THE MEDIUM TO LONG TERM SEQUELAE OF ENDOSCOPIC SPHINCTEROTOMY IN THE MANAGEMENT OF COMMON DUCT STONES IN HUSM

(1992 – 1998)

By

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II ABSTRAK

Perkembangan terkini berkenaan dengan peralatan dan teknik kanulasi, litotripsi dan pembedahan secara laparoskopi telah mengubah cara rawatan batu di dalam saluran hempedu. Sebelum ini pembedahan adalah cara utama rawatan, tetapi kini kebanyakannya berjaya dirawat dengan kaedah endoskopi. Endoskopi Retrograde Cholangiopancreatografi (ERCP) dan Sphincterotomi secara Endoskopi (EST) kini diterima sebagai satu rawatan yang ideal untuk batu di dalam saluran hempedu.

Banyak laporan berkenaan dengan kesan awal sphincterotomi secara endoskopi tetapi hanya sedikit sahaja laporan berkenaan dengan kesan jangka pertengahan dan jangka panjang kaedah rawatan ini dalam merawat batu dalam saluran hempedu. Terlalu sedikit data tempatan berkenaan dengan perkara ini. Oleh itu suatu kajian telah dilakukan yang meliputi demografi, kadar kejayaan dan kesan jangka pertengahan dan jangka panjang kaedah sphincterotomi secara endoskopi untuk merawat penyakit batu di dalam saluran hempedu.

Kajian ini adalah secara deskripsi retrospektif yang dilakukan keatas pesakit dengan batu dalam saluran hempedu yang menjalani rawatan sphinterotomi secara endoskopi di Unit Endoskopi Hospital Universiti Sains Malaysia dari tahun 1992 hingga 1998.

Kajian ini menunjukkan bahawa sebahagian besar dari pesakit adalah kaum Melayu yang kebanyakkannya adalah wanita. Kejadian ini berlaku dalam kumpulan yang lebih muda berbanding dengan kajian yang lain. Walau bagaimanapun sebahagian besar dari mereka telah hilang dari rawatan susulan sebab mereka adalah dirujuk dari hospital lain.

Kajian kami menunjukkan kadar kejayaan sebanyak 90% iaitu setara dengan laporan yang lain. Dalam kajian kami sebanyak 53.5% dari mereka tidak mengalami apa-apa gejala sementara 46.5% pula menunjukkan gejala semasa rawatan susulan. Daripada 20 orang pesakit yang mempunyai gejala,15 orang (75 %) mempunyai penyakit yang berkait dengan sistem hempedu, sementara 2 orang (10%) bukan sistem hempedu dan 3 orang yang lain mempunyai diagnosa yang tidak dapat ditetapkan. 9 orang pesakit (45%) telah didiagnoskan mengalami penyakit batu di dalam pundi hempedu, samada yang berkait dengan penyempitan saluran hempedu, 'ascending cholangitis' ataupun batu di dalam pundi hempedu. 2 orang lagi mengalami penyakit batu di dalam pundi hempedu. 1 orang pesakit untuk setiap yang berikut, ascending cholangitis, biliary chirrosis, pembengkakan pundi hempedu dan batu di dalam pundi hempedu, oriental cholangitis, gastritis dan barah carcinoma pada bahagian sigmoid usus besar.

III ABSTRACT

Recent development of new cannulation instruments and techniques, improvement in the lithotripsy methods and the advent of laparoscopic surgery have changed the management of common duct stones. Previously surgical intervention was the mainstay of treatment, but now most can be successfully treated endoscopically. Endoscopic Retrogradecholangiopancreatography (ERCP) and Endoscopic Sphincterotomy (EST) is accepted as the gold standard for the management of common duct stones.

There are many reports of early results of EST, however few reviews regarding the medium to long term sequelae of EST for the treatment of common duct stones. The local data about this subject is very scanty. Hence forth a study conducted to include the demography, success rate and medium to long term sequelae of EST in patients with common duct stones.

This is a retrospective descriptive study done on 224 patients with common duct stones who underwent EST in Endoscopy Unit of Hospital Universiti Sains Malaysia from 1992 to 1998.

The study showed that majority of the patients was Malays with female preponderance. The incidence occurred in the younger age group compared with other reported series. However majority of them were lost from follow up as they were being referred from other hospitals.

Our study showed a success rate of 90% which are comparable with other series. In our study 53.5 % were symptom free, while the remainder (46.5 %) were noted to have some digestive complaints during the follow-up period. Out of 20 patients who were symptomatic during follow up after EST, biliary consequences occurred in 15 (75 %) of patients and non biliary consequences occurred in 2 (10 %) of patients and non specific diagnosis in 3 (15 %) of patients. 9 patients (45 %) were diagnosed to have choledocholithiasis with or without associated strictures, ascending cholangitis or cholelithiasis. 2 patients had cholelithiasis. Another 1 patient had ascending cholangitis, biliary chirrosis, cholecystitis with cholelithiasis, oriental cholangitis, gastritis and sigmoid colon carcinoma, respectively.

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1.0: INTRODUCTION

Since its introduction into Endoscopic Retrograde Cholangiopancreatography (ERCP)in 1974, Endoscopic Sphincterotomy (EST) has become a common procedure and well-established therapeutic procedure , as an alternative to biliary tract surgery.[1,2] Endoscopic sphincterotomy is most commonly performed to remove bile-duct stones and is often substituted for surgical exploration of the common bile duct in patients undergoing laparoscopic cholecystectomy. It also performed to facilitate the placement of stent through malignant and benign biliary strictures and for other biliary and pancreatic problems. Endoscopic sphincterotomy (EST) , is a technically complex endoscopic procedure performed under visual and fluoroscopic guidance . The usual approach involves deep insertion of a cannula into the bile duct through the ampulla of Vater, followed by electrocautry to incise the spinchter of Oddi. [1]

Sphincterotomy and associated pancreatic and biliary instrumentation can cause pancreatitis, hemorrhage, perforation and other complications [1] There are many reports of early and intermediate-term results of endoscopic sphincterotomy. However, few data are available on long-term clinical outcome of endoscopic sphincterotomy for removal of common bile duct stones .[3]

This dissertation is a study on the medium to long term sequele of patients with common duct stone who underwent endoscopic sphincterotomy at Hospital Universiti Sains Malaysia from 1st January 1992 to 31st December 1998 .

It is hoped that the result derived from this study would help in improving the management of patient with common bile duct stone in the future.

2.0: LITERATURE REVIEW ON CHOLEDOCHOLITHIASIS

2.1:ANATOMY

2.1.1: EMBRYOLOGY OF THE GALLBLADDER AND BILIARY SYSTEM

At the fourth week of embryologic development, a diverticulum develops on the ventral surface of the foregut just cephalad to the yolk sac and just caudad to the fusiform dilation that is the gastric precursor . This ventral diverticulum grows more ventrally into the septum transversum. Two buds of solid epithelial cells develop at its tip and create the right and left lobes of the liver by developing into hepatic cylinders and forming a meshlike network with rich vascular channels. The early developing liver is like a vascular sponge attached to the duodenum by the original hepatic diverticulum, which soon becomes the bile duct system. The bile duct system starts out as a solid outgrowth, from which another bud arises to become the cystic duct and gallbladder. As the distal portion of the bile duct branches into right and left limbs and enters the developing right and left lobes of the liver, it vacuolates and then canalizes and forms into one continuous epithelial-lined lumen. The same type of canalization occurs in the cystic duct and finally in the gallbladder at about 3 months' gestation. The right and left ducts, which also begin as solid outgrowths from the original diverticulum, likewise canalize and drain the liver of its bile. A migration across the right face of the foregut brings the origin of the bile duct toward the dorsal mesentery of the second portion of the duodenum, where it is joined with the ventral pancreatic duct, another bud from the proximal portion [4]

2.1.2:ANATOMY OF THE EXTRAHEPATIC BILIARY TRACT

The extrahepatic biliary tract consists of the three hepatic ducts (right, left and common), the gallbladder and cystic duct, and the bile duct. The right and left hepatic ducts exit from the liver and join to form the common hepatic duct near the right end of the porta hepatis. In a surgical sense, it is only the confluence of the hepatic ducts which is accessible without dissection into the liver substance. But prior to its emergence from the liver, the left hepatic duct may run along the base of the quadrate lobe only partly surrounded by the liver substance. The *common hepatic duct* so formed passes down between the two peritoneal layers at the free edge of the lesser omentum. The common hepatic duct is soon joined on its right side at an acute angle by the cystic duct from the gallbladder, to form the bile duct . When the liver is retracted at operation the ducts are seen to descend below the liver, but at rest they lie in loose contact with the porta hepatis.[5]

2.1.2.1: GALLBLADDER

The gallbladder stores and concentrates the bile secreted by the liver. It is a globular or pear-shaped viscus with a length of 7 to 10cm and capacity of about 50 ml, and consists of three parts—fundus, body and neck.[5] It lies in the gallbladder fossa on the visceral surface of the right lobe of the liver, adjacent to the quadrate lobe.[5]

Its bulbous blind end, the findus, usually projects a little beyond the sharp lower border of the liver and touches the parietal peritoneum of the anterior abdominal wall at the tip of the ninth costal cartilage, where the transpyloric plane crosses the right costal margin, at the lateral border of the right rectus sheath This is the *surface marking* for the fundus and the area of abdominal tenderness in gallbladder disease. (The fundus of the normal gallbladder is not palpable but may become so if distended by biliary tract obstruction.) The fundus lies on the commencement of the transverse colon, just to the left of the hepatic flexure. The body passes backwards and upwards towards the right end of the porta hepatis and is in contact with the first part of the duodenum. The upper end of the body narrows into the neck which, when the liver is in its normal position (not retracted upwards), lies at a higher level than the fundus. The neck continues into the cystic duct, which is 2—3 cm long and 2—3 mm in diameter. It runs backwards, downwards and to the left to join the common hepatic duct, usually in front of the right hepatic artery and its cystic branch (but variations are common). The wall of the neck where it joins the cystic duct may show a small diverticulum (Hartmann's pouch). This is not a feature of the normal gallbladder and is always associated with a pathological condition; it may be the site of impaction of a gallstone.

The fundus and body of the gallbladder are usually firmly bound to the undersurface of the liver by connective tissue; small cystic veins and lymphatic pass from the gallbladder into the liver substance. Small bile ducts (accessory bile duct) may also pass from the liver to the gallbladder, and if undetected they may drain bile into the peritoneal cavity after cholecystectomy. The

peritoneum covering the liver passes smoothly over the gallbladder. Occasionally the gallbladder hangs free on a narrow 'mesentery' from the undersurface of the liver. Rarely the gallbladder may be embedded within the liver. Very rarely the gallbladder may be absent.

The gallbladder varies in size and shape. In rare cases it is duplicated with single or double cystic ducts. It may be septated with the lumen divided into two chambers. The fundus may be folded in the manner of a Phrygian cap; this is the most common congenital abnormality , which has no pathological significant [5,6]

2.1.2.1.1: BLOOD SUPPLY

The cystic artery is usually a branch of the right hepatic artery (95 %). It runs across the triangle formed by the liver, common hepatic duet and cystic duct *(Calot's triangle),* to reach the gallbladder.[5] One branch runs along the peritoneal surface of the gallbladder and the other branch in the gallbladder fossa between the gallbladder and liver. Variations in the origin of the artery are common. It may arise from the main trunk of the hepatic artery, from the left branch of that vessel or from the gastroduodenal artery, and in either ease may pass in front of the cystic and bile ducts. When the cystic artery arises from the right hepatic artery, its course is often parallel and medial to the cystic duct. Double or accessory cystic arteries have been reported in up to 20% of people. The cystic artery may be short or long, and may pass either behind the hepatic duct (84%) or may cross the hepatic duct anteriorly.[6]

Venous return is by multiple small veins in the gallbladder bed into the substance of the liver and so into the hepatic veins. One or more cystic veins may be present but these are uncommon; they run from the neck of the gallbladder into the right branch of the portal vein. Cystic veins do not accompany the cystic artery.[5]

2.1.2.1.2: LYMPY DRAINAGE

Lymphatic channels from the gallbladder drain to nodes in the porta hepatis, to the cystic node (in Calot's triangle at the junction of the common hepatic and cystic ducts), and to a node situated at the anterior boundary of the epiploic foramen. From these nodes lymph passes to the celiac group of preaortic nodes.[5]

2.1.2.1.3: HISTOLOGY

The gallbladder is a fibromuscular sac which has five layers : epithelium, lamina propria, muscularis, perimuscular connective tissue layer, and serosa [6] . Its mucous membrane is a lax areolar tissue lined with a simple columnar epithelium. It is projected into folds which produce a honeycomb appearance in the body of the gallbladder, but are arranged in a more or less spiral manner in the neck and cystic duct (the *'spiral valve'* of Heister). Mucus is secreted by th e columnar epithelium but there are no goblet cells, and mucus-secreting glands are present only in the neck. [6] The basal surface of the epithelium is in contact

with the lamina propria rich in loose connective tissue, elastic fibers, blood vessels, and lymphatics. The muscularis is an arrangement of circular, longitudinal, and oblique fibers without any well developed layers [5,6] Ganglia may be found between the muscle fibers of the muscularis. The subserosa contains loosely arranged collagen and elastic fibers, as well as larger blood vessels and lymphatics. This thick subserosal layer attaches the gallbladder to the liver[6]

2.1.2.2: COMMON HEPATIC DUCT

The right and left hepatic ducts emerge from the porta hepatis and unite near its right margin in a Y-shaped manner to form the common hepatic duct.[5] In 95% of cases, this union takes place outside the liver, just below the level of the porta hepatis. In 5% of cases, the left and right hepatic ducts join within the substance of the liver.[6] This is joined, usually after about 3 cm, by the cystic duct to form the bile duct. The common hepatic duct is about 4 cm long with a diameter of 4 mm; it lies in the free edge of the lesser omentum, in front of the right edge of the portal vein and with the hepatic artery on its left. The right branch of the hepatic artery normally passes behind the common hepatic duct but may run in front of it. The site of union of the cystic and common hepatic ducts is usually on the right side of the common hepatic duct about 1—2 cm above the duodenum, but sometimes the cystic duct runs parallel to and on the right of the hepatic duct for a variable distance before uniting with it, and it may also spiral round behind the hepatic duct before joining it on its left side. Rarely the cystic duct may be absent and the gallbladder drains directiy into the

pressure and may function to block passage of gallstones into the common bile duct. They may make catheterization difficult during intraoperative cholangiogram [6]

2.1.2.4: BILE DUCT

The bile duct is formed by the union of the cystic duct and common hepatic duct. [6]Formerly called the common bile duct it is about 8 cm long and 8 mm in diameter, and is best described in three parts or thirds. The upper (supraduodenal) third lies in the free edge of the lesser omentum in the most accessible position for surgery ,in front of the portal vein and to the right of the hepatic artery, where the lesser omentum forms the anterior boundary of the epiploic foramen.[5] This anatomic relationship allows the surgeon to compress these three structures between an index finger inserted through the foramen of Winslow into the lesser sac and a thumb placed anteriorly across the hepatoduodenal ligament. This maneuver is referred to as the Pringle maneuver and allows rapid occlusion of the blood supply to the liver, which is useful for controlling major liver hemorrhage. [6] The middle (retroduodenal) third runs behind the first part of the duodenum and slopes down to the right, away from the almost vertical portal vein which now lies to the left of the duct with the gastroduodenal artery. The inferior vena cava is behind the duct. The lower (paraduodenal) third slopes further to the right in a groove between the back of the head of the pancreas and the second part of the duodenum (it may even be embedded in a tunnel of pancreatic tissue) and in front of the right renal vein. It joins the pancreatic duct at an angle of about 60^0 at the hepatopancreatic

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ampulla (of Vater). The ampulla and the ends of the two ducts are each surrounded by sphincteric muscle, the whole constituting the *ampullary sphincter* (of Oddi). Sometimes the muscle fibres surrounding the ampulla and the pancreatic duct are absent, leaving only the bile duct sphincter. When all three are present the arrangement allows for independent control of flow from bile and pancreatic ducts. The ampulla itself opens into the posteromedial wall of the second part of the duodenum at the major duodenal papilla, which is situated 10 cm from the pylorus [5]

2.1.2.5: AMPULLA OF VATER

The ampulla of Vater is formed by the union of the common bile duct and the main pancreatic duct. The length of the ampulla is variable, and if there is no junction of the common bile duct and main pancreatic duct, there is no true ampulla of Vater. In a study of the pancreatic duct system in 250 autopsy specimens, Rienhoff and Pickrell found an ampulla longer than 2 mm in 46% of cases (range from 3 to 14 mm), an ampulla less than 2 mm in 32% of cases, and no junction of the pancreatic and bile ducts in 29% of cases [6] The common bile duct narrows significantly as it passes through the wall of the duodenum, and the ampulla narrows before it enters the duodenal lumen These narrowings are frequent sites for stones to lodge and cause either biliary or pancreatic obstruction. Additionally, these are potential sites of injury when instrumented during common bile duct exploration. [6]

2.1.2.6: SPHINCTER OF ODDI

The intraduodenal segment of the common bile duct and the ampulla is surrounded by a sheath of smooth muscle fibers referred to collectively as the sphincter of Oddi. The sphincter of Oddi is a unique group of muscle fibers that arise from the bile duct wall and manometric studies have verified that the sphincter acts independently of the duodenal musculature. The resting pressure of the sphincter of Oddi is approximately 13 mm Hg above duodenal pressure. Regulation of bile flow is primarily controlled by the sphincter of Oddi. Relaxation of the sphincter occurs with Cholecystokinin (CCK) stimulation and is facilitated by parasympathetic stimulation. Sympathetic stimulation causes increased sphincter tone.

The preampullary portion of the common bile duct is invested in a sheath of circular muscle referred to as the sphincter choledochus (sphincter of Boyden). The distal main pancreatic duct may have a short sphincter called the sphincter pancreaticus. If present, the sphincter pancreaticus and sphincter choledochus may intertwine in a figure-of-eight manner. The smooth muscle sheath surrounding the ampulla is called the sphincter of the ampulla; if there is no ampulla, the distal sphincter is simply called the sphincter of the papilla. During endoscopic sphincterotomy, the sphincter of Oddi is divided using electrocautery to relieve common bile duct obstruction from a common duct stone [6]

2.1.2.7: BLOOD SUPPLY OF THE BILIARY TRACT

The extrahepatic biliary tract receives small branches from the cystic and right hepatic arteries and the posterior branch of the superior pancreaticoduodenal artery; they form anastomotic channels on the duct. [5] The arterial blood supply to the extrahepatic bile ducts is segmental. The hepatic ducts and the supraduodenal portion of the common bile duct are nourished by small arterial branches from the cystic artery. The retroduodenal portion of the common bile duct is supplied by branches of the retroduodenal and posterior superior pancreaticoduodenal arteries The pancreatic and intraduodenal segments of the common bile duct are supplied by both the anterior and posterior superior pancreaticoduodenal arteries. Because of the segmental nature of the blood supply, extensive mobilization of the extrahepatic bile ducts may lead to ischemic injury and development of post-operative biliary stricture. [6]. Small veins from the biliary tract drain to the portal vein or enter the liver. [5]

2.1.2.8: LYMPHATIC

The lymphatic drainage from the hepatic ducts and upper common bile duct flows superiorly along the course of the common bile duct to lymph nodes in the porta hepatis. Some lymphatic drainage arising from the inferior portion of the common bile duct may reach the deep pancreatic nodes near the origin of the superior mesenteric artery. All lymphatic drainage ultimately reached the celiac lymph nodes. [6]

2.1.2.9: NERVE SUPPLY OF THE BILIARY TRACT

Parasympathetic fibres, mainly from the hepatic branch of the anterior vagal trunk, stimulate contraction of the gallbladder and relax the ampullary sphincter, and sympathetic fibres from cell bodies in the coeliac ganglia (with preganglionic cells in the lateral horn of spinal cord segments T 7-9) inhibit contraction, but the hormonal control of gallbladder activity (Cholecystokinin from enteroendocrine cells of the upper small intestine) is much more important than the neural. Afferent fibres including those subserving pain (e.g. from a duct distended by a gallstone) mostly run with right-sided sympathetic fibres and reach spinal cord segments T7—9, but some from the gallbladder may run in the right phrenic nerve (C3-5), through connections between this nerve and the coeliac plexus. Any afferent vagal fibres are probably concerned with reflex activities, not pain. Biliary tract pain is usually felt in the right hypochondrium and epigastrium, and may radiate round to the back in the infrascapular region, in the area of distribution of spinal nerves T7-9. The phrenic nerve supply explains the occasional referral of pain to the right shoulder region. [5]

2.1.2.10: HISTOLOGY

The mucosa of the extrahepatic bile ducts contains columnar epithelium surrounded by a layer of connective tissue. The epithelium contains many mucous glands. Muscle fibers in the hepatic ducts and proximal common bile duct are relatively few and discontinuous, and may be arranged in either a longitudinal or circular direction. As the common bile duct approaches the

duodenum, it begins to develop a more substantial muscle layer, which merges into the sphincter of Oddi complex, where distinct bundles of muscle fibers are evident [6]

2.2: CHOLEDOCHOLITHIASIS

2.2.1: PATHOGENESIS

2.2.1.1: SECONDARY DUCTAL STONES

Concomitant choledocholithiasis is found in 12% to 15% in patient with cholecystitis .The prevalence of choledocholithiasis increases in older age groups. In patients younger than 59 years of age, the prevalence of concomitant common duct stones removed at cholecystectomy was 4% to 6.7%, but the rate increased to 13% to 18% for those 60 to 79 years of age and to 33.3% for those older than 80 years of age. [7]

In the Western countries it was reported as 70% to 80% of gallbladder stones are cholesterol stones, and 20% to 30% are pigment stones. Approximately 55% to 70% of common duct stones are cholesterol stones. Most of the common duct stones are secondary stones. Several lines of evidence support this. First, when stones are found in the CBD and gallbladder at the time of surgery, the CBD stones are similar in chemical composition to gallbladder stones . Pigment stones in the common duct and gallbladder of the same patient differed more

than the cholesterol stone pairs; they contained more bilirubin and less residue than their gallbladder counterparts. Second, only 10% to 20% of patients with common duct stones have no stones in their gallbladders [7]

2.2.1.2: PRIMARY DUCTAL STONES

Formation of stones in the bile duct de novo is supported by several observations. First, 20 of 47 symptomatic patients with congenitally absent gallbladders had CBD stones. Second, in cholecystectomized animals, stones form proximal to experimental strictures of the CBD, and in humans, benign and malignant strictures of the bile duct frequently result in sludge and stones proximal to the obstruction. The chemical composition of primary duct stones, which are mostly calcium bilirubinate with a cholesterol content of less than 25%, is very different from that of the predominant type of gallbladder stones.[7]

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The true incidence of primary duct stones in the West is difficult to ascertain because of tremendous disagreement about diagnostic criteria. In 1924, Aschoff proposed that primary duct stones could be differentiated morphologically. They are light brown, greenish brown, or black; "earthy" and soft; frequently laminated; and easily crushed to form biliary mud. These are frequently referred to as brown pigment stones or bile pigment calcium stones, in contrast to the black stones, which are hard and brittle, almost structureless, and originate from the gallbladder. Brown stones consist mainly of calcium bilirubinate, with little cholesterol, and always contain calcium palmitate, but

black stones mainly contain bilirubin polymers, usually calcium carbonate or phosphate, seldom cholesterol, and never calcium palmitate. [7]

Using only morphologic criteria, Madden reported that 56% of the CBD stones are primary. However, morphologic criteria alone may be unreliable. More than one half of the common duct stones were found at the time of initial operation for cholecystectomy. Many of these stones could have originated in the gallbladder and grown in the CBD to give the appearance of a primary stone. If the gallbladder is still in place or only recently has been removed, the origin of the duct stone is impossible to discern. Saharia and colleagues, using strict criteria for the diagnosis of primary duct stones, found only a 4% prevalence of primary duct stones in 758 patients undergoing common duct exploration. Their criteria consisted of a 2-year asymptomatic period after cholecystectomy, common duct stones with the morphologic appearance of primary duct stones, and absence of a long cystic duct remnant or biliary stricture from the previous surgery. Most gastroenterologists would accept that, if a common duct stone is found within 1 year after a cholecystectomy, it is more likely to be a retained gallbladder stone (i.e., secondary stone). A common duct stone found more than 2 years after cholecystectomy is usually considered to be a primary common duct stone. This distinction is important, because the clinical course, prognosis, and management may differ [7]

Although the pathogenesis of primary duct stone formation remains unknown, several factors seem to play major roles under certain circumstances, including stasis, bacterial or parasitic infections, diet, foreign material in the duct, and

juxtapapillary diverticula. Experimental obstruction and stasis result in stone formation in animals. In humans with benign or malignant strictures, sludge and stones frequently occur proximal to strictures. [7,8]

In examining the role of bacteria in the pathogenesis of primary duct stones, Tabata and Nakayama cultured bile aerobically and anaerobically from 200 consecutive gallstone cases. They found the prevalence of positive culture ($>10^5$ colony-forming units/mL bile) depended on the type of stone and the location of the stone. For stones localized to the gallbladder, only 5% of cases with black stones and 15% of cases with cholesterol stones were culture positive, but 80% of cases with brown stones were positive. For stones in the CBD, 100% of cases with brown stones were culture positive, and 74% of cases with cholesterol stones were culture positive. More than two organisms commonly were found in cases of brown stones. The most common organisms isolated were *Escherichia coli*, *Klebsiella*, and other enteric gram-negative organisms. Anaerobes such as *Bacteroides* and *Clostridium* were also frequently isolated. These anaerobes possess B-glucuronidase activity like *E coli*. The investigators suggest that bacteria play a major role in the pathogenesis of brown stones. Bilirubin is excreted in bile mainly as diglucuronide and partly as monoglucuronide. These molecules are subsequently transformed to unconjugated bilirubin by B-glucuronidase and combine with calcium to form calcium bilirubinate, which precipitates in aqueous media. Tissue lysosomal B-glucuronidase activity occurs in bile, but the optimal pH for its activity is 4.2. Bacterial B-glucuronidase has an optimal pH of 7.0, and the pH in bile is 6.25 to 8.10. It is therefore likely that bacterial

B-glucuronidase activity leads to formation of unconjugated bilirubin, which later forms bile pigment calcium stones. In addition, bacterial phospholipases can hydrolyze lecithin present in bile, which can account for the high content of fatty acid calcium soaps in these stones. [7]

The association of biliary infection with primary common duct stones has been found by other investigators. Lygidakis found that 73% of cases with primary duct stones had bile that was culture positive, compared with only 16% of cases with secondary stones. He also observed that positive cultures were significantly associated with the number of previous biliary tract interventions, diameter of the CBD (35%–100% positive in cases with >1.5–5-cm CBD diameter), increasing age, and duration of symptoms. Anaerobes were more likely to be cultured in those with primary duct stones. Bacterial cytoskeleton are found in all stones by scanning electron microscopy. [8]

Some argued that the association between bacteria and brown stones is impressive but cannot prove a cause-and-effect association. Bacterial infection may result from common duct stones and bile stasis. This is supported by the high prevalence of positive cultures in some reports of secondary duct stones. However, Cetta documented bile infection by *E coli* preceded rather than followed brown stone formation, and Kaufman and colleagues showed that bacteria were observed within only brown pigment stones and not in black pigment or cholesterol stones. This type of evidence lends more support to the pathogenic role that bacteria play in primary, but not secondary, duct stones.

The association of parasitic infection and primary duct stones has been made predominantly in Asia. However, Schulman, from South Africa, documented that 13 of 13,500 patients (<0.001%) who underwent abdominal ultrasound examination had intrahepatic calculi. None of the patients had travelled to the Far East, and all ate a predominantly Western diet. Only 1 of the 13 patients had evidence of gallbladder stones. All except one patient had documented *Ascaris* infection, implicating ascariasis as the etiologic factor in intrahepatic duct stones formation in these patients. He updated his series to include 40 patients, again strongly implicating ascariasis in the pathogenesis of these stones in that region. Roundworm elements were reported in as many as 55% to 70% of patients with intrahepatic brown stones in series from Southeast Asia just after World War II. Although worms of the biliary tree may cause obstruction and infection leading to calcium bilirubinate precipitation, roundworm infestation occurs worldwide and is endemic in underdeveloped countries, but intrahepatic duct stones rarely occur outside Southeast Asia. This suggests that additional factors contribute to the high prevalence of cholangiohepatitis in Asia.

Dietary factors can be important. Bilirubin is excreted in bile as diglucuronide and monoglucuronide, which may then be subjected to breakdown by *B*-glucuronidase to glucuronic acid and free bilirubin. Inhibitors of *B*-glucuronidase, such as glucaro-1,4-lactone (measured as glucaric acid), free bilirubin, glucuronic acid, and Cu^{2+}, occur in bile. The primary inhibitor appears to be glucaro-1,4-lactone; the levels of the other inhibitors in normal bile are too low to exert any appreciable effect. Glucaro-1,4-lactone is a degradation

product of hepatic metabolism of glucuronic acid. The level of glucaro-1,4-lactone was lowered in animals fed diets low in protein and fat. *E coli* has been shown to metabolize glucaric acid into glycerate and pyruvate. Perhaps protein and fat malnutrition leads to bile low in glucaric acid and high in B-glucuronidase activity. A diet low in fat and protein may promote bile stasis because of decreased cholecystokinin release, which normally relaxes the sphincter of Oddi. *E coli* infection in the bile can further worsen this imbalance by degrading the glucaric acid present and by providing its own B-glucuronidase activity. All of these factors may contribute to formation of calcium bilirubinate.

Indirect support for dietary factors in the pathogenesis of primary duct stones comes from studies in Asia, especially Japan, where the prevalence of calcium bilirubinate stones among patients with stones before World War II and the ensuing 10 years was 60% to 80%. After 1953, the prevalence of cholesterol gallstones rose, and that of calcium bilirubinate stones decreased. From 1972 to 1974, cholesterol gallstones accounted for 85% of stones in Japan. From 1975 to 1978, the prevalence of intrahepatic stones found in patients undergoing biliary surgery at 40 hospitals in western Japan was only 3.03%, and the prevalence was much higher in rural hospitals than in urban hospitals (4.97% versus 1.5%). All of these changes coincided with dietary changes that took place in Japan. The average daily protein intake increased from 65 to 78 g and fat intake from 16 to 48.7 g between 1949 and 1971. Parasites were virtually eradicated after 1965, which may have contributed to the decreased prevalence of brown stones

Foreign material in the bile duct can be a factor in stone formation. In at least two series, 30% of recurrent stones in the CBD after cholecystectomy contained unabsorbable suture material in the center of the stone. This could have served as a nidus for stone growth. Nonabsorbable suture material should be avoided in surgical procedures in the vicinity of the CBD [7] .Hemostatic clip also can provide nidus for bacrerial colonization and subsequently stone growth [8]

The association of juxtapapillary diverticula and common duct stones has been observed by several researchers. The prevalence of duodenal diverticula varies from 3% to 22% in autopsy series and 18.8% to 23% among patients who underwent endoscopic retrograde cholangiopancreatography (ERCP). Ninety percent of duodenal diverticula occur on the medial wall of the duodenum, and two thirds are juxtapapillary. The ampulla may be adjacent to the diverticulum or may empty into it. In an ERCP study of stone recurrence after cholecystectomy, 88% of patients with juxtapapillary diverticula had recurrent common duct stones, but only 32% of patients without diverticula had recurrent common duct stones. The stones were much more likely to be pigmented and to be recurrent after cholecystectomy. In another study, 59% of patients with recurrent duct stones found 3 or more years after cholecystectomy had diverticula, but only 13% with stone-free ducts had diverticula.[7]

Manometric studies found significantly lower sphincter of Oddi (SO) pressures in patients with juxtapapillary diverticula. Theoretically, bacterial overgrowth in the diverticula may colonize the bile duct. These observations strongly support the association of juxtapapillary diverticula and common duct stones. How the diverticula develop in the first place and whether they predispose to the formation of duct stones is only speculative. [7]

Two other findings associated with common duct stones are low entry of the cystic duct (<3.5 cm from the ampulla) and abnormal motor activity of the sphincter of Oddi. Touli and co-workers found no difference in the CBD pressure, SO basal pressure, SO phasic wave amplitude, frequency and duration, or percentage of simultaneous SO contractions between patients with common duct stones and normal controls. The only significant difference was the direction of SO pressure wave propagation. In controls, 60% (±4%) of wave sequences were antegrade, and 26% (±3%) were retrograde. In patients with common duct stones, 18% (±5%) of wave sequences were antegrade, and 53% (±9%) were retrograde. It is unclear whether this abnormal motility pattern contributes to the cause of common duct stones or is a secondary effect of the common duct stones.[7]

2.2.2: PATHOLOGY

The presence of stones within the biliary tree can affect bile duct pressure. The consequence of such pressure changes on liver and bile duct was examined histologically. The common duct diameter and intraluminal pressure in 121

prospectively evaluated patients undergoing biliary tract surgery for symptomatic cholelithiasis (n = 26; control group) or common duct stones with (n = 45) or without (n = 50) concommitant cholangitis were significantly greater with choledocholithiasis. Moreover, patients with cholangitis had a significantly greater common bile duct diameter (mean, 20 mm versus 16 mm) and intraluminal pressure (mean, 20 cm H_20 versus 13 cm H_2O) than did those with common duct stones but no cholangitis.[8]

Gross pathologic inspection of the common duct may reveal varying degrees of mucosal edema and thickening of the duct wall. When cholangitis supervenes, ulceration with fibropurulent exudate may be observed. On macroscopic examination, the liver is enlarged, swollen, and stained green with bile. The dilated intrahepatic ducts initially contain dark bile. With continued obstruction, "white bile" (colorless fluid) is found because increased intraductular pressure suppresses secretion of bile by the liver. The already secreted pigment is progressively absorbed or decolorized by leukocytic and bacterial action and is replaced by mucinous secretion from the glands in the duct wall. When cholangitis supervenes, the duct may contain pus or be surrounded by small abscesses. [8]

Histologic changes in the liver were found in only 8% of patients without duct stones, in contrast to 89% of patients with cholangitis and 47% with common duct stones alone . The changes consisted of acute and chronic inflammatory infiltration of the portal areas, cellular and nuclear pleomorphism in the parenchyma, isolated or focal hepatocyte necrosis, variable degrees of