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Acute noncalculous cholecystitis : with special reference to the surgical treatment

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ACUTE NONCALCULOUS CHOLECYSTITIS

WITH SPECIAL REFERENCE TO THE SURGICAL TREATMENT

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"And if so be any man object unto me that this discourse is only compilede together of certayne rapsodyes of the antique Chyrurgians, I willingly heere confes and acknowledge that in this Treatise there is verye little, or nothing at all, of myne own Invention." (68)

Introduction

In the past it has been the tendency for the surgeons to treat all cases of cholecystitis surgically, and the internist has tended to treat all cases medically. Sadly enough, gall bladder surgery, when considered as a whole, leaves a large percentage of patients with symptoms requiring further exploration and advice. On the other hand, many patients with gall bladder disease, who were treated medically, have had longer periods of morbidity and mortality from the sequelae of gall bladder disease which might well have been removed by surgical means.(34)

Gall bladder disease is much more accurately diagnosed since the introduction of current radiological technics. The underlying basic physiology and pathology has provided special impetus in the progress of this disease.

Cholecystitis occurs twice as frequently as peptic ulcer and gastric carcinoma combined, and is an important condition from both a diagnostic and therapeutic standpoint. Although most cases eventually come into the hands of the surgeon, it is the physician whose responsibility it is to make an accurate diagnosis and to advise the proper line of treatment.

It is the purpose of this thesis to discuss acute noncalculous cholecystitis in its ramifications, to pay special attention to the treatment, and to differentiate between those cases which would best be handled medically or surgically.

History

The Babylonian and Assyrian priests were probably the first to recognize the gallbladder and bile ducts. They cast the entrails of a sacrificial animal upon the ground, the pattern thus made by the entrails was to express the will of the gods. (93)

The Ebers Papyrus which was found in 1872-3 was written about 1552 B.C.. It contains the earliest record of hardening and inflammation of the abdomen. (26)

Hippocrates, born on the Island of Cos about 460 B.C., was the first to separate medicine from religion and philosophy, and to make it an independent subject. Probably his greatest contribution was that of medical diagnosis. It was Galen, born in Greece about 130 A.D., who first described jaundice. Galen's last great volume marked the peak of the ancient scientific medicine. (68) He believed nausea was induced when cardia took on a bitter character due in turn to a preponderance of bile in the stomach.(34) Galen noted the collecting function of the gall bladder and was familiar with stones, however the early Greeks had little to say about gallstones even though they were excellent observers. This leads one to suspect that cholecystitis was a rare disease probably due to their simple diet and adequate excercise. Rufus of Ephesus in the first century A.D. seemed to be aware that obstruction of biliary flow produced jaundice. (93)

Roman medicine furnished very little to the sum total of medical knowledge, their greatest contribution being in the field of

public sanitation. "Medicine owes much to the Arabians, who snatched the torch of Hellenistic culture before it was snuffed out in the Dark Ages and preserved the remains until the flame burned brightly once more with the reviving of scholarship in the fifteenth and sixteenth centuries."(68) They preserved the ancient Greek texts, and as such the vast teachings of antiquity were preserved. The Arabs were great users of amulets, however they introduced many new drugs as camphor, senna, myrrh, nutmeg, clove, ambergris, and cannabis; they originated syrups, alcohol, and aromatic waters. (68)

The Hindus discovered the surgical use of loadstone, plastic surgery and they make knives of steel which could divide a hair, catheters, trochars, and many blunt instruments. The School of Salerno was the main link between the later Greek physicians and the teaching institutions which remain with us to this day. Their pathology was of four humors: blood, phlegm, yellow and black bile.(34)

Vesalius was the founder of modern anatomy and was unblinded by the venerations of Galen. Vesalius dissected the human body and made"accurate" observations thereof, thus dispelling much of the inaccurate work of Galen,(68) however, Stieda noted that the models and drawing made by the Babylonian and Assyrian priests were more accurate in their detail than Vesalius' "Anatomy". (93)

Antonio Benivieni attempted to correlate a patient's complaints with the findings at necropsy of a stone in the biliary tract in 1507. Toward the middle of the sixteenth century numerous accounts

of gallstones appeared in the literature, most noteable wa perhaps that of Fallopius. Jean Fernel, in 1581, wrote an adequate account of the symptoms produced by gallstones. Johann Fabricius in 1618 attempted surgical drainage of the gallbladder, this report is considered doubtful though the procedure may have been performed on a cadaver.(93) Francis Glisson reported the modern concepts then known concerning the anatomy of the biliary system.(40) He also related the expulsion of gallstones through the intestinal tract of himself.(93) Van der Wiell and Thilesius in 1687 mentioned evacuation of gallstones on opening an abscess which presented through the abdominal wall. Sylvius thought the gallbladder made bile and hence writings of the time were confused. Sylvius noted the discoloration of urine produced by jaundice and that it imparted a yellow stain on paper and linen. Ettmuller, in 1708, described the classical stone symptoms, types of jaundice and the classical side effects of the obstruction of the common duct. He paved the way for modern surgery by the statement, "There are no medicines which will dissolve gallstones, for even when cholelithiasis appears, healed stones soon recur and lead to death." Also he made mention of Teckof who removed a dog's gall bladder without producing any definite effect on its health.(93) Talbor cured Louis XIV's biliousness with rose leaves soaked in water with lemon juice,to which was added Cinchona bark.(68) Heister was the first to consider the possible motor activities of the gallbladder and bile ducts,

and noted that chemical irritants might be the causes of contraction in these structures. Portal described in 1813, the dilatation of the bile ducts secondary to the presence of stones in the ducts.(93) Faithhorn, in 1822, reported to the medical world that the inflammation of the liver extended down the several ligaments to the gall bladder and ducts causing their walls to become thickened so as to occlude the passage thus producing jaundice. He seemed to have a fair knowledge as to the formation of bile but no idea as to the concentrating function of the gallbladder.(30) In 1846, cholecystitis became an entity of its own not requiring a preceding inflammatory process of the liver. (14) Pujol described in 1823, his own symptoms and recorded for the first time a satisfactory explanation for the recurrence of biliary colic. The phenomenon he felt was due to the impaction of stones in the cystic duct with associated contraction of the gallbladder, the stone later dropping back into the gallbladder as the colic subsided. Charcot's description of the intermittent fever of obstructive biliary disease appeared in 1877. Naunyn decided in 1896 that it was better if the surgeons did not operate a gallbladder while it was under acute attack but to wait until the viscus had ruptured and the shock had subsided.(74) Jean Louis Petit advocated direct incision into the inflammed gallbladder which had become adherent to the abdominal wall, in order to discharge the pus and stones. Fear of opening the peritoneum held the surgeons

of the day in check. Sebastian, Graves, and Thudichum working independently advocated a two stage operation. The first stage was to adhese the gallbladder to the abdominal wall, the second stage was the drainage of the gallbladder itself. Bobbs of Indianapolis performed the first cholecystostomy in this country in 1867. He removed the stones and returned the gallbladder to the abdomen - the patient lived. Tait in the pre-Listerian era performed fourteen operations for surgical drainage of the gallbladder between 1879 and 1885 with one death. Sims performed cholecystectomy on a jaundiced patient in Paris and was the first operation of its kind under antiseptic conditions. The first cholecystectomy is credited to Langenbuch in 1882. The ninth cholecystectomy to appear in literature was the first in the United States in 1887 by Justus Ohage of St. Paul. The development of a satisfactory surgical technic and the application of the principles of gallbladder surgery to cure the disease of the biliary tract developed rapidly within the next forty years. Pioneered by Mayo-Robson, and Moynihan in England, Kehr in Germany, and William J. and Charles H. Mayo in this country. Wm. J. Mayo reported two operations for the relief of obstruction from gall stones and one for stricture of the common bile duct in 1892; a year later he and his brother described making an anastamosis between the gallbladder and the jejunum in a case of complete obstruction to the common duct. (93)

Graham and Cole, in 1923, discovered that the administration of tetrabromophenolphthalein allowed visualization of the gallbladder by X-ray. This was then the beginning of cholecystography and also the beginning of the routine use of cholecystography in the diagnostic work-up of patients suspected of having cholecystitis and / or cholelithiasis.(42)

Under the stimulus of these and many other noted surgeons, cholecystostomy, cholecystectomy, and choledochostomy and related procedures rapidly developed until they are now standard, and widely practiced procedures which can be carried out with minimal risk.

ANATOMY

In the three millimeter embryo, the floor of the future duodenum gives rise to a sacculation named the hepatic diverticulum. This consists of a cranial portion which becomes liver and bile ducts, and of a caudal portion that becomes the gall bladder and the cystic duct. The hepatic diverticulum forces its way ventrad into a mass of splanchnic mesoderm that will furnish most of the substances of the diaphragm. In the five millimeter embryo the gall bladder is a solid cylinder which is carried away from the duodenum by the elongating common duct. The cystic duct is then recognizable and in the seventh week a lumen has been established throughout most of the tract which then appears like an offshoot from the main biliary passage. Bile is secreted in fetuses about three months old. (3)

The gall bladder is a pear-shaped musculomembranous sac, lodged in the fossa vesicae fellea e on the undersurface of the right lobe of the liver, and extending from near the right extremity of the porta to the anterior border of the organ. The gall bladder is from 7 to 10 centimeters in length, 2.5 centimeters in breadth at its widest part, and holds from 30 to 35 cubic centimeters. It is divided into a fundus, body, and a neck. The fundus is directed downward, forward, and to the right, and generally projects beyond the anterior border of the liver; the body and neck are directed upward, backward, and to the left. The upper surface of the gall bladder is attached to the liver by connective tissue

and vessels. The under surface is covered by peritoneum, which is reflected on to it from the surface of the liver. Occasionally the whole of the gall bladder is surrounded by the serous membrane in which case it is connected to the liver by a kind of mesentery. (45)

The gall bladder consists of three distinct coats. The external or serous coat is derived from the peritoneum; it completely invests the fundus, but covers the body and neck only on their under surfaces. The fibromuscular coat is a thin but strong layer forming the framework of the sac. It consists of dense fibrous tissue, which interlaces in all directions, and is mixed with plain muscular fibers, disposed chiefly in a longitudinal direction, a few running transversely. The internal or mucous coat is loosely connected with the fibrous layer. (45) This inner surface of the gall bladder is lined by tall columnar epithelium. There are acinous glands producing a mucinous secretion in the ducts and in the neck of the gall bladder; they are absent, however, from the body and fundus. Beneath the epithelium is a scanty connective tissue layer, the lamina propria, which contains the capillaries. The inner surface of the gallbladder is immensely enlarged by the presence of deep polygonal spaces bordered by connecting ridges of varying heights called rugae.(2) Opposite the neck of the gall bladder the mucous membrane projects inward in the form of oblique folds, forming the spiral valves of Heister.(45)

The cystic duct is usually about 2 to 3 centimeters long and extends from the neck of the gall bladder to the porta hepatis; here it joins the hepatic duct to form the common bile duct. It usually passes downward for a short distance with the common hepatic duct before joining it.(89) Variations of the cystic duct will be considered later.

The right and left hepatic ducts which issue from the liver at the porta hepatis unite to form the hepatic duct which passes downward for about 3 centimeters to a point where it is joined, usually at an acute angle, by the cystic duct, this union produces the common bile duct. The common duct is about 7 centimeters long and normally its lumen is about 3 millimeters in diameter. It runs in the right border of the lesser omentum, and therefore anterior to the foramen of Winslow, passes behind the superior portion of the duodenum and then runs in a groove on the posterior surface of the head of the pancreas, where it lies in fromt of the inferior vena cava. At times it is completely imbedded in the substance of the pancreas. For a short distance it lies along the right side of the terminal part of the pancreatic duct and with it passes obliquely through the wall of the duodenum. The common duct traverses a distance in the duodenum varying from 1 to 3 centimeters. After uniting, the two ducts open by a common orifice at the papilla of Vater about 7 to 10 centimeters from the pylorus, located at the mesial side of the descending portion of the duodenum. The union

of the two ducts dilated into an ampulla, is known as the Ampulla of Vater.(42)

The sphincter of Oddi should be described because of its part in gall bladder function. There is disagreement as to the existence of a special sphincter but there is a definite arrangement of circular muscle fibers of the duodenum at the lower portion of the intramural part in the common duct which may be described as the sphincter of Oddi.(25)

The cystic artery usually branches from the right hepatic artery just to the right of the common duct, and passes downward and forward along the neck of the gall bladder, and divides into two branches, one of which ramifies on the free surface, the other on the attached surface of the gall bladder.(45) Anomalies of the cystic artery will be discussed later. The cystic vein drains the blood from the gall bladder, and, accompanying the cystic duct usually ends in the right branch of the portal vein.(45)

The large lymphatic vessels running over the gall bladder bring lymph from the liver and coats of the gall bladder. They follow the inner side of the cystic duct and end in mesenteric lymph glands. These vessels unite and pass into a gland which is nearly constant at the neck of the gall bladder and it is this "sentinel gland" which is often enlarged in cases of cholecystitis. Subserous layer lymphatics drain to these larger vessels; the layer has an irregular network and vary greatly in size and shape of the vessels. Submucous

lymphatics are in connective tissue folds but are at their lowest part or more frequently at their base. Lymphatic network is almost absent in the dense muscular part. Normally there are no solitary lymph follicles in the gall bladder as are found in the appendix. Lymphatics of the gall bladder have a very intimate anastamosis with those of the liver.(42)

There still exists considerable confusion regarding the details of the innervation of the gall bladder, common duct, and the sphincter of Oddi. The majority of nerve fibers distributed to the biliary system and portal vessels are sympathetic in origin and are derived from the motor cells of the semilunar ganglion of the celiac plexus. They give rise to the hepatic plexus which may be subdivided into the anterior and posterior hepatic plexuses. Parasympathetic fibers join the liver through the hepato-gastric ligaments or directly through the celiac plexus. The spinal system reaches the region through the phrenics and phrenico-abdominalis. As the phrenic arises from the third or fourth cervical nerves it is easily comprehended why afferent impulses during gallstone colic carried through these segments through the right phrenic nerve may produce reflex pains in the right shoulder region.

Among the anatomical variations which occur in this area, two are of great importance, these are anomalies of the cystic artery and cystic duct. The cystic artery is usually a branch of the right hepatic artery which is derived from the celiac axis. The

cystic artery may arise as a branch of the right hepatic artery from the gastroduodenal artery or of the superior mesenteric artery. Less frequently encountered anomalies of the cystic artery occur when the cystic artery arises as a branch of the common hepatic artery from the celiac axis, or as a branch of the gastroduodenal from the hepatic artery which has arisen from the celiac axis. The cystic artery may arise directly from the celiac axis, or from the abdominal aorta. It may also arise from the superior mesenteric artery or branch from the right gastroepiploic artery, or lastly branch from the superior pancreatico-duodenal artery. Anatomical variations of the cystic duct include complete absence in which case the neck of the gall bladder joins the common hepatic duct to form the common bile duct. The cystic duct may be elongated to join the common hepatic duct on the left side or to run parallel to the hepatic duct the two being joined by connective tissue. The last variation of the cystic duct is that of elongation and the cystic duct running with the common hepatic duct to join it at the usualloblique angle just before the common duct pierces the duodenum.(89)

Thus we see that the gall bladder has a weak, diffuse, but very adequate muscular coat; that the mucosal lining is so arra nged as to bring the contents of the gall bladder into the closest possible apposition with the surface lining to fit the vessels for its role of absorption. We see too, that the gall bladder is

endowed with an excellent lymphatic network, and that a surgeon working in the area must always be on the alert for the not infrequent anomalies of the cystic duct and artery.

PHYSIOLOGY

Bile is the product of the liver cells and is a complex liquid. Apparently it is being produced continually and its quantity and composition are subject to wide variations. According to a conservative estimate by Sobotka, about 0.6 c.c. of bile is produced per hour per kilogram of body weight. Bile contains an average of 3 per cent total solids, the rest being water. The substances it contains are alkali salts of the bile acids and bile pigments, cholesterol, mucoprotein, and the electrolytes common to all body fluids: sodium, calcium, potassium, and magnesium, as chlorides, bicarbonates, carbonates, and phosphates. The pH of the bile is between 7.1 and 7.3.(2)

Bile is prevented from entering the duodenum continuously during secretion by the liver, by a regulatory mechanism at the distal end of the common duct. As a result of almost complete closure of the common duct during fasting, the bile enters the gall bladder. The filling of the gall bladder seems to depend almost entirely upon the occlusion of the distal end of the common duct with subsequent rise of pressure in the extrahepatic biliary duct system.(42) Bile reaches the gall bladder through the cystic duct, which has a lumen about one-fourth the diameter of the common duct. The lumen is ridged with a series of folds, the valves of Heister, which regulate the inflow of bile. The main force driving the bile into the gall bladder is the pressure exerted on the liver during inspiration.(2) The intralumenary pressure of the bile ducts

during fasting reaches a height of between 50-70 millimeter of water. (8) The muscular coat of the gall bladder adjusts in size to the change in volume. Overdistention is prevented by the resorption of water.(79)

Gall bladder bile may be some ten times more concentrated in total solids than bile collected from the hepatic ducts. Water and inorganic salts are absorbed through the lymphatics and blood vessels of the gall bladder wall. The composition of the absorbed fluid is practically that of physiological saline. Under normal conditions, bile pigments, bile salts, and cholesterol are not absorbed to any appreciable degree.(8) It has been shown experimentally, by Halpert, et al, that the gall bladder can resorb half the volume of its content per hour.(2) In this process of concentration, the bile becomes slightly acidified.(25)

It is undecided whether cholesterol is excreted by the normal gall bladder mucosa, though Elman and Taussig present evidence for such a process.(28) In this connection, it may be mentioned that a pronounced diffuse deposition of a cholesterol ester in the connective tissue of the human gall bladder wall is seen as a pathological condition. The tissue of the vesicle is stiff and greatly thickened as a result of its impregnation with lipoid material. The disturbances leading to this condition, which is spoken of as cholesterosis of the gall bladder or, from the appearance of the mucosa, as the "strawberry gallbladder", are unknown; the existence

of this condition cannot, however, be used as evidence for the secretion of cholesterol by the gall bladder mucosa under physiological conditions.(27)

The gall bladder secretes 20 c.c. of a thick mucinous fluid every 24 hours.(25) This material adds to the viscosity of the bile. Little or none of this material is furnished by the bile ducts, nor were the ducts observed to have any concentrating power but were found, on the contrary, to dilute the bile with a thin watery fluid. When the ducts were obstructed by ligation and the gall bladder tied off, after some days a clear colorless fluid was found to have collected in the ducts. This fluid, "white bile", is not uncommonly seen during an operation upon an obstructed bile duct associated with a functionless gall bladder. The "white bile", under these circumstances, is furnished solely by the mucosa of the ducts. It contains no pigment, bile salts, or cholesterol and bears almost no resemblance to bile. A healthy gall bladder left in communication with an obstructed common bile duct will cause a thick greenish bile to collect in the ducts and bladder as a result of the gallbladder's concentrating function. After a lapse of weeks, the imprisoned bile develops an almost tarry consistency. Therefore, the functions of the gall bladder and the bile ducts are opposite, the former concentrating the bile and the latter tending to dilute the bile. With time the bile ducts will overcome the functional activity of the gall bladder resulting in hydrops of the gall bladder.

Other functions of the gall bladder subsidiary to its concentrating power are the reduction in the alkalinity of the bile and the equalization of pressure withing the biliary duct system. Without the ability to absorb fluid and reduce the bulk of the bile its power to equalize pressure would be negligible. It is to be remembered that the amount of bile secreted in 24 hours is some twenty times or so greater than could be contained in the gall bladder. The loss of its action in equalizing the pressure within the duct system is probably a factor leading to the dilatation of the bile ducts, which so frequently follows cholecystectomy. After this operation the flow of bile into the intestine is at first nearly continuous, but later the adaptation of the ducts permits intermittent discharge.(8)

The importance of the gall bladder in the control of pressure within the biliary ducts is apparent from the results of the experiments of Mann and Bollman. They found that after ligation of the common duct in dogs a rise in the bilirubin concentration of the blood did not occur until from 24-36 hours had elapsed, and jaundice did not appear for 2 days. If, on the other hand, the gall bladder was removed at the time the duct was ligated jaundice was fully developed within 24 hours, due, presumabley, to the rise in duct pressure, and the suppression of secretion of the bile by the liver cells.(66)

The nature of the force by which the gall bladder is evacuated

has been a question of some debate. The wall of the gall bladder is so thin, and its muscle fibers so sparse, that it seemed unlikely that it could exert the pressure required to discharge its contents--especially since the gall bladder is evacuated with considerable difficulty by manual compression. Intra-abdominal pressure, "milking" action exerted by the duodenal movements, and simple leaking into the duodenum as a result of the relaxation of the sphincter of Oddi have been varously suggested as possible factors. It has, however, been proved quite definitely as a result of evidence derived from several modes of investigation that the contractions of the gall bladder wall itself are responsible for the expulsion of its contents. The times of emptying of the gall bladder are related to gastric digestion. During fasting it remains distended with bile though the sphincter guarding the common duct is relaxed, plainly indicating that the viscus is cometent to retain bile without the aid of the sphincter of Oddi. That changes in intra-abdominal pressure are not responsible for its emptying was shown by Mann and Higgins.(65)

When the walls of the gall bladder contract, bile is discharged along the cystic and common ducts into the duodenum. The sphincter or sphincters guarding the lower end of the common bile duct normally can withstand a pressure of 100 to 120 mm. of water but the pressure developed by the contractions of the gall bladder in dogs was shown to amount to over 250 mm. water.(8) The power of the gall bladder

to contract is never greater than the circulatory pressure of the bile.(25) It is probable, moreover, that relaxation of the sphincter occurs as part of a coordinated mechanism when the bladder wall contracts, and that the passage of bile through the sphincter is not simply a matter of the latter "giving away" before the biliary pressure created by the gall bladder contractions. The duodenal muscle surrounding the oblique intramural portion of the common bile duct is capable when contracted of offering a resistance of over 750 mm. of water. Since this is much higher than the pressure which contractions of the gall bladder can exert, the flow of bile is completely blocked during contractions of the duodenal muscle but during the latter's relaxation, the pressure is relieved. Therefore, during the evacuation of the gall bladder and active duodenal movements, the bile may be observed to enter the duodenum in squirts. This is not due to the "milking" action of the peristaltic movements of the bowel but is the result of the alternate blockage and release of the duct, the bowel movements being incapable of causing any flow of bile when the gall bladder is not contracting.

The most effective stimulus for the discharge of bile is fatty food, particularly egg-yolk, cream or olive oil. It appears that some degree of digestion of the fat must occur before evacuation results. The effect of fat upon the gall bladder was shown definitely by Boyden. He found that during a period of fasting the gall bladder in the cat was distended with bile, and its walls so stretched that

they were reduced to about one-fifteenth of their thickness in the collapsible state. It emptied slowly after a meal, being collapsed, or nearly so, in from 1½ to 2 hours. The effect of meat upon the ischarge of bile is much less than that of fat. Pure protein, such as egg white, and carbohydrate food is almost without effect. These findings have been amply confirmed by several observers. Whitaker and his associates, for example, observed changes in the contour of the gall bladder after filling it with iodized oil and examining it radioscopically. The human gall bladder when rendered opaque to the X-rays by the administration of tetraiodophenolphthalein can also be seen to discharge its contents in response to a meal of fat. Its contractions during operations have also been observed frequently. The products of fat digestion, hydrochloric acid of a strength comparable to that in the chyme, or magnesium sulphate when placed in the duodenum, cause evacuation of the gall bladder and relaxation of the sphincter choledochus. Bile salts injected intravenously, on the other hand, cause relaxation of the gall bladder. Liquid Petrolatum introduced into the duodenum is without effect. Them emptying time of the gallbladder is prolonged in duodenal ulcer, during pregnancy and in pernicious anemia.(8) The mechanisms controlling the evacuation of the gall bladder are of two types: nervous and hormonal and will be discussed in that order.

It has been mentioned that relaxation of the sphincter of Oddi probably occurs as the gall bladder contracts.(63) A coordinated

action of this nature points to a nervous mechanism. The latter may depend upon intrinsic nervous plexuses in the walls of the biliary structures. The gall bladder contractions initiated by the stimulus of meal might be due similarly to short reflexes through the intrinsic plexuses of the stomach or duodenum and biliary tract. Nervous mechanisms are also indicated by the following observations. Electrical stimulation of the stomach and duodenum in animals is followed by contractions of the gall bladder. Contractions are occasionally induced by psychic factors as the smell or taste of food. The gall bladder also responds to experimental excitation of the vagus or sympathetic nerves. Experiments attempting to demonstrate the precise actions of the extrinsic nerves upon the gall bladder movements have, however, given very conflicting evidence. Several observers have obtained weak moter effects from both vagal and sympathetic stimulation, a motor action of the latter is also indicated by the fact that adrenaline is excitatory. It is to be considered that the nervous control of the gall bladder is of little import as compared with the hormonal control.(8)

Even in animals nervous mechanisms are not essential to gall bladder activity; this is evident from the fact that the reaction to the introduction of fat into the duodenum occurs after all nervous connections between the biliary and gastro-intestinal tracts, and between the former and the central nervous system have been

severed. That gall bladder contractions can occur under such circumstances suggests, of course, a hormonal or humoral mechanism. (56) Boyden found that the blood of an animal taken at the height of digestion, when injected into a fasting animal causes the evacuation of bile; blood from a starved animal has no such effect.

Ivy obtained as acid extract from the mucosa of the upper part of the intestine which caused contraction of the gall bladder when injected intravenously into animals. The injection of acid alone is without effect. Nor will fat or its derivative excite contractions of the gall bladder when administered intravenously. Acid and other substances which are excitatory when placed in the duodenum or fed therefore act apparently byy causing the production or liberation of a hormone in or from the intestinal mucosa. The active principle is related to secretin but not identical with this hormone, for it does not cause pancreatic secretion, and secretion does not cause gall bladder contractions. In crossed circulation experiments the introduction of acid into the duodenum of one animal caused contractions of the gall bladder of the other. Ivy and Oldberg named this hormone "cholecystokinin".(55) As little as 0.2 mg. of the solid material prepared from a potent extract causes definite contraction of the gall bladder. It is free from histamine and other vasodilator substances. Its effect has been demonstrated upon man. The transfustion of blood from a human subject digesting egg yolk has been found to cause evacuation of the gall bladder of

the recipient. No effect was observed with blood from a fasting donor.(8)

Thus we see that the gall bladder acts as a storehouse for the bile, concentrates it and slightly acidifies the product. The gall bladder serves as an important functional unit in the equalization of the pressure in the biliary system. The gallbladder adds a thick mucinous material to the bile increasing its viscosity. The role played by the gall bladder in cholesterol metabolism remains obscure. The very adequate evacuation system of the gall bladder based primarily upon hormonal and secondarily upon nervous stimulation has been presented.

ETIOLOGY AND PATHOLOGY

The exact mechanism by which acute inflammation of the gall bladder is initiated is not known. Occasionally, vascular obstruction produces hemorrhagic infarction of the gall bladder with subsequent acute cholecystitis. These mechanical factors producing obstruction of the cystic artery give rise to much debate. (2, 53, 61, 75, 95) The proponents of the vascular obstruction theory feel that the mechanical factors are primary and that bacterial invasion of the damaged tissue is a secondary reaction. (27, 95) Bisgard feels that it is impossible to infect a normal gall bladder. In his experiments, he found that neither stasis of bile nor the reflux of pancreatic juice, as a single factor, was productive of cholecystitis. When combined they invariabley produced pathologic changes in the gall bladder. Unfiltered bile or bile containing bacteria was found to activate the pancreatic enzymens.(11) The majority of etiologic literature seems to favor bacterial invasion as the primary cause of acute noncalculous cholecystitis. Usually it is seen either as a complication of certain generalized infections, such as typhoid fever, paratyphoid fever, or influenza, or it results from infection by any such organisms as colon bacilli, hemolytic streptococci, staphlococci, enterococci, pneumococci, or gass bacilli.(18,19,53,96) To aid in supporting this theory, two investigators have found that childhood acute cholecystitis was almost always preceded by infections sueh as scarlet fever, diphtheria, influenza, and typhoid fever.

Also, they found that there is a lowered incidence of acute cholecystitis in the past ten years as compared to the period 1930-1940. They feel this is due to the use of antibiotics early in the infections.(12, 77) Patey felt that the cystic artery was the easiest route for the bacteria to reach the gall bladder. He felt that the liver was not an efficient filter, therefore a bacterial embolus from a portal focus could easily reach the gall bladder by descending in the bile. He offered no evidence for lymphatic spread from the liver to gall bladder, and felt that ascending infection up the ducts was a rare possibility at best.(75) Microorganisms may also reach the gall bladder by direct extension from neighboring organs, in which case, the inflammatory process extends from the outer layers of the gall bladder inward and may not reach the mucosa -- pericholecystitis.(2)

So we see that the source of the infection, the method of entry into the gall bladder and the relative importance of these infective agents in the production of cholecystitis are points concerning which there has been some disagreement. In about 1 per cent of cases of typhoid and paratyphoid fever, acute typhoidal cholecystitis is a complicating factor. It may be encountered among typhoid carriers long after the fever has subsided, and it may even be found in cases in which there never was any clinically demonstrable typhoid fever. Apparently, the typhoid bacillus has a special affinity for the biliary tract and may perist in this situation when no trace of it

can be found elsewhere in the body. In a high percentage of cases this organism can be cultured from the wall of the excised gall gladder or from its contents. Acute cholecystitis due to such organisms as colon bacilli is not at all uncommon.

Toxins of pathogenic organisms have been shown to produce hemorrhagic lesions of the gall bladder. All these lesions apparently heal spontaneously, leaving no trace of their presence. The significance of this chemical or toxic cholecystitis is not well understood, but it should be borne in mind that metabolic disturbances may be responsible for certain forms of acute or chronic cholecystic disease.(19)

Gall stones are precusors to acute calculous cholecystitis. Lieber found a high degree of correlation between the incidence of gall stones and the following diseases: diabetes mellitus, portal cirrhosis, tuberculosis, pernicious anemia, carcinoma, and ulcers.(60)

The quintad of female, fair, fat, forty, and having had four pregnancies has been offered by some men.(36)

In acute cholecystitis, from whatever cause, the involvement generally commences with the mucosa and extends outward.(2) Some investigators have subdivided the pathological finding of acute cholecystitis into a catarrhal, a suppurative, or empyema of the gall bladder, and a phlegmonous or gangrenous type.(18, 23, 42)

The catarrhal type is characterized by a dilated gall bladder whose walls are thickened by edema. The serosa is usually dull and reddish in color. Generally the contents contain more mucus than normally is present. The vessels are dilated and hemorrhage is often found in the vicinity of the vessels.(2, 19, 48) Generally the surface epithelium is well preserved.(2)

Findings in the suppurative or empyema type of acute cholecystitis reveal a swollen tense gall bladder, whose serosa is dull and occasionally granular. The viscus appears to have a reddish to brown cast with occasional necrotic areas present.(2, 19, 23, 42, 48) The gall bladder generally contains a thick mucopus material, which occasionally may be blood tinged.(2, 18) The surface epithelium may be lifted off or is desquammated. (2) Generally the viscus is adhesed to neighboring organs by the fibrinous exudate.(23)

With the phlegmonous variety the walls of the gall bladder appear brown to black with large areas of necrosis throughout the various layers of the gall bladder. The walls are not markedly enlarged, and the contents are usually bloody.(2, 42)

There are varying degrees of lymphocytic and leukocytic infiltration of the above types.(19)

The acute process may end in perforation of the gall bladder with acute focal or diffuse peritonitis, or it may subside. (2)

SYMPTOMS AND SIGNS

The symptoms and signs vary with the pathological background, however a constant sever pain in the right hypochondrium usually marks the onset of acute cholecystitis. This pain may be in the epigastrium and may wax and wane but does not cease.(15, 35, 48, 53, 64, 96) The pain may or may not have radiation to the right posterior chest below the scapula. Definite tenderness and rigidity of the right rectus muscle in the upper quadrant can be demonstrated.(15, 19, 48) Nausea, vomiting, anorexia, and a sense of fullness or distention usually accompany the pain, fever is usually present.(15, 48) Occasionally a mass may be palpable in the right upper quadrant, this, of course, depends upon the degree of obstruction due to inflammatory swelling of the cystic duct.(15, 19, 48) These patients generally do not lie quietly, but are generally found in a sitting position somewhat doubled upon themselves and are seen to "bob and weave" about. With the acute suppurative or empyema type of cholecystitis the patient exhibits chills, fever, and sweating. The patient appears more toxic and the abdominal tenderness is more marked.(15, 96)

Infrequently, jaundice may be present in acute noncalculous cholecystitis due to edema and hyperemia of the mucosa about the cystic duct producing occlusion of the viscus.(15, 19)

DIFFERENTIAL DIAGNOSIS

The early signs and symptoms of acute cholecystitis are often superficially similar to those of volvulus of the small intestine, of appendicitis, of acute pancreatitis, of coronary thrombosis with or without myocardial infarction, of pneumonia, of rupture of a peptic ulcer, and of obstructive neoplasm of the transverse colon. The late signs and symptoms of acute cholecystitis are much like those of a neoplasm of the hepatic flexure of the colon. Diaphragmatic pleurisy, ureteropelvic obstruction with hydronephrosis, pyelitis, or perinephritic abscess, as well as omental cysts are easily confused with acute cholecystitis.(20, 35, 48)

It might be said that when something is missing from the diagnositic triad of acute cholecystitis -- namely, the typical pain, the tenderness and spasm beneath the right costal margin, and the palpation of a mass -- the diagnosis of acute cholecystitis can not be made with certainty.(48)

DIAGNOSIS

In making the diagnosis of acute noncalculous cholecystitis, one should constantly bear in mind the numerous afore-mentioned entities which may present a similar picture.

In the history one should make an attempt to elicit a story of preceeding "biliousness", with a gradual onset accompanied by such minor symptoms as nausea, loss of appetite, a shivering attack and slight fever followed by indefinite aching pains in the epigastrium and right upper quadrant of the abdomen.(19) Such is the typical picture of acute noncalculous cholecystitis, however, the pains may increase to the severity of colic, accompanied by chills, fever, sweats, and jaundice when the cystic duct is occluded due to inflammatory changes.(15, 19, 53, 57, 64) A history of food intolerance to such as fatty or fried foods, cabbage, onions, raw apples, and spicy foods.(15, 19, 53, 57, 96) These foods are gass formers and give rise to and unpresidented amount of belching shortly after their ingestion. Often the patient will speak of a bloated feeling, of heartburn, anorexia, constipation, diarrhea, and/or weight loss.(15) A history of darker urine and lighter stools is typical as is the radiation of the epigastric or right upper quadrant pain to the shoulder or to the tip of the right scapula.

The patient may be jaundiced which should be noted while doing the physical examination. Murphy's sign is frequently present. This is elicited by the examining physician hooking his fingers

deep beneath the right costal arch below the hepatic margin. The patient is instructed to take a deep breath--when the diaphragm forces the hypersensitive gall bladder onto the fingers the inspiration ceases very suddenly as though "turned off".(64) Right upper quadrant tenderness is practically always present.(15, 19, 48, 53,57,64,96) Infrequently, one may be able to palpate the dilated viscus.(15)

The laboratory findings are an increased white blood cell count--predominately polymorphonuclear cells (19, 48, 96), an increased sedimentation rate (48, 96), and occasionally and anemia is present.(48)

Practically all authors favor cholangiography in suspected cases of biliary tract disease.(6, 9, 42, 50, 64, 69, 72, 84, 96) Cholangiography had its introduction in 1923 by Graham and Cole who used tetrabromophenolphthalein. The progression through the other halogenated compounds was rapid and centered primarily on tetraiodophenolphthalein or Pyridax.(42) "Telepaque" is the most recent dye in general usage. These dyes are excreted from the liver in the bile -- the bile is then normally concentrated in the gall bladder. It is this concentration of the dye which enables visualization of the viscus. Faint visualization indicates that the concentrating power of the gall bladder has been impaired, thereby suggesting a mucosal change -- most often pathological.

Nonvisualization, barring technical errors in preparation or filming, means that gall bladder function has been lost or that no bile has reached its lumen, or that the liver has not secreted bile in normal amounts.(50) Faint or nonvisualization is often used to detect and interpret pathology and much definitive treatment has been and is based on the interpretation of the films. All cholangiograms are of no, rather little, significance in the presence of jaundice in that evacuation of the viscus can not be studied.(19, 48, 50)

COMPLICATIONS

The immediate complications of acute cholecystitis are gangrene with subsequent perforation.(19, 21, 24, 31, 48, 53, 70) These resulting in diffuse or local peritonitis with or without abscess formation.(19, 21, 24, 31, 48, 53, 70, 94) Among the many other complications which may occur either preoperatively or postoperatively are bronchopneumonia, atelectasis, pulmonary embolism, empyema, hepatic insufficiency, common duct injury, pancreatic necrosis, fistula formation, and hemmarrhage. (4, 19, 21, 24, 31, 48, 53, 70, 82, 94)

MEDICAL TREATMENT

The nonsurgical or medical management of acute noncalculous cholecystitis revolves primarily about the patient's diet. Some authors propose a stimulating type of diet which consists of food high in fat and protein and fruit juices.(32, 42) Other authors forbid their patients to eat fatty or fried food, fatty fish, eggs, and pork. They also suggest the following foods be used in moderation: butter, milk, cream, and olive oil.(54, 96) The latter dietary management fits asèditive type of diet which the proponents of the stimulating diet also use.(32, 42) The means of determining which diet to use and when could not be determined from the literature. These diets are called stimulating and sedative by their ability to cause the production of cholecystokinin in the duodenum. Roughage, cellulose, and foods containing cholesterol were omitted on some diet lists.(54, 57, 96) Some authors report that the body is as conservative with cholesterol as it is with iron, and therefore reason that if cholesterol is withheld nothing is gained.(42) Antispasmotics are frequently given to relax the sphincter of Oddi. Some accomplish this with olive oil to increase the evacuation of the gall bladder and to increase the flow of bile in the hope that biliary stasis will be prevented.(32, 57, 96) Hydrochloric acid or alkalis were given according to the functional needs of the patient.(57) Pancreatic extracts, whole bile or bile salts have been used as have decholine and ketochol.(57, 96)

Most of the literature reviewed seemed agreeable on the use of

sedatives for the patient's comfort and as to the treatment of the source and control of infection with antibiotic therapy.(32,42,96) The use of biliary antiseptics such as salicylates, methenamine, salyrgan, and tetraiodophenolphthalein were once advocated.(32)

Improvement of the patient's cardiac, renal, and hepatic function are also important steps in therapy.(42)

SURGICAL TREATMENT

In this section, the first decision to be made is whether or not to operate. The affirmative can be answered only following a thorough search for complicating diseases.(22) Those patients who are elderly, hypertensive, or have renal or cardiovascular disease are obviously surgical risks and a number of authors have suggested that these people not be operated upon.(23, 37, 38, 39, 41, 49, 81, 83) A number of others prefer cholecystostomy for these patients.(16, 19, 29, 78, 86) Some have felt that operation was unnecessary with the first mild attack, in a stoneless gall bladder by cholangiography.(23, 44, 46, 73, 96) The other reason for not operating is peritonitis due to perforation.(37, 38, 39, 49)

Interest has been aroused in the early surgical treatment of acute cholecystitis due to unfortunate experiences of having gall bladders perforate while under observation. Most investigators use forty-eight to seventy-two hours following the onset of symptoms as "early".(51, 80) This range of hours constitutes the time until which cholecystectomy can be carried out with ease. Over this period of time the anatomy of the biliary system often becomes obscured due to inflammation, induration, and exudation. In the case of obscured anatomy a few surgeons are so disposed as to do a cholecystostomy.(16, 19) The resolution of the inflammatory process after an attack of acute cholecystitis is extremely slow and incomplete regardless of the clinical course of the patient. There-

fore, after a short period devoted to restoration of the fluid balance and antibiotic therapy, there is nothing to gain by delaying surgery if the patient is doing well. The inflammatory process lasts for months and sometimes years after the clinical symptoms subside, the period of hospitalization is prolonged, and the technical difficulties of surgery increase. On the other hand, if the patient is doing badly, some authors suggest that surgery is mandatory, and it is in such cases that simple cholecystectomy under local anesthesia may be a life saving process.(51, 52, 53, 80) Some authors feel that acute cholecystitis is not a surgical emergency except perhaps in the case of the suppurative or empyema type and the phlegmonous type of gall bladder. Generally most surgeons are letting the viscus "cool off" prior to surgery.(19, 48)

The incidence of gangrene, absdess, and perforation in acute cholecystitis is between 10-30 percent, and as in appendicitis, the mortalities are mostly in this group. By approaching the case with a surgical attitude and deferring operation only when there is no confusion of signs, symptoms, laboratory findings, and the appearance of the patient, the mortality for acute cholecystitis may be reduced. The incidence of gangrene, abscess, and perforation is higher in the older age group begining with 50 years and especially after 60 years. Therefore, one should approach this group with a more definite surgical attitude.(10)

Choledochostomy has been shown to increase the morbidity and

mortality rates.(7, 41)

Cholecystostomy has been reserved for those patients in whom the anatomy is obscured or who are considered as bad surgical risks. (16, 19, 29, 78, 86)

Cholecystectomy is the operation of choice in acute cholecystitis, and the earlier the operation is performed, the lower the morbidity and mortality.(1, 10, 16, 17, 18, 19, 22, 23, 24, 29, 33, 37, 42, 43, 44, 53, 62, 67, 70, 71, 76, 79, 80, 85, 86,87, 88, 90, 91, 92, 94, 97,98)

CONCLUSIONS

It has been my privilege to explore the literature on acute cholecystitis and extract salient facts which have been presented in the foregoing pages. This section will serve to summarize the evidence in view of present day concensus of opinion.

It is the purpose of medical therapy to rehabilitate the disordered gall bladder when physiological alterations are present; and by surgical means when anatomical alterations are present.

The borderline where medical treatment ends and surgical treatment begins is less easily defined in gall bladder pathology than in diseases elsewhere. In acute cholecystitis, changing local conditions may, in a very few hours, so alter the plan of treatment that immediate operation may be necessary to save the patient's life.

Until 1933, the concensus among most surgeons was that it was wise to postpone operating on a patient with acute cholecystitis until the acute manifestations of the inflammation had subsided, providing his general condition improved. However, from this date onward, there has been an increasing number of advocates of the early treatment primarily because the physicians, internists, and surgeons alike, have found that the early operative treatment avoids the complications of gall bladder disease, and at the present time one can not be certain of the exact pathological changes which have occured in the gall bladder.

Bibliography

1. Alexander, J.H.; The Indications for Surgical Intervention In Cholecystic Disease, Penn. State Med. Journ., 42:904, 1939.

2. Anderson, W.A.D.: Pathology, C.V. Mosby Co., St. Louis, 1948.

3. Arey, L.B.: Developmental Anatomy, W.B. Saunders Co., Phila. and London, 1946.

4. Bachhuber, J.H., et al: Gangrene and Perforation of the Gall Bladder, Am. Journ. Surg., 67:40-47, 1950.

5. Barksdale, J. and Johnston, J.H.: Acute Cholecystitis, Ann. Surg., 127:816, 1948.

6. Beilin, D.S.: Cholecystographic Diagnosis of Gall Bladder Disease, Med. Clinics, No. Am., 23:3, 1939.

7. Berman, J.K.: Principles and Practice of Surgery, C.V. Mosby, St. Louis, 1950.

8. Best, C.H. and Taylor, N.B.: The Physiological Basis of the Practice of Medicine, Williams and Wilkins Co., Baltimore, 1950.

9. Best, R.R. and Hicken, N.F.: Cholangiographic Demonstration of Biliary Dysenergia, Journ. Am. Med. Assn., 107:1615, 1936.

10. Best, R.R.: Acute Gallbladder, Journ. Surg., Gyn. and Obst., 73:312, 1941.

11. Bisgard, J.D. and Baker, C.: Experimental Studies of Pancreatic Enzymes as Possible Etiological Agents in Cholecystitis, Trans. of Am. Surg. Assn., Vol. LVIII, No. 6, 1940.

12. Bonta, J.A. and Lovingwood, C.G.: Acute Cholecystitis in Childhood, Surg., 309, Feb. 1952.

13. Brandenberg, Rudolph: Cholecystitis, Acta Chir. Scand., 100:57, 1950.

14. Budd, George: Diseases of the Liver, Lea and Blanchard, Phila., 1846.

15. Burghardt, Michael: Gall Bladder Surgery, A Five Year Survey, Am. Journ. Surg., 66:203, 1944.

16. Buxton, R.W.; Ray, D.K.; and Coller, F.A.: Acute Cholecystitis, Journ. Am. Med. Assn., Vol. 146, No.4:301, 1951.

17. Cecil, R.L. and Loeb, R.F.: Textbook of Medicine, W.B. Saunders Co., Phila., 1951.

18. Christian, H.A.: Osler's Principles and Practice of Medicine, Appleton Century Co., New York and London, 1944.

19. Christopher, F.: A Textbook of Surgery, W.B. Saunders Co., Phila. and London, 1950.

20. Clapp, W.A.: Surgical Diseases of the Gall Bladder and Diagnosis, Journ. of Maine Med. Assn., 38:283, 1947.

21. Clute, H.M. and Albright, H.: The Complications of Gall Bladder and Stomach Surgery, Am. Journ. Surg., 40:282, 1938.

22. Cole, Warren H.: Treatment of Cholecystitis, Post Grad. Med., 9:349, 1951.

23. Cole, W.H. and Elman, R.: Textbook of General Surgery, Appleton Century Co., New York and London, 1948.

24. DeCamp, Paul T. and others: Timing in the Surgical Treatment of Acute Cholecystitis, Ann. Surg., May, 1952.

25. Decker, Harry R.: Anatomy and Physiology of the Gall Bladder, Penn. Med. Journ., 42:389, 1938.

26. Ebers, G.: The Ebers Papyrus, (Tr. from German by Bryan), Geoffrey Bles, London, 1930.

27. Elman, R. and Graham, E.A.: The Pathogenesis of the "Strawberry" Gall Bladder, Arch. Surg., 24:14, 1932.

28. Elman, R. and Taussig, J.B.: The Cholesteral Function of the Gall Bladder, Journ. Exp. Med., 54:775, 1931.

29. Estes, W.L.,Jr.: Acute Gangrenous Cholecystitis, the Use of Partial Cholecystectomy in its Treatment, Am. Journ. Surg., 40:197, 1938.

30. Faithhorn, John: Liver Complaints and Bilious Disorders, Hickman and Hazzard, Phila., 1822.

31. Fletcher, A.B. and Ravdin, I.S.: Perforation of the Gall Bladder, Am. Journ, Surg., 81:178, 1951.

32. Foley, E.F.: The Medical Treatment of Gallbladder Infection, Med. Clinics No. Am., 23:55, 1939.

33. Foss, H.L.: Indication for Operation in Gallbladder Disease, Am. Journ. Surg., 40:205, 1938.

34. Garrison, F.H.: History of Medicine, W.B. Saunders Co., Phila., 1929.

35. Gatewood, L.C.: Gall Bladder Disease, Clinical Signs and Symptoms, Differential Diagnosis, Med. Clinics No. Am., January, 1939.

36. Gerwig, W.H. and Thistlethwaite, J.R.P.: Cholecystitis and Cholelithiasis in Young Women Following Pregnancy, Surg., 28:983, 1950.

37. Glenn, Frank: The Surgical Treatment of Acute Cholecystitis, Surg., Gyn., and Obst., 90:463, 1950.

38. Glenn, Frank: The Early Surgical Treatment of Acute Cholecystitis, Am. Journ. Surg., 40:186, 1938.

39. Glenn, Frank: The Surgical Treatment of Aoute Cholecystitis, Surg., 23:397, 1948.

40. Glisson, Francis: Anatomia Hepatis, London, 1654.

41. Goldman, Leon, and Bell, H.G.: Surgical Management of Disease of the Gall Bladder, Journ. Am. Med. Assn., 117.2:1582, 1941.

42. Graham, E.A.; Cole, W.H.; Copher, G.H.; and Moore, S.: Diseases of the Gallbladder and Bile Ducts, Lea and Febinger, Phila., 1928.

43. Graham, E.A.: A Consideration of the Stoneless Gallbladder, Journ. Am. Med. Assn., 103:1497, 1934.

44. Gray, H.K.: Surgical Treatment of Diseases of the Gallbladder, Surg. Clinics No. Am., 19:881, 1939.

45. Gray, Henry: Anatomy of the Human Body, Lea and Febinger, Phila., 1949.

46. Hall, A.A.: Practical Approach to the Diagnosis and Treatment of Diseases of the Gall Bladder, Ohio State Med. Journ., 35:593, 1939.

47. Hallendorf, L.C.; Dockerty, M.B.; and Waugh, J.M.: Acute Cholecystitis, Surg. Clin. No. Am., 28:979, 1948.

48. Harrison, T.R.: Principles of Internal Medicine, The Blakiston Co., New York, Phila., and Toronto, 1951.

49. Heuer, G.J.: Surgical Aspects of Acute Cholecystitis, Ann. Surg., 105:758, 1937.

50. Hodges, F.J.; Lampe, I.; and Holt, J.F.: Radiology for Medical Students, The Year Book Publishers, Inc., Chicago, 1948.

51. Holden, W.D.; Cebul, F.A.; and Loughry, C.W.: Management of Acute Disorders of the Biliary Tract, Journ. Am. Med. Assn., Vol. 148, No. 11:879, 1952.

52. Hurst, A.R.: Pre-operative and Post-operative Treatment of Gall Bladder Disease, British Hourn. Surg., 20:444, 1932.

53. Hyman, H.T.: An Integrated Practice of Medicine, W.B. Saunders Co., Phila. and London, 1947.

54. Ivy, A.C.: Etiology and Treatment of Biliary Tract Disease, Ohio State Med. Journ., 32:1185, 1936.

55. Ivy, A.C. and Oldberg, E.: A Hormone Mechanism for Gallbladder Contraction and Evacuation, Am. Journ. Physiology, 86:599, 1928.

56. Johnson, F.E. and Boyden, E.A.: The Effect of Sectioning of Various Autonomic Nerves upon the rate of Emptying of the Biliary Tract in the Cat, Surg., Gyn., and Obst., 76:395, 1943.

57. Kruse, F.H.: Diagnosis and Treatment of Diseases of the Gall Bladder and Related Biliary Disorders, Am. Journ. Surg., 40:178, 1938.

58. Lester, L.S.: Acute Cholecystitis, Surg.. 21:675, 1947.

59. Lichtman, S.S.: Diseases of the Liver, Gallbladder, and Bile Ducts, Lea and Febinger, Phila., 1942.

60. Lieber, Marshall M.: The Incidence of Gallstones and Their Correlation with Other Diseases, Ann. Surg., Vol.135, No. 3, 1952.

61. Liedberg, Nils: Etiology and Treatment of Acute Cholecystitis, Acta Chir. Scand., 101:1, 1951.

62. Liedberg, Nils: Surgical Treatment of Acute Cholecystitis, Acta Chir. Scand., Suppl. 47, 1937.

63. Lueth, H.C.: Studies on the flow of bile into the Duodenum and the existence of a sphincter of Oddi, Am. Journ. Physiology, 99:237, 1931.

64. Major, R.H.: Physical Diagnosis, W.B. Saunders Co., Phila. and London, 1945.

65. Mann, F.C.: The Physiologic Consideration of the Gallbladder, Journ. Am. Med. Assn., 83:829, 1924.

66. Mann, F.C. and Bollman, J.L.: The Relation of the Gall Bladder to the Development of Jaundice Following Obstruction of the Common Bile Duct, Journ. Lab. and Clin. Med., 10:540, 1925.

67. Marshall, S.F. and Phillips, E.S.: The Acute Gall Bladder, Surg. Clinics No. Am., 28:633, 1948.

68. Massengill, S.E.: A Sketch of Medicine and Pharmacy from the Fifteenth to the Twentieth Century, The S.E. Massengill Co., Bristol, Tenn., 1942.

69. McIntyre, C.H.: Combined Cholecystography and Liver Function Determination Following the Intravenous Administration of Iso-iodeikon, Am. Journ. Surg., 40:152, 1938.

70. Mentzer, S.H.: The Acute Gall Bladder Manifesting Few Signs or Symptoms, Journ. Surg., Gyn., and Obst., 55:709, 1932.

71. Miller, R.H.: Acute Cholecystitis, Ann. Surg., 92:644, 1930.

72. Mixter, C.G.: A Critical Evaluation of Cholangiography, Am. Journ. Surg., 40:223, 1938.

73. Nadler, W.H.: Indications and Contraindications for Medical Management of Gall Bladder Disease, Med. Clinics No. Am., 23:43, 1939.

74. Naunyn, B.: A treatise on Gholelithiasis, The New Sydenham Society, London, 1896.

75. Patey, D.H. and Whitby, L.E.H.: The Paths of Gallbladder Infection, Brit. Journ. Surg., 20:580, 1932-1933.

76. Patterson, H.: Acute Fulminating Cholecystitis, Surg., Gyn., and Obst., 89:364, 1949.

77. Penberthy, G.C. and Benson, C.D.: Surgery of the Biliary Tract in Infants and Children, Am. Journ. Surg., 40:232, 1938.

78. Pfeiffer, D.B. and Patterson, F.M.S.: The Surgical Management of Acute Cholecystitis, Penn. Med. Journ., 47:564, 1944.

79. Ravdin, I.S. and Hagen, W.H.: Diseases of the Biliary System, Med. Clinics No. Am., 35.2:1679, 1951.

80. Ross, F.P.; Boggs, J.D.; and Dunphy, J.E.: Studies in Acute Cholecystitis, Surg., Gyn., and Obst., 91:271, 1950.

81. Rouse, Clyde C.: Indications and Contraindications for Gall Bladder Surgery, Med. Journ. State Ala., July, 1941.

82. Rudnikoff, I. and Headland, C.I.: Pulmonary Changes Following Cholecystectomy, Journ. Am. Med. Assn., Vol. 146, No. 11, 989, 1951.

83. Russe, J.R.: Gall Bladder Surgery, Review of 337 Consecutive Gall Bladder Operations, Am. Journ. Surg., 58:388, 1942.

84. Scott, W.G. and Moore, S.: Consideration of Faint Gallbladder Shadows in Intravenous Cholecystography, Am. Journ. Surg., 40:157, 1938.

85. Smith, Beverly Chew: Acute Cholecystitis, Surg. Clinics No. Am., 25:285, 1945.

86. Smith, Morris K.: The Treatment of Acute Cholecystitis, Am. Journ. Surg., 40:192, 1938.

87. Stone, H.B. and Owings, J.C.: The Acute Gall Bladder as a Surgical Emergency, Tr. Am. Surg. Assn., 51:281, 1933.

88. Strohl, E.L. and Diffenbaugh, W.G.: Acute Cholecystitis, Surg., Gyn., and Obst., pp.156, August, 1952.

Thorek, Philip: Anatomy in Surgery, J.B. Lippincott Co., 1951.

90. Timoney, Francis X.: Cholecystitis, Am. Journ. Surg., 67:57, 1945.

91. Wallace, R.H. and Allen. A.W.: Acute Cholecystitis, Arch•. Surg., 43:762, 1941.

92. Walters, W.: Newer Concepts in the Management of Acute Cholecystitis, Surg. Clinics No. Am., 17:961, 1937.

93. Walters, W. and Snell, A.M.: Disease of the Gallbladder and Bile Ducts, W.B. Saunders Co., Phila. and London, 1940.

94. Waugh, J.M., et al: Annual Report on Surgery of the Biliary System and Pancreas for 1951, Proceedings of the Staff Meeting of the Mayo Clinic, Vol. 27, No. 27, 578, 1952.

95. Womack, N.A. and Bricker, E.M.: Pathogenesis of Cholecystitis, Arch. Surg., 44:658, 1942.

96. Yater, W.M.: Fundamentals of Internal Medicine, Appleton Century Co., New York and London, 1944.

97. Zinninger, M.M.: Surgical Treatment of Acute Cholecystitis, Ann. Surg., 96:406, 1932.

98. Zollinger, R.M. and Cutler, Elliot C.: The Treatment of Acute Cholecystitis, Journ. Am. Med. Assn., 121:481, 1943.