cholecystitis, surgery should be performed early during the current admission, once the patient has been stabilized.

2.2.4 COMPLICATIONS

Acute cholecystitis normally resolves spontaneously, usually within three days. Inflammation may progress to necrosis, empyema or perforation in about one-third of cases. These complications will be heralded by: (1) a continuation of the pain, along with tachycardia, fever, peritoneal signs and leukocytosis; (2) features of a secondary infection, such as empyema or cholangitis; or (3) a suspected perforation. Urgent surgery then becomes mandatory.

Empyema is suppurative cholecystitis with an intraluminal abscess (i.e., inflamed gallbladder containing pus). It develops from continued obstruction of the cystic duct leading to secondary infection. The abdominal findings of acute cholecystitis are accompanied by systemic features of bacteremia, with a hectic fever and rigors. Treatment consists of antibiotics and surgery.

Perforation of the gallbladder occurs when unresolved inflammation leads to necrosis, often in the fundus, a part of the gallbladder that is relatively avascular. Gallstones also may erode through a gangrenous wall. Free perforation with bile peritonitis is fortunately uncommon, as the mortality reaches 30%. If localized, the perforation spawns an abscess, clinically evident as a palpable, tender mass in the right upper quadrant. The pain and temperature may also transiently resolve, only to be replaced by acute peritonitis. Both localized and free perforations demand surgical drainage of the abscess. Rupture into adjacent viscera (e.g., the small intestine) creates an internal biliary fistula. Large stones that pass through this type of fistula can produce a mechanical small intestine obstruction (*gallstone ileus*). Obstruction usually occurs at the terminal ileum, rarely at the duodenal bulb or the duodenojejunal junction. This is a rather common cause of distal small bowel obstruction

in the elderly. Radiologic diagnosis comes from finding air in the biliary system, a small bowel obstruction and perhaps a calcified gallstone ectopically located. Urgent surgery with appropriate antibiotic coverage is imperative.

Hydrops of the gallbladder occurs when the inflammation subsides but the cystic duct remains obstructed. The lumen becomes distended with clear mucoid fluid. The hydropic gallbladder is evident as a right upper quadrant mass that is not tender. Treatment is cholecystectomy.

Limy bile occurs when prolonged gallbladder obstruction causes loss of the pigment material from bile and the residual calcium salts precipitate. The hydropic, obstructed gallbladder secretes calcium into the lumen. Calcium can also accumulate in the wall of the gallbladder, producing a *porcelain gallbladder*. The mural calcifications are easily identified on plain films of the abdomen. Although presumably there has been at least one episode of acute cholecystitis in the past, most patients with a porcelain gallbladder are asymptomatic. One-quarter will develop carcinoma of the gallbladder, making prophylactic cholecystectomy necessary.

2.3 Choledocholithiasis (Common Duct Stones)

Stones in the common duct are classified according to their site of origin: primary stones form in the bile ducts; secondary stones originate in the gallbladder and then migrate into the common duct. In North America, virtually all cholesterol stones and most pigment stones are considered secondary when the gallbladder is intact. Thus, more than 85% of patients with common duct stones also have stones in the gallbladder. Conversely, about 10% of patients undergoing cholecystectomy for chronic cholecystitis also have common duct stones. Residual stones are those missed at the time of cholecystectomy; recurrent stones develop in the ductal system more than three years after surgery. The composition of stones also varies with their site of origin. Stones are predominantly (approximately 80%) cholesterol when situated in the gallbladder and in the common duct. After cholecystectomy, the proportion of ductal stones that are pigment rises with time: most recurrent ones (more than three years after surgery) are pigment stones. These brown stones result from stasis (e.g., a postoperative stricture) and infection. Bacteria and inflamed tissues release ß-glucuronidase, an enzyme that deconjugates bilirubin. The result is calcium bilirubinate, which polymerizes and precipitates along with calcium soaps. Biofilm, a glycoprotein produced by bacteria as its glycocalyx, then agglomerates this pigment material, leading to brown stones.

2.3.1 CLINICAL FEATURES

Most common duct stones eventually become symptomatic, causing biliary colic, obstructive jaundice, cholangitis or pancreatitis (Figure 2). Biliary colic

results from sudden obstruction of the common duct, which increases biliary pressure. The abdominal pain is steady, located in the right upper quadrant or epigastrium, and can bore through to the back.

Acute cholangitis results when duct obstruction leads to infection. Obstruction and ductal damage permit bacteria to regurgitate across the ductal epithelium into the hepatic venous blood, causing a bacteremia with chills and a spiking fever. The raised intrabiliary pressure also causes abdominal pain. The classical "Charcot's triad" consists of jaundice, upper abdominal pain and fever. Jaundice results from the mechanical obstruction of the ducts plus a component of intrahepatic cholestasis due to sepsis (endotoxin, for example, impairs hepatic bile formation). Pain and fever are common, though jaundice may not be clinically apparent on presentation. Most patients are toxic. There is abdominal tenderness; a large, tender liver should raise a suspicion of coexistent liver abscesses. Hypotension, confusion and a septic picture predominate in critical cases.

Pancreatitis can result from gallstones impacting at the ampulla of Vater. The pancreatitis may either be due to obstruction of the pancreatic duct at the ampulla, or from bile reflux into the pancreas when the stone is impacted in a common biliopancreatic channel. Acute biliary pancreatitis does not differ clinically from other forms of acute pancreatitis. Biliary pancreatitis tends to be more commonly associated with jaundice and higher serum levels of bilirubin, alkaline phosphatase and aminotransferase than alcohol-induced pancreatitis, but there is significant overlap. Ultrasound should detect any gallstones and the inflamed pancreas, with or without biliary dilatation.

2.3.2 DIAGNOSIS

Mild leukocytosis and abnormal liver biochemistry are common. Although usually cholestatic in pattern, the liver enzymes may be predominantly hepatitic (aminotransferases affected more than alkaline phosphatase) in the early phases of the attack. Urine may be positive for bilirubin and the urine is often tea-coloured (which may be interpreted as hematuria by some patients). Ultrasound (the diagnostic imaging technique of choice) will often show dilated ducts (80% sensitivity for ductal dilatation) and, in advanced cases, liver abscesses. Ultrasound is insensitive for the ductal stone itself (30-40%) but is highly specific. Scintigraphy is insensitive. Helical CT is reasonably accurate for biliary dilatation and bile duct stones. The duct normally dilates with age (1 mm every decade above the age of 60) and can be up to 10 mm in diameter if the gallbladder has been previously removed.

ERCP (endoscopic retrograde cholangiopancreatography) is the "gold standard" for biliary imaging but requires conscious sedation and injection of dye into the ampulla of Vater. It is associated with a 2-5% risk of pancreatitis, and

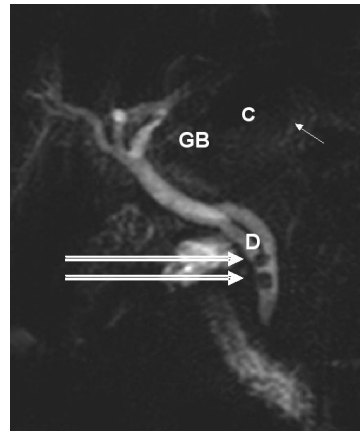

FIGURE 4A. MRCP showing 2 stones (large arrows) in the common duct. Small arrow indicates the pancreatic duct. D- Duodenum. GB- Gallbladder. C- Cystic Duct.

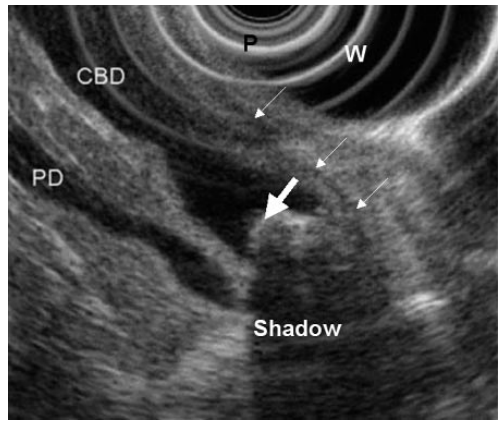

FIGURE 4B. A radial endoscopic ultrasound image showing part of a "stack sign" imaged through the duodenal bulb (common bile duct (CBD), pancreatic duct (PD), and portal vein (not shown) in long-axis view, seen as dark (hypoechoic) stripes parallel to one another). A wedge shaped dark (hypoechoic) acoustic shadow is seen behind the bright (hyperechoic) 4-5 mm stone (arrow), making even this small stone appear quite obvious. P=probe at tip of scope. W= water-filled balloon around probe. Small arrows indicate tangential view of duodenal wall.

10% mortality in the 1% of patients who develop severe pancreatitis. Therapeutic procedures, including cutting open the sphincter of Oddi with cautery (sphincterotomy), stone removal, lithotripsy and stenting can be performed at the same time. Bleeding, perforation, and cholangitis are other rare complications.

Magnetic resonance cholangiopancreatography (MRCP) is a heavily T2-weighted MRI, with single breath hold techniques available to avoid breathing-related movement artefact. The T2-weighting allows stagnant fluids such as bile to be highlighted without the need for a contrast agent. MRCP is highly sensitive and specific for stones, ductal dilatation and to identify the site of biliary obstruction (Figure 4A).

Endoscopic ultrasound (EUS) involves the use of a specialized endoscope with an ultrasound probe at the tip (echoendoscope) to image the bile duct through the apex of the duodenum, under conscious sedation. It is also highly sensitive and specific for ductal stones and is likely more sensitive than MRCP when biliary dilatation is absent and/or when stones are small (< 5 mm) (Figure 4B).

If cholangitis is present, fever and a more marked leukocytosis is seen. Blood cultures may reveal the causal microorganisms, which are usually enteric (e.g., E. coli or Klebsiella) in origin. Cholangiography (usually via ERCP – endoscopic retrograde cholangiopancreatography) is necessary to locate the site and cause of obstruction.

2.3.3 MANAGEMENT

Noninvasive biliary imaging (MRCP, EUS) is most appropriate for scenarios with a low to intermediate probability of ductal stones, as an ERCP will follow for therapy in the minority of cases. Intermediate to high probability situations (e.g., cholangitis, jaundice, biliary dilatation) have a higher probability of requiring a therapeutic ERCP (sphincterotomy and stone removal), and generally should go directly to ERCP.

The presence of cholangitis necessitates urgent decompression of the biliary system, preferably by ERCP. Broad spectrum antibiotics should be given to cover gram negatives, anaerobes, and enterococcus (e.g., gentamycin, metronidazole and ampicillin). ERCP with sphincterotomy followed by extraction of the stone is definitive therapy for cholangitis. If ERCP is unavailable or unsuccessful, percutaneous trans-hepatic cholangiography (PTC) with a drain can be performed. Large common duct stones may need fragmentation, either by mechanical means using a basket for crushing (mechanical lithotripsy), or by energy delivered as shock (electrohydraulic lithotripsy) or laser waves.

The latter two options generally require direct vision of the stone with a "baby" cholangioscope. A large stone that cannot be extracted, or a patient with an untreated coagulopathy that does not allow for a sphincterotomy to be performed, can be treated with a temporary plastic stent. Laparoscopic cholecystectomy should then be done electively, but preferably within a few weeks of the attack. Another less preferred option is open cholecystectomy with common duct exploration, removing the gallbladder and all stones, but this

has a longer recovery period and a higher operative morbidity than the combination of ERCP with laparoscopic cholecystectomy. Laparoscopic common bile duct exploration is a consideration if this expertise is locally available but is generally restricted to stones < 7-8 mm.

In gallstone pancreatitis, the bile duct stone passes into the duodenum in 70-80% of patients, but a retained bile duct stone remains in < 30%. Rising liver enzymes (over the first few days), bilirubin more than twice normal and ultrasonographic biliary dilatation are independent predictors of a retained stone (40-80% chance when one or more are present). Early ERCP (24-48 hrs) and sphincterotomy benefit both morbidity and mortality in the subgroup of patients with severe pancreatitis, cholangitis, or other signs of ongoing biliary obstruction (jaundice, ultrasonographic biliary dilatation).

Cholecystectomy should follow, ideally prior to discharge, but preferably in the following few weeks as the rate of recurrent biliopancreatic symptoms is high in the next few months. In mild-to-moderate gallstone pancreatitis, ERCP should be performed selectively in patients with rising liver enzymes, jaundice or biliary dilatation. Mild-to-moderate cases with falling enzymes should undergo laparoscopic cholecystectomy with intraoperative cholangiography (with post-operative ERCP if the operative cholangiogram is positive). Patients with mild-to-moderate pancreatitis and previous cholecystectomy should be considered for some type of non-invasive biliary imaging (e.g., MRCP or EUS), followed by ERCP if positive. Unlike alcoholic pancreatitis, gallstone-related disease does not progress to chronic pancreatitis.

3. ACALCULOUS GALLBLADDER DISEASE

3.1 Congenital Anomalies

Congenital abnormalities of the gallbladder and biliary system result from embryonic maldevelopment and are most interesting for the surgeon attempting to identify biliary anatomy at cholecystectomy. Agenesis of the gallbladder is rare. Curiously, it is associated with common duct stones, likely because the duct takes over some of the reservoir role.

3.2 Acalculous Cholecystitis

3.2.1 ACUTE ACALCULOUS CHOLECYSTITIS

Inflammation of the gallbladder can occur in the absence of gallstones. Though uncommon in adults, acute acalculous cholecystitis may appear associated with AIDS, pregnancy, trauma, burns, sepsis or following major surgery. In young children, acute cholecystitis frequently occurs without gallstones and follows a febrile illness, although no definite infectious agent is

identified. Biliary stagnation sometimes accompanied by sludge appears to be a factor. Impaired blood flow to the gallbladder, coagulation factors and prostaglandin may also have roles. Cytomegalovirus or Cryptosporidia can cause gangrenous cholecystitis in AIDS.

Clinical presentation is identical to that of acute cholecystitis, with pain, fever and abdominal tenderness in the right upper quadrant. These features are often obscured by the patient's underlying critical condition. Diagnosis is then revealed at laparotomy, but sometimes can be determined preoperatively by nonvisualization of the gallbladder on cholescintigraphy (although nonvisualization is less sensitive here because of the prolonged fast many are on) or by ultrasonographic evidence of a thickened gallbladder wall. Perforation, gangrene and empyema are all too frequent complications. The best treatment is prompt cholecystectomy. Prevention is possible in some patients on complete TPN (total parenteral nutrition with no oral intake) following major surgery, trauma or burns. Daily injections of cholecystokinin (CCK) can prevent sludge formation and its complication, cholecystitis.

3.2.2 CHRONIC ACALCULOUS CHOLECYSTITIS

Recurrent biliary-type pain in the absence of gallstones has been associated with rather modest inflammation. It may be best classified as functional biliary pain. The basis is presumed to be a motility disorder, impaired gallbladder evacuation; hence the alternative term "biliary dyskinesia." Relief can follow cholecystectomy. Difficulties arise in attempting to make this diagnosis: the symptoms are often not clear-cut (sometimes having features of the irritable bowel syndrome or non-ulcer dyspepsia), and there are no gallstones to detect. Abnormal gallbladder evacuation in response to CCK may be evident on cholescintigraphy. Sensitivity and specificity of these tests remain unclear. CCK infusion alone can reproduce the biliary pain, but the value of this provocative test is uncertain. The entity remains poorly defined. In some, the origin of the problem is dysfunction of the sphincter of Oddi, either as a motor disorder or hypersensitivity. In many, it may represent a facet of the irritable bowel syndrome or visceral hypersensitivity of an adjacent structure such as the duodenal sweep.

3.3 Cholecystoses

Cholesterolosis consists of deposits of cholesterol esters and triglycerides within the gallbladder wall. These submucosal deposits produce a fine yellow reticular pattern on a red background of mildly inflamed mucosa, providing an appearance like a strawberry: hence the term "strawberry gallbladder." Some of the cholesterol deposits protrude like polyps and can be detected on ultrasound. There is no well-defined symptom complex linked to this entity.

Although frequently an incidental finding at post mortem, it is sometimes associated with vague dyspeptic complaints, the irritable bowel syndrome or recurrent right upper quadrant abdominal pain. The importance of CCK provocative tests to reproduce the pain or demonstrate reduced gallbladder emptying on quantitative cholescintigraphy in response to CCK is unclear.

Adenomyosis is characterized by hyperplasia of the gallbladder mucosa and by deep clefts. The meaning of any biliary-type symptoms is moot.

3.4 Postcholecystectomy Syndrome

Cholecystectomy relieves the symptoms of most, but definitely not all patients with biliary calculi. The occasional patient will experience diarrhea following cholecystectomy, perhaps the result of unmasking a malabsorption of bile acids, which leads to a cholerrheic (bile acid-induced) diarrhea. Symptoms persist or recur in five to 50%, depending upon selection bias. Most often the original complaint was not true biliary pain, but rather reflux esophagitis, peptic ulcer disease or the irritable bowel syndrome. There may be recurrent biliary tract problems such as a biliary stricture, retained common duct stone or even pancreatic disease which is best investigated with MRCP, EUS or ERCP.

Sphincter of Oddi dysfunction (SOD): Occasionally, increased tone in the sphincter of Oddi (sphincter dysfunction) will produce recurrent biliary-type pain, often with abnormal liver biochemistry tests, a dilated bile duct, or even pancreatitis. Morphine aggravates the spasm. The modified Milwaukee clinical classification of SOD includes three factors: elevated liver enzymes (during an attack of pain), dilated bile duct, and typical biliary pain. Type I SOD patients have all three criteria, type II patients have pain with one of the other two criteria, and type III patients have pain alone. Nuclear medicine scanning in the absence of the gallbladder (cholescintigraphy with morphine provocation) and/or sphincter of Oddi pressure measurements (manometry via ERCP showing pressures > 40 mmHg) provide diagnostic clues. Endoscopic sphincterotomy relieves pain in selected patients. Sphincterotomy is most helpful in Type I patients (90-95% pain relief) and is least helpful in Type III patients with (50-60% relief) and without (< 10% relief) abnormal manometry. ERCP, with or without manometry, in patients with suspected SOD has a high risk of post-ERCP pancreatitis (up to 20%), which may be reduced by temporary pancreatic duct stenting.

3.5 Neoplasms of the Gallbladder

Carcinoma of the gallbladder is fortunately uncommon, as its prognosis is extremely poor. Adenocarcinoma is generally cured only when incidentally discovered at cholecystectomy for cholelithiasis. Gallstones are present in most (75%) cases, probably as innocent bystanders rather than as causal agents

(Figure 2). Any risk is too low to advocate prophylactic cholecystectomy in the many people with asymptomatic gallstones. A porcelain gallbladder with calcifications in the wall predisposes to adenocarcinoma and calls for cholecystectomy. Large gallstones (> 3 cm) are also a risk factor for carcinoma.

The clinical features of gallbladder carcinoma consist of pain, a hard mass in the right epigastrium, jaundice, pruritus and weight loss. Ultrasound and CT scan help define the mass and metastases. Prognosis is grim, as it is common for the cancer to spread. The five-year survival is less than 5%. Therapy is palliative; most are not resectable unless removed incidentally at the time of cholecystectomy.

Benign tumors of the gallbladder are uncommon. Adenomas are asymptomatic, being detected on ultrasound or found incidentally at surgery. Small masses in the wall of the gallbladder, however, are relatively common findings on ultrasound; when multiple they usually represent cholesterol polyps or adherent gallstones. Polypoidal masses warrant a repeat ultrasound in six months. If these are larger than 1 cm, surgery is necessary to exclude a carcinoma.

4. DISEASES OF THE BILE DUCTS

4.1 Congenital

Fibrocystic disorders: This group of disorders comprising biliary tree maldevelopment, cystic dilatation and/or fibrosis are due to genetic abnormalities in the remodelling of the ductal plate. The type of disease depends on the part of the ductal plate involved. Various infections may also contribute as is hypothesized for biliary atresia. All, except Caroli's disease, may be associated with polycystic kidney disease. The prognosis usually depends on the extent of renal involvement. The later the presentation, the less significant the renal component of the syndrome (90% in perinatal vs 25% in three- to six-month-old infants).

Caroli's disease (congenital intrahepatic biliary dilation) is a rare condition in which saccular, dilated segments of the intrahepatic bile ducts lead to stone formation, recurrent cholangitis and hepatic abscesses with sepsis. Episodes of abdominal pain, fever and jaundice may onset at any age, most commonly in childhood or young adult life. About 75% of patients are male and hepatomegaly is common. Cholangiocarcinoma and amyloid can be late complications.

Cholangiography reveals the irregularly dilated segments of the intrahepatic bile ducts that connect with the main ducts. The common duct is normal. Endoscopy (or surgery) can remove some stones but does little for the process that affects small bile ducts in the liver. If involvement is unilateral (usually left-sided), partial hepatectomy can be curative. Otherwise, management is conservative, using antibiotics for infectious complications of the duct

system. These recurrent episodes of cholangitis sometimes progress to secondary biliary cirrhosis, portal hypertension and eventually cholangiocarcinoma. Partial hepatectomy of an affected segment sometimes is feasible. Liver transplantation may become necessary in other cases.

Congenital hepatic fibrosis frequently accompanies Caroli's disease and the combination is termed *Caroli's syndrome*. This phenomenon perhaps reflects a developmental defect of the small interlobular ducts. Congenital hepatic fibrosis clinically presents as portal hypertension with esophageal varices in children. Liver biopsy is diagnostic, revealing broad bands of fibrous tissue entrapping bile ducts but no cirrhosis (i.e., no regeneration). Liver transplantation may be necessary in complicated cases.

Choledochal cyst is a congenital dilation of a portion of the common bile duct (1 in 200,000 incidence, being more common in Asian races). These cysts develop because of an uneven proliferation of the duct epithelial cells. The characteristic pathology is a cyst wall consisting of fibrous tissue, lacking epithelium or smooth muscle. More than 50% of cases are associated with an anomalous pancreaticobiliary junction, due to an arrest of the normal descent of this junction from outside the duodenum to within the duodenal wall in the last eight weeks of gestation. The long common pancreaticobiliary channel (> 15 mm) is proposed to allow pancreatic juice reflux in the bile duct, causing distal structuring in some cases, and thinning of the bile duct proximally.

These are classified (Todani classification) into several subtypes. Type 1: fusiform dilatation of the extrahepatic bile duct (most common); Type 2: sidewall diverticulum of the extrahepatic duct; Type 3: choledochocele, bulging into the duodenum; Type 4 is a combination of intrahepatic bile duct cysts and Type 1 anatomy or combined Type 1 plus Type 3; and Type 5 is generally considered to be synonymous with Caroli's disease (see above). This classification of Caroli's as a type of choledochal cyst is controversial as Caroli's differs from the other types because of the lack of associated renal disease and the lack of extrahepatic biliary cysts.

Presentation may be as cholestasis in infants (if the cyst and/or stricture is complicated by sludge), as an abdominal mass, or as an acute abdomen if the cyst bursts and causes bile peritonitis. The cysts can be 2-8 cm in size and have up to 8 L of dark brown fluid. Later in life, it can present as intermittent jaundice and biliary pain with or without fever (cholangitis). Complications include chronic obstruction leading to biliary cirrhosis and the development of ductal carcinoma. Diagnosis is provided by ultrasound or CT scan and verified by endoscopic cholangiography. Because of the risk of malignancy, either due to the cyst itself or due to the abnormal pancreaticobiliary junction, and the postoperative risk of stricturing and stone formation when the bile duct is attached to the intestine, the preferred therapy is a radical excision with hepaticojejunostomy.

Alagille's syndrome is a marked reduction in intrahepatic (actually interlobular) bile ducts. Although it is believed to be congenital, being inherited in an autosomal dominant pattern, presentation may be as a neonatal jaundice or as cholestasis in older children. There are associated triangular facies, cardiovascular anomalies (e.g., pulmonary artery stenosis) and vertebral body abnormalities. A mutation in the JAG1 gene is found in 70% of cases. Outcome is variable, depending upon the attendant anomalies and the severity of the liver disease.

Biliary atresia is a common cause of neonatal cholestatic jaundice. Although congenital (appearing at birth), it is not inherited. Complete absence of the extrahepatic bile ducts reflects either an arrest in remodelling of the ductal plate in utero or, more probably, an inflammatory destruction of the formed bile ducts during the postpartum period. The latter process is evident by an inflammatory infiltrate in the portal tracts and, in some, features of neonatal hepatitis, perhaps initiated by a viral infection. Large duct obstruction then leads to small duct injury within the liver and hence secondary biliary cirrhosis. Severe cholestasis develops in the neonatal period. The stools are pale and the urine is dark and devoid of urobilinogen. Cholestatic features predominate, with the development of steatorrhea, skin xanthoma, bone disease and failure to thrive. Surgery is usually necessary to confirm the diagnosis and attempt some form of biliary drainage. In some, existence of a patent hepatic duct or dilated hilar ducts potentially allows correction of the obstruction by anastomosis to the small intestine (e.g., a Roux-en-Y choledochojejunostomy). Much more common is an absence of patent ducts; dense fibrous tissue encases the perihilar area and precludes conventional surgery. Such obliteration of the proximal extrahepatic biliary system requires the Kasai procedure. A conduit for biliary drainage is fashioned by resecting the fibrous remnant of the biliary tree and anastomosing the porta hepatis to a Roux-en-Y loop of jejunum. With either surgery, most children eventually develop chronic cholangitis, hepatic fibrosis/cirrhosis and portal hypertension. When the child is larger, hepatic transplantation dramatically improves the prognosis.

Von Meyenberg's complexes are biliary microhamartomas. These cysts are small, multiple, and are usually asymptomatic. They are thought to arise from a maldevelopment of the ductal plate. They can be complicated by cholangiocarcinoma, but are usually only treated if symptomatic.

Of note, some of the conditions of neonatal cholestasis are becoming clarified with an understanding of the transport system (see Liver Structure and Function) necessary for bile formation and the responsible genes for each transporter, a classification of familial intrahepatic cholestatic syndromes.

4.2 Inflammatory

4.2.1 CHOLANGITIS

Cholangitis is any inflammatory process involving the bile ducts, but common usage implies a bacterial infection, usually above an obstructive site. The presence of bacteria in the biliary tree plus increased pressure within the system results in severe clinical features of cholangitis (*suppurative cholangitis*). Any condition producing bile duct obstruction is likely to cause bacterial infection of bile. Most commonly, this takes the form of a common duct stone (Section 2.3), a benign biliary stricture (trauma from biliary surgery, ischemia following liver transplantation or sclerosing cholangitis), stasis in a congenital biliary cyst (Section 4.1), a parasite residing in the ducts (Clonorchis sinensis, Opisthorchis viverrini or Fasciola hepatica), an occluded biliary stent or extrinsic compression from a diseased papilla or pancreas. A less likely cause of infection is neoplastic obstruction (only 10-15% of malignant biliary obstructions are associated with infection). The difference relates to the high-grade, fixed obstruction of neoplasms versus the intermittent blockage with a stone or an inflammatory stricture. Such intermittent blockage allows retrograde ascent of bacteria; the stone may act as a nidus for infection. The bacteria are commonly thought to ascend the biliary tree (hence the term "ascending cholangitis"), but may enter from above via the portal vein or from periductular lymphatics.

In acute bacterial cholangitis, particularly if severe, the classical Charcot's triad of intermittent fever and chills, jaundice and abdominal pain may be followed by septic shock. Most cases are less severe and life-threatening; jaundice may be absent. Mild cases may respond to antibiotics and conservative measures. Investigation and decompression of the biliary system are mandatory in all patients, whether by ERCP, percutaneous trans-hepatic cholangiography or surgery. The duration of antibiotics needed after successful biliary drainage can likely be as short as three to five days.

4.2.2 SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis (PSC) is a chronic cholestatic syndrome of unknown etiology characterized by progressive inflammation of the intra- and extrahepatic bile ducts found in six to eight per 100,000 persons. The mean age is 40 at diagnosis, with a male predominance. The entity may appear either alone (20%) or in association with inflammatory bowel disease (80%), particularly ulcerative colitis, and less commonly, Crohn's colitis. In some races, e.g., Japanese, IBD is less commonly associated (20-25%). Serology may include a positive p-ANCA (80% of cases). Primary sclerosing cholangitis

may precede inflammatory bowel disease (especially ulcerative colitis) and runs a separate course, not being cured by colectomy. The patchy scarring (sclerosis) leads to fibrotic narrowing and eventually obliteration of the bile ducts. Like other organs, the biliary tract exhibits a limited number of responses to injury: here it responds with diffuse strictures and segmental dilations. Five percent of cases involve the extrahepatic bile duct only. The basis may be an infectious agent, an enterohepatic toxin or an immunological attack on the biliary epithelium. A genetic predisposition is suggested by human leukocyte antigen (HLA) associations and by its developing in multiple family members.

Periductal inflammation and fibrosis in the portal areas, termed "pericholangitis," probably represents the intrahepatic extension of this process, and the inflammatory component responds to steroids and tends to parallel IBD activity. Pericholangitis can occur without PSC.

Diffuse stricturing also occurs in *secondary sclerosing cholangitis* (SSC), which may complicate a biliary obstruction from a common duct stone, ischemia, biliary stricture or cholangiocarcinoma, or some AIDS-related infections. An infiltrative process (e.g., diffuse liver metastases, lymphoma, prominent regenerative nodules, and sarcoidosis) can also give a beaded appearance to the intrahepatic ducts that can mimic PSC. There is a long list of other causes for SSC.

The presentation in primary sclerosing cholangitis is insidious in most cases, with fatigue, pruritus or just an elevated alkaline phosphatase level. The liver biochemistry is cholestatic with elevated alkaline phosphatase and GGT. In others, acute cholangitis develops with obstructive jaundice, pruritus, abdominal pain and fever. Biliary stagnation leads to pigment stones. Eventually, secondary biliary cirrhosis supervenes with portal hypertension, pronounced cholestasis and progressive liver failure. Antimitochondrial antibody is negative. MRCP has reasonable accuracy for PSC but lacks resolution for third and fourth order branch abnormalities that ERCP provides.

Therapeutic trials of corticosteroids and immunosuppressive agents (for the presumed immunologically mediated inflammatory process), penicillamine (to mobilize copper, because this potentially toxic material accumulates in cholestasis) and proctocolectomy in patients with inflammatory bowel disease have all failed. As some patients may be asymptomatic for a decade, only careful observation is probably warranted early on. Recurrent bacterial cholangitis requires antibiotics and a dominant stricture should be suspected and treated when present. Extrahepatic "dominant" predominantly large-duct strictures respond to step-wise, progressive endoscopic or trans-hepatic dilation and stent placement. Ursodeoxycholic acid, by displacing toxic bile acids and providing local anti-inflammatory effects, decreases liver enzymes but

has not been shown to change outcomes, except in one study when combined with selective endoscopic therapy showed survival was improved. Evaluation of other potent immune suppressants and modulators are ongoing.

Prognosis from diagnosis to death or liver transplantation is about 12 years. The development of jaundice, and features of cirrhosis (ascites, portal hypertension with esophageal bleeding are indications for liver transplantation). Some 10-15% of patients develop cholangiocarcinoma, creating a diagnostic challenge. Unexplained weight loss, a rising CA19-9 serum tumor marker, or recent worsening of cholestasis should raise suspicion and imaging and/or biliary brushings should be considered. Primary sclerosing cholangitis is a frequent indication for liver transplantation with a Roux-en-y choledochojejunostomy that has a good outcome. Although unexpected cholangiocarcinoma in the X-plant liver has a good prognosis, known cholangiocarcinoma prior to transplantation has a poor prognosis, with progression of the cancer with immunosuppression, and is a contraindication to transplantation.

4.2.3 POST-CHOLECYSTECTOMY INFLAMMATORY CONDITIONS

Bile Leaks can occur after cholecystectomy because of either a cystic duct clip that is not secure or because of a right intrahepatic duct (duct of Luschka) that runs through the gallbladder bed on its way to the common duct. The presentation is that of post-operative pain, sometimes with fever or peritoneal signs from bile irritation of the peritoneum, and increased bilirubin and liver enzymes. Bile may be seen in the peritoneal drains. Diagnosis can be made by HIDA scan or a biloma seen on ultrasound. The treatment (and confirmation of the diagnosis) is ERCP with sphincterotomy and stent placement for four to six weeks. The leaks often heal in the first few weeks on their own, with the stent encouraging bile to flow into the duodenum, rather than through the hole, by decreasing resistance in that path. In 20-30% of patients, another obstructing diagnosis, such as a retained bile duct stone or an ampullary adenoma, coexists.

Strictures can occur after cholecystectomy either for mechanical reasons or due to focal ischemia. The former, including clipping of the bile duct instead of, or along with, the cystic duct (due to a low-inserting cystic duct), presents with early jaundice and pain. They often need re-operation and biliary reconstruction, but endoscopic therapy may be attempted in non-complete ligation. Ischemic strictures can present months later, with progressive cholestasis, or abrupt jaundice if they are complicated by sludge, and are diagnosed and treated with ERCP and progressive balloon dilatation and stenting with larger calibre stents and/or multiple stents. Often multiple procedures are needed.

4.3 Neoplasia (Including Cholangiocarcinoma)

Benign tumors (adenomas, papillomas, cystadenomas) are rare causes of mechanical biliary obstruction. Ampullary adenomas can be associated with colonic polyposis syndromes. Localized adenomas of < 2 cm can be assessed for endoscopic removal by an advanced endoscopist. Ampullary adenocarcinomas should be considered for Whipple's pancreaticoduodenectomy.

Adenocarcinoma, the most common malignancy, is uncommon in the Western world. Predisposing factors are chronic parasitic infestations of the biliary tract (e.g., a liver fluke, such as Clonorchis sinensis or Opisthorchis viverrini), congenital ectatic lesions (anomalous pancreaticobiliary junction, Caroli's disease, choledochal cyst) and primary sclerosing cholangitis.

Painless jaundice is the hallmark presentation, but the presentation is varied. Cholestasis and weight loss eventually develop. There may be a deep-seated, vague pain localized in the right upper quadrant of the abdomen, in contrast to the severe pain of biliary colic and the septic picture of cholangitis. Indeed, cholangitis is uncommon (10-15%) if no biliary manipulations have been performed, such as an ERCP-placed stent. Hepatomegaly is frequent. A distended, non-tender gallbladder may rarely be palpated, feeling like a small rubber ball, if the common duct is obstructed below the entry of the cystic duct ("Courvoisier's sign"). Obstruction produces dilation of the biliary tree that can be readily detected on ultrasound or CT scan. Cholangiography, usually by ERCP, should reveal the diagnosis. An elevated INR is common due to cholestasis and anorexia, and needs to be corrected prior to ERCP/PTC. At least, double sampling (brushing plus either intrabiliary biopsy or intrabiliary needle aspiration) is recommended to increase the cytologic yield above mono-sampling with a brush (30-40% yield). This slow-growing tumor often unfortunately presents late, but if non-invasive imaging reveals a resectable lesion in a young surgical candidate, it may be reasonable to go straight to surgery as some data suggests an increase in surgical infectious complications when the patient has been stented.

Palliation using biliary stents placed across strictures helps improve quality of life via alleviating jaundice, pruritus, and more controversially, by improving appetite and reducing nausea. Plastic biliary stents last three to four months but more expensive self-expandable metal stents can last over six months. Metal biliary stents are cost-effective unless tumors are large or distant metastases are present. A surgical consultation should be obtained regarding resectability. Intrabiliary PDT (photodynamic therapy) has been recently studied and appears to be a promising palliative manoeuvre.

Hilar cholangiocarcinomas are classified according to the Bismuth classification depending on whether one or more main hepatic ducts or secondary branches are involved. Because ERCP in such cases, as with PSC,

can contaminate biliary segments that may not be endoscopically drainable, and because MRCP is quite accurate at staging these tumors and determining resectability when combined with an enhanced T1-weighted abdominal MR, MRCP/MR should generally be used to stage these tumors and determine resectability. If unresectable, the MRCP can help determine the feasibility of endoscopic/percutaneous drainage, without risking biliary sepsis. Only 30% of the biliary tree needs be drained to alleviate jaundice, therefore, draining one lobe is often sufficient for palliation. Hilar tumors should be suspected when the characteristic painless jaundice of cholangiocarcinoma occurs in the presence of intrahepatic biliary dilatation *without* extrahepatic biliary dilatation.

OBJECTIVES

1. Recognize the normal anatomy of the biliary tree.
2. Understand the mechanisms for the stimulation of bile secretion and the hormonal mediators of this response.
3. Describe the physicochemical characteristics of normal bile, its production and the physiologic mechanism of bile salt reabsorption.

Acute and Chronic Gallbladder Disease, Carcinomas of the Biliary Tract

1. Identify the common types of gallstones and describe the pathophysiology involved in their formation.
2. Recognize the mechanisms by which risk factors predispose to gallstone formation.
3. List the tests commonly used in the diagnosis of calculous biliary tract disease. Describe the indications for, limitations of and potential complications of each.
4. Describe the probable natural history of a young patient with asymptomatic gallstones.
5. Know the complications that can occur from biliary calculi and describe the history, physical examination and laboratory findings for each.
6. Outline the management of a patient with acute cholecystitis.
7. Describe the symptoms and signs of choledocholithiasis; construct the management of this problem.
8. Outline a diagnostic and management plan for a patient with acute right upper quadrant pain.
9. Describe the diagnostic evaluation and management of a patient with fever, chills and jaundice.

10. Describe the following:
    a. Murphy's sign
    b. Courvoisier's sign
    c. Gallstone ileus
11. Contrast carcinomas of the gallbladder, bile duct and ampulla of Vater with regard to presenting features and survival.

Diagnostic Studies in Biliary Tract Disease

1. Contrast the liver enzyme abnormalities in cholestasis and viral hepatitis.
2. Identify the most common bacteria found in cholecystitis and cholangitis.
3. Describe the indications for and risks of oral cholecystogram, trans-hepatic cholangiogram and ERCP.
4. Accurately interpret an abnormal ultrasonogram of the gallbladder, oral cholecystogram, trans-hepatic cholangiogram and ERCP.

Skills

1. Given a patient with acute cholecystitis, demonstrate the right upper quadrant physical findings that indicate this diagnosis.

Section 1: Gallstone Disease

1.1 Identify the two major types of gallstones.
1.2 Describe the pathophysiology involved in the formation of gallstones.
1.3 Explain the risk factors for gallstone formation.
1.4 Describe the clinical features of gallstone formation.
1.5 List the tests and diagnostic imaging techniques used to diagnose gallstones.
1.6 Discuss the management protocols for asymptomatic and symptomatic patients with gallstone disease.

Section 2: Cholecystitis

2.1 Differentiate between chronic calculous cholecystitis and acute cholecystitis with regard to clinical features, diagnosis and management.
2.2 Discuss the complications that can result from acute cholecystitis.
2.3 Discuss choledocholithiasis (common duct stones), including classification, clinical features, diagnosis, and management.

Section 3: Acalculous Gallbladder Disease

3.1 Differentiate between acute and chronic acalculous cholecystitis with regard to definition, clinical presentation, diagnosis, and management.
3.2 Define cholecystoses, including cholesterolosis and adenomyosis.

3.3 Identify an approach to acalculous biliary pain.
3.4 What is the postcholecystectomy syndrome?
3.4 Discuss neoplasms of the gallbladder.

Section 4: Diseases of the Bile Ducts

4.1 Discuss congenital disease of the bile duct, including Caroli's disease, congenital hepatic fibrosis, choledochal cyst, Alagille's syndrome, and biliary atresia.
4.2 Define cholangitis and primary sclerosing cholangitis.
4.3 Describe benign and cancerous tumors of the bile duct.

LEARNER WORKBOOK

EXERCISE 1

1.0 List two major types of gallstones.
Answer (Section 1.1, Table 2)
1.1 What are the three stages of cholesterol gallstone formation?
Answer (Figure 1)
1.2 Fill in the blanks in the following table:
Risk factors for gallstone formation:

Factor	Pigment Stone	Cholesterol Stone
Race		
Familial		
Diet		
Gallbladder stasis		
Associated disease		

Answer (Table 3)
1.3 Briefly describe the clinical features of gallstone formation, including laboratory tests, presenting signs, and symptoms.
Answer (Section 1.4)
1.4 How are gallstones diagnosed?
Answer (Section 1.5)
1.5 Discuss three management strategies for gallstones.
Answer (Section 1.6)
1.6 What is the difference between open and laparoscopic cholecystectomy?
Answer (Section 1.6.2)

EXERCISE 2

2.0 What is the difference between chronic calculous cholecystitis and acute cholecystitis with regard to definition, clinical features, diagnosis, and management?
Answer (Section 2.1 & 2.2)

2.1 Describe four complications of acute cholecystitis.
Answer (Section 2.2.4)

2.2 Define the following common duct stones: primary, secondary, residual, recurrent.
Answer (Section 2.3)

2.3 What are the clinical features of common duct stones?
Answer (Section 2.3.1)

2.4 How is cholangitis managed?
Answer (Section 2.3.3)

EXERCISE 3

3.0 What is the difference between acute and chronic acalculous cholecystitis with regard to definition and clinical presentation?
Answer (Section 3.2.1 & 3.2.2)

3.1 What is cholesterolosis?
Answer (Section 3.3)

3.2 Describe the postcholecystectomy syndrome. Define acalculous biliary pain.
Answer (Section 3.4)

3.3 Give two major risk factors for neoplasms of the gallbladder.
Answer (Section 3.5)

3.4 What are the clinical features of gallbladder carcinoma?
Answer (Section 3.5, second paragraph)

EXERCISE 4

4.0 Describe five congenital diseases of the bile duct.
Answer (Section 4.1)

4.1 What is cholangitis?
Answer (Section 4.2.1)

4.2 What is primary sclerosing cholangitis?
Answer (Section 4.2.2)