Biliary motility

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The delivery of bile to the duodenum depends on hepatic secretion of bile plus onward propulsion through the biliary tract. Biliary kinetics involve a series of complex interrelationships between gall bladder, cystic duct, common bile duct, sphincter of Oddi and upper small intestine, with control modulation by various neural and hormonal agents. The application of modern techniques to the study of biliary motility has allowed a composite physiological picture to emerge. Moreover, alterations in biliary motility are increasingly implicated in the aetiology of gall stones and postcholecystectomy symptoms. The present review examines recent developments in the understanding of biliary motility and discusses the detailed events involved in delivering bile to the duodenum.

Anatomical considerations

The anatomy of the biliary tree has been studied extensively in several species including man.¹⁻⁴ The considerable species variation in biliary structure and function should prevent uncritical extrapolation from one species to another. Most vertebrates possess hepatic ducts, cystic duct, gall bladder, common bile duct, and sphincter of Oddi, but for some reason the gall bladder is absent in certain species including horse, deer, rat, and pocket gopher. Among mammals there are three different patterns in the relationship between the termination of the bile and pancreatic ducts: (1) the two ducts join to form a common channel; (2) the common bile duct and pancreatic duct are distinct but share a common entrance into the duodenum; (3) the biliary and pancreatic ducts open separately into the duodenum.² All three patterns can be seen in man, but type 1 predominates.

In man thickened muscle at the proximal and distal margins of the sphincter of Oddi make up the 'sphincter choledochus' and the 'sphincter ampullae' respectively. Boyden⁴ divided the sphincter choledochus into a superior portion, which encircles the distal common duct just before it enters the duodenum, and an inferior portion surrounding the submucosal intra-duodenal portion of the common duct. The sphincter ampullae surrounds the ampullary duct at the duodenal papilla. Cineradiographic studies have shown the interaction of the various human sphincters during the passage of bile into the duodenum.⁵ Thus, a contraction begins in the middle of the intramural portion of the duct and propagates both upwards and downwards. The superior or retention sphincter pushes the bile in its segment up into the extramural bile duct, while the inferior or evacuation sphincter and the sphincter ampullae propel the bile in their segments into the duodenum.⁵

Hess⁶ has observed that each contraction of the human sphincter is followed by passive filling of

the ampulla, which in turn is followed by another contraction. He likened this rhythmical contraction and relaxation of the sphincter segment to systole and diastole, with filling of the ampulla occurring during diastole and propulsion of bile into the duodenum during systole.⁶ Using low compliance manometric techniques, Tooili has shown that during fasting the human sphincter of Oddi exhibits phasic contractions of peristaltic type which propel bile into the duodenum and prevent reflux of duodenal contents into the bile and pancreatic ducts.⁷

Physiological motility

BILE DUCT

Bile flow is governed by a combination of hepatic secretion, gall bladder contraction and sphincter of Oddi activity. The biliary tract is a low pressure system undergoing minimal pressure changes, whether during fasting or after feeding, despite substantial changes in bile flow.^{3,8} The human liver secretes at least 1000 ml of bile per day. Secretion decreases when the common duct pressure rises above 10 cm of water, and with occlusion of the duct the pressure stabilises at about 30 cm of water.⁹ Thus pressure is maintained at a relatively low level even in the presence of outflow obstruction. Surgeons recognise prolonged biliary obstruction by the presence of white bile, which indicates that hepatic secretion has virtually ceased, residual pigment has been reabsorbed and the duct is full of mucus derived from its own epithelium.

GALL BLADDER

Pattern of emptying

Recent data have shown that filling and emptying of the gall bladder are complex processes. The human gall bladder does not empty completely in response to food entering the duodenum, and there are frequent changes in its absolute storage volume and rate of emptying.¹⁰ Furthermore, partial emptying and refilling occur synchronously with the migrating myoelectric complex (MMC) of the intestine during the interdigestive period. Thus, entry and exit of bile from a healthy gall bladder resemble more the gentle ebb and flow of the tide than myocardial systole and diastole.

Gall bladder tone reflects the inherent compliance of the smooth muscle and fibroelastic tissue within its wall, which in turn are modulated by autonomic and hormonal mechanisms. The static compliance of the gall bladder, measured by pressure volume relationships, takes 12-16 hours to adjust to the volume of the organ.¹¹ Over shorter periods of two to four hours compliance remains relatively constant despite large fluctua-

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Accepted for publication
10 July 1989

tions in volume.¹¹ This property of slow tone adjustment would allow refilling during the period of increased bile secretion after gall bladder contraction. Gall bladder emptying starts as the stomach begins to empty, and gall bladder refilling starts when gastric emptying is nearly complete.¹²

Lanzini and colleagues¹⁰ have now defined the events occurring in bile flow between meals. Most hepatic bile is diverted into the gall bladder not only during fasting but also after meals. This storage process alternates at short intervals with ejection of bile from the gall bladder into the duodenum. Thus, the gall bladder behaves like a set of bellows, and this property may be important for thorough mixing of its contents.

The role of cholecystokinin

Sixty years ago Ivy and Oldberg¹³ observed that the intravenous injection of an extract of upper gastrointestinal mucosa caused contraction and evacuation of the gall bladder in cats and dogs. Their classical cross-circulation studies showed that acid injected into the duodenum of one animal caused gall bladder contraction in the parabiotic partner. They proposed the name 'cholecystokinin' for the hormone or active principle that caused the gall bladder to contract. In 1968 Jorpes and Mutt isolated cholecystokinin (CCK) and described the chemical sequence of its amino acids.¹⁴ Cholecystokinin is released from the duodenum by luminal acid and nutrients, in particular fat and amino acids.¹⁵ The half life of CCK in the plasma of both man and dog is about 2.5 minutes.¹⁵ The kidney is its major site of uptake from the systemic circulation.¹⁵ The predominant forms of CCK (CCK-8, CCK-33, CCK-39, and CCK-58) are all released by the upper gastrointestinal mucosa. In portacaval transposition studies in dogs, Sakamoto and colleagues showed that nearly all CCK-8 in the portal circulation is metabolised on first passage through the liver¹⁶ and maintains a systemic activity; it is probably these forms of CCK that are primarily responsible for stimulating gall bladder contraction and pancreatic secretion.¹⁷

The presence of pancreatic enzymes (particularly trypsin) inhibits CCK release from the duodenum.^{18,19} By contracting and stimulating bile flow, the gall bladder also plays a role in the negative feedback suppression of CCK release by the upper gut. In man and in dogs with bile diversion, bile salts have been shown to inhibit the endogenous release of fat stimulated CCK and neurotensin from the ileum.²⁰ Thus, a self regulating feedback loop has been established for gall bladder emptying in response to duodenal food.

Infusions of CCK-8 cause the human gall bladder to contract,²¹ and the degree of change in gall bladder volume is directly proportional to the concentration of CCK detected in the plasma by radioimmunoassay.²¹ The volume and intraluminal pressure of the human gall bladder are inversely proportional to the circulating level of lipid-stimulated endogenous CCK.^{22,23} It is now generally believed that endogenous CCK is the main driving force behind gall bladder empty-

ing.²³ Thus CCK regulates the length of time that bile stays in the gall bladder and remains subject to the concentrating capability of its mucosa. Cholecystokinin therefore regulates the bile acid/cholesterol saturation index by gall bladder volume change²⁴ rather than by altering the absorption or secretion of water and electrolytes across the gall bladder mucosa.²⁵ So, at low bile acid secretion rates the bile secreted by the liver becomes more saturated with cholesterol: bile acid secretion rates are low when the enterohepatic circulation of bile acids is sluggish, for instance at night, as nocturnal fasting is associated with diminished CCK secretion and therefore decreased gall bladder volume changes.

Cholecystokinin acts directly on receptors in the muscle coat of the gall bladder.²⁶ Optimal binding of ¹²⁵I-CCK-33 occurs at pH 5.5 and requires the presence of magnesium.²⁶ Binding of ¹²⁵I-Bolton Hunter-CCK-8 to the CCK receptor requires the expenditure of cellular energy.²⁷ There is both regional and cellular heterogeneity of CCK receptors throughout the gut. There is a 20-fold decrease in sensitivity to the C-terminal residue of CCK-8 from gall bladder muscle to ileal circular muscle. Cholecystokinin receptors on cholinergic neurones in ileal muscle are between 80–300 times more sensitive to CCK-8 than the adjacent muscle cells.²⁸ Multiple exposures of guinea pig gall bladder to CCK-8 appear to increase the number of CCK receptors (sensitisation), whereas in the guinea pig ileum the opposite is seen (desensitisation), associated with changes in the cholinergic receptors.²⁹ These findings probably relate to the primary neuronal nature of CCK receptors in the ileum and the combined neuronal and muscular location of CCK receptors in the gall bladder. There is a wide range of binding capacity of CCK to its receptor between one gall bladder and another, but in general the binding affinity of ¹²⁵I-D-Tyr-Gly-[(N1e)²⁸ 30 CCK-26-33] to gall bladder muscle has a K_d of around 1 nmol and 50% of this binding can be inhibited by 0.9 nmol CCK-8, 0.8 µmol gastrin-17 and 5 µmol CCK (gastrin)-4.³⁰ The gall bladder muscle CCK receptor has been shown by covalent cross linking studies to have a molecular weight in the region 85 000–95 000.³⁰

The response of the gall bladder to CCK is calcium dependent. It is inhibited by the addition of calcium channel blocking agents.³¹ Removal of calcium from the extracellular fluid in gall bladder strip preparations decreases the contractile response to CCK by 80%.³¹ Hypercalcaemia induced in normal volunteers by iv infusions of calcium chloride enhances CCK-stimulated gall bladder contraction *in vivo*.³²

Gall bladder contraction in response to CCK is also mediated by cholinergic vagal neurones. Truncal vagotomy reduces the sensitivity of canine gall bladder to CCK (as measured by changes in intraluminal pressure).³³ Truncal vagotomy may not alter the rate of gall bladder emptying,³⁴ motility being unchanged in the early postoperative period in dogs.³⁵ In man, however, the postcontraction volume of the gall bladder is greater after complete vagotomy, suggesting a parasympathetic role in normal emptying.³⁴

Not only does vagal stimulation facilitate the response of the gall bladder to CCK, but it may also regulate this response.³⁶ Using ultrasound it can be shown that sham feeding stimulates gall bladder emptying in up to 50% of people, suggesting a major role for vagal activity in gall bladder motility. This response is eliminated by cholinergic blockade with atropine, again suggesting that the vagus can stimulate the gall bladder to contract.³⁷ Cholecystokinin receptors on cholinergic postganglionic parasympathetic neurones are much more important in mediating the response of the gall bladder to CCK than they are in mediating the response of pancreatic acini to this hormone.³⁸ Either hypersensitivity of the gall bladder to CCK or hyposensitivity of the sphincter of Oddi to CCK (resulting in the gall bladder contracting against a closed biliary system) may be the cause of acalculous biliary colic in the small group of patients whose symptoms can be reproduced by CCK infusion and who benefit from cholecystectomy.³⁹

Other neurohumoral agents

Other gastrointestinal peptides and neurotransmitters have either cholecystokinetic actions (direct and/or CCK potentiating) or cholecystostatic actions (direct and/or CCK inhibiting). Gastrin-17 belongs to the same family of peptides as CCK. It causes gall bladder muscle contraction in some species, though much less potently than CCK⁴⁰ and not at all in man.⁴¹ Secretin, released from the upper gut by the presence of acid, abolishes the net water absorption from bile in the gall bladder.⁴² On its own secretin has no effect on gall bladder muscle,^{42,43} but it has been shown to potentiate the action of CCK on the gall bladder.⁴⁴ Substance P is a direct stimulant of gall bladder contraction in both dogs and rabbits,⁴⁵ but its cholecystokinetic potency is only about one 600th that of CCK.⁴⁶ Similarly motilin is weakly cholecystokinetic, but this effect is limited to the quiescent period between meals.⁴⁷ The response of the gall bladder to neurotensin is species-specific. In dogs it causes gall bladder contraction with about one 50th the potency of CCK.⁴⁸ In man, neurotensin causes gall bladder relaxation *in vivo*, but this appears to be an indirect effect as neurotensin produces no response *in vitro*.⁴⁹ Histamine (H₁) receptor stimulation causes gall bladder muscle contraction, whereas stimulation of type 2 receptors (H₂) causes gall bladder muscle relaxation.⁵⁰

Pancreatic polypeptide causes relaxation of the gall bladder and decreased intraluminal pressure,⁵¹ which encourages refilling after contraction.⁵² Infusions of CCK in man bring about release of pancreatic polypeptide, as measured by radioimmunoassay.⁵³ Pancreatic polypeptide remains raised for up to six hours after a meal, suggesting that pancreatic polypeptide could play a role in the regulation of postprandial gall bladder filling.⁵² Vasoactive intestinal peptide decreases resting gall bladder pressure in a dose-dependent manner, eliminating spontaneous contractile activity.⁵⁴ Vasoactive intestinal polypeptide inhibits the contractile response of the gall bladder to CCK *in vivo*^{54,55} and *in vitro*.⁵⁶ The

gall bladder is supplied by three types of vagal nerve fibre: cholinergic, CCK-ergic and VIP-ergic. Thus vagally regulated gall bladder tone and contraction is the net result of the interplay of stimulatory fibres (mediated by acetylcholine and CCK) and inhibitory fibres (mediated by vasoactive intestinal polypeptide).⁵⁵ Besides diminishing the hepatic secretion of bile,⁵⁷ somatostatin is a potent inhibitor of gall bladder emptying in man, whether meal-stimulated, vagally-mediated or CCK-induced.⁵⁸ Peptide YY has recently been shown to potentiate gall bladder relaxation and refilling after CCK-induced contraction,⁵⁹ and calcitonin gene related peptide⁶⁰ and pancreastatin⁶¹ inhibit CCK-induced gall bladder contraction in the guinea pig.

SPHINCTER OF ODDI

The role of the sphincter of Oddi is to regulate bile flow into the duodenum, divert hepatic bile into the gall bladder and prevent reflux of duodenal contents into the biliary tree.³ The physiological sphincter of Oddi is characterised by a high pressure zone located at the choledochoduodenal junction.^{62,63} Physiological studies of the sphincter of Oddi have centred on three main areas: (1) the relationship between sphincter of Oddi activity and the activity of the surrounding duodenum; (2) the mechanism by which the sphincter controls the flow of bile into the duodenum, and (3) the factors that control sphincter of Oddi function.

Functional independence of the sphincter

Early investigators⁶⁴ considered biliary flow to be solely dependent on changes in duodenal tone and muscular activity. Others held that the sphincter of Oddi was functionally independent of the duodenal musculature and was responsible for changes in biliary pressure.⁶⁵⁻⁶⁷ More recently, Mochinaga and colleagues⁶⁸ have shown that in the fasted state gastroduodenal motor activity plays a role in the regulation of bile flow. Using a canine model they observed that bile entered the duodenum only when the duodenal wall at the level of the choledochoduodenal junction was not contracting or when the amplitude of contraction was small compared with the maximum amplitude of contraction during phase III, the active phase of the MMC. They therefore suggested that when the duodenal wall contracts, it constricts the common bile duct and the choledochoduodenal junction to impede bile flow. Others have showed a pylorocholecystic reflex⁶⁹ and another a gastrosphincter of Oddi reflex,⁷⁰ indicating a relationship between gastrointestinal and sphincter of Oddi motility.

Both morphine and noradrenaline contract the sphincter but relax the duodenum.⁷¹ These findings were confirmed by studying the effect of adrenaline and noradrenaline on the isolated terminal bile duct.⁷² Ono and colleagues simultaneously recorded bile flow and electrical activity from the sphincter and duodenum in humans. They found a negative correlation between bile flow and sphincter of Oddi elec-

trical activity – that is, bile flowed into the duodenum only in the absence of sphincter electrical activity.⁷³ Nevertheless, it seems reasonable to assume that the activity of the duodenal musculature can modify the rate of bile delivery into the duodenum.

Bile flow into the duodenum

Several studies in animals and man show that the sphincter of Oddi has spontaneous phasic contractions.^{74–80} In man these phasic contractions occur at about four/minute and have a duration of four to five seconds.⁷⁵ Using a triple lumen catheter with orifices spaced at 2 mm intervals from the distal end for manometric measurements, Toouli and his colleagues found that 60% of human phasic pressure waves propagate towards the duodenum, 14% propagate in a retrograde fashion towards the common bile duct while 26% are simultaneous – that is, propagate in both directions at once.⁸¹ Species differences in phasic wave direction make the physiological purpose of this phenomenon unclear. In dogs the biliary sphincter may act as a pump to expel bile into the duodenum,⁸² yet it has also been observed that flow through the common bile duct stops with each phasic contraction of the sphincter.^{73 79 81 83} Moreover in cats, increased sphincter activity is associated with increased resistance to flow through the choledochoduodenal junction.⁷¹

These apparent contradictions have now been resolved by Toouli's simultaneous analysis of the opossum sphincter, using cine-radiography, transsphincteric flow and electromyographic recordings.⁸⁴ The main mechanism of common bile duct emptying in the opossum is antegrade contraction of the sphincter of Oddi. A wave of contraction begins at the junction of the bile duct and sphincter and strips the contents of the sphincter segment into the duodenum (the systolic phase). During sphincter contraction no flow occurs from the bile duct into the sphincter segment. The sphincter then relaxes, and there is passive flow of bile from the duct into the sphincter segment (the diastolic phase). A wave of contraction then begins again at the ductal/sphincter junction, and the cycle repeats itself. The overall effect of phasic contractions is therefore to promote flow from the common bile duct into the duodenum. Initially, increased contractions are accompanied by increased flow across the sphincter; but when the contractions exceed a certain level, the diastolic interval is abolished completely and flow ceases. In the opossum, this phenomenon occurs when the frequency of contractions exceeds eight/min.⁷

A similar phenomenon has been described in dogs.⁸⁵ Intense phasic motor activity appears to impede bile flow, whereas less intense activity facilitates flow. Although species differences probably exist, the radiological studies of Torsoli⁵ and Hess⁶ and the manometric observations of Toouli and colleagues⁸¹ indicate that the human sphincter of Oddi also exhibits peristaltic phasic contractions, which propel bile into the duodenum and prevent reflex of duodenal contents into the bile and pancreatic ducts. Thus, the purpose of phasic waves appears to be the

promotion of bile flow through the sphincter of Oddi into the duodenum.

Control mechanisms

The activity of the sphincter of Oddi is subject to many influences. In 1917 Meltzer proposed his 'Law of contrary innervation' whereby reciprocal contraction of the gall bladder and relaxation of the sphincter of Oddi was due to a fine nervous mechanism. Potter and Mann⁶⁴ observed that perception of food caused a reduction in resistance to bile flow, again indicating a neural influence on the sphincter. In 1926 Whitaker demonstrated, however, that the denervated gall bladder can still contract in response to food.⁸⁶

Sandblom showed the hormonal action of cholecystokinin on the sphincter of Oddi in 1935.⁸⁷ Since then, several other hormones including secretin,⁷⁵ pentagastrin,⁸⁸ serotonin,⁸⁹ caerulein,⁸⁸ glucagon⁷⁵ and motilin⁹⁰ have all been shown to affect the sphincteric activity. A role of neural mediation has reemerged from recent work showing regulation of the sphincter by excitatory and inhibitory pathways.⁹¹ Humoral and neural stimuli are in any case likely to be interlinked.

(a) Hormonal factors

The response of the sphincter of Oddi to CCK varies according to species. In man CCK decreases phasic wave activity and reduces baseline pressure,⁷⁵ while a similar response is found in primates⁷⁶ and cats.⁷⁷ In these species the sphincter relaxes in response to CCK, thus facilitating the passive flow of bile from the common duct into the duodenum. The effect of CCK in the rabbit,⁷⁸ opossum⁷⁹ and prairie dog,⁹² however, is to increase the phasic wave activity of the sphincter without affecting baseline pressure. In these species increased sphincter of Oddi activity propels bile actively into the duodenum in response to CCK.

Until recently, the inhibitory actions of CCK on the sphincter of Oddi were thought to be caused by a direct action of the hormone on the sphincter muscle. New data now show that the effects of CCK on the sphincter of Oddi are mediated by non-adrenergic, non-cholinergic neurones that inhibit the feline sphincter of Oddi. This effect masks a direct excitatory effect of CCK on the sphincter muscle.⁷⁷ In the opossum, on the other hand, excitation of the sphincter of Oddi by CCK appears to be the result of a direct action of the hormone on the sphincter muscle.³

Other gastrointestinal hormones and peptides can also affect the sphincter of Oddi. Caerulein is a potent inhibitor of sphincter activity in a number of species.^{88 93 94} Gastrin, which shares an identical carboxyterminal pentapeptide with CCK and caerulein, also influences the choledochal sphincter.⁸⁸ The potency of this hormone, however, is considerably less than that of CCK or caerulein. Agosti *et al*⁹⁴ showed that human gastrin has only 10–40% of the activity of CCK in relaxing the sphincter of Oddi in the anaesthetised guinea pig. Secretin reduces sphincter resistance in the dog, probably indirectly by

potentiating the action of CCK. Glucagon also decreases sphincter resistance in dogs⁸⁸ and man,⁶³ and it is often used to relax the sphincter to facilitate cannulation during ERCP.³ Recently, motilin, serum concentrations of which fluctuate with phases of the interdigestive MMC, has also been found to influence the sphincter of Oddi.^{3,90} In the dog⁸⁵ and opossum⁹⁵ phasic contractions exhibit cyclical variations in phase with the interdigestive MMC. Thus, the physiological role of motilin on the sphincter of Oddi may be to regulate this cyclical activity during the interdigestive period. The actions of motilin on the sphincter of Oddi may be mediated by an intramural excitatory pathway, which appears to consist of opiate, serotonergic and cholinergic neurones.⁹⁶

The effects of pancreatic polypeptide, peptide-YY, and neuropeptide-Y on biliary motility are controversial. Both pancreatic polypeptide and peptide-YY have been shown to enhance gall bladder filling in the prairie dog.^{97,98} Tatemoto and Mutt reported that peptide-YY stimulates gall bladder contraction *in vitro*⁹⁹ but does not affect CCK-8-stimulated gall bladder contraction in the anaesthetised guinea pig.¹⁰⁰ Likewise, peptide-YY does not influence resting gall bladder tension or CCK-stimulated gall bladder contraction in dogs;¹⁰¹ we have shown similar results in the prairie dog.¹⁰² Nonetheless, peptide-YY inhibits the increase in phasic contractions of the sphincter usually observed with CCK-8. Thus, pancreatic polypeptide and peptide-YY may play a role in modulating biliary motility in the postprandial state by inhibiting bile flow into the duodenum and promoting gall bladder filling. Since neuropeptide-Y increases sphincter of Oddi activity and gall bladder pressure in the prairie dog,¹⁰³ it could be a neurotransmitter or neuromodulator regulating bile flow.

(b) Neural factors

Perception of food causes a reduction in the resistance to bile flow through the choledochoduodenal junction,⁶⁴ indicating a neural influence on the biliary sphincter. Recent neurohistochemical studies have shown both adrenergic and cholinergic neurones within the sphincter of Oddi of the cat and dog.¹⁰⁴ Persson¹⁰⁵ suggests that the cat gall bladder and sphincter contain both adrenergic α -receptors (mediating contraction) and adrenergic β -receptors (mediating relaxation). In the gall bladder β -receptors predominate, while in the sphincter α - and β -receptors are more evenly distributed. Relaxation of the sphincter in response to adrenergic stimulation, however (β -receptors), occurs only when the α -receptors have previously been blocked with phenoxybenzamine.¹⁰⁵ Although both receptor types exist in sphincter smooth muscle, mainly α -adrenoreceptors are activated by sympathetic nerve stimulation. Thus, adrenergic stimulation causes the sphincter of Oddi to contract and the gall bladder to relax. This mechanism may be important during gall bladder filling by promoting the entry of bile into the gall bladder.

The biliary tract receives a parasympathetic innervation from the vagus nerve.¹⁰⁶ Acetylcholine contracts both the gall bladder and the sphincter of Oddi in the cat and calf.^{72,106,107} Cholinergic stimulation of the sphincter by bethanecol increases the frequency of phasic contractions in the opossum.⁸⁴ The function of the vagus nerve in sphincter of Oddi function remains obscure,^{108,109} though recent work in the prairie dog has demonstrated increased resistance to flow through the sphincter after truncal vagotomy.⁸⁰ Vagal stimulation studies have also failed to define clearly the role of the vagus in biliary dynamics. Some investigators have reported sphincter contraction during vagal stimulation,¹¹⁰ but others could not detect any response to either central or peripheral stimulation of the vagus.¹¹¹

Behar and Biancani have suggested the presence of non-cholinergic, non-adrenergic neurones in the sphincter of Oddi.⁷⁷ Studying the feline sphincter of Oddi, they observed that CK-induced sphincter relaxation was not antagonised by either adrenergic or cholinergic blockade. Either CCK has a direct action on sphincteric smooth muscle, therefore, or its effects are mediated by a different neurotransmitter. In support of such a neurological pathway, administration of tetrodotoxin, which blocks nerve transmission without affecting smooth muscle, completely antagonised the effects of CCK on the sphincter.⁷⁷

(c) Pharmacological factors

Morphine has long been known to increase resistance to bile flow. Studies in a number of species^{71,82} have shown that the sphincter of Oddi is very sensitive to opiates, responding with marked contractions to low doses of morphine sulphate. In man small doses of morphine increase the rate of phasic contractions of the sphincter of Oddi;³ phasic wave amplitude and baseline pressure are also increased.¹¹² Thus, morphine is contraindicated in the management of biliary pain. Pethidine also produces a marked rise in biliary pressure but its effect is only half that of morphine.¹¹³ Amyl nitrate consistently relaxes the sphincter of Oddi across several species.^{83,111,114} This inhibitory effect has been used clinically to distinguish sphincter spasm from stenosis.

Nifedipine, a calcium channel blocker, has also been shown to reduce baseline sphincter of Oddi pressure as well as the frequency, amplitude and duration of phasic contractions.¹¹⁵ Intravenous butylscopolamine bromide (given iv) will decrease sphincter of Oddi motility without affecting baseline pressure.¹¹⁶ Alcohol administered either iv or into the duodenum causes a moderate decrease in baseline pressure without affecting sphincter motility.¹¹⁶ Recent endoscopic manometry in humans given pentazocine has shown higher baseline pressures and increased amplitude of phasic contractions in the sphincter.¹¹⁷ Fentanyl has also been associated with sphincter spasm during peroperative cholangiography,¹¹⁸ whereas diazepam is without such effects.⁶³

Various anaesthetic agents influence sphincter of Oddi function. Thus small iv doses of barbiturate increase flow through the sphincter.¹¹⁹ Xylazine and ketamine affect biliary tract motility in the prairie dog and should therefore be avoided during physiological studies of the sphincter.^{120 121} Lastly, a recent study in dogs has shown inhibition of endogenous CCK release by several different anaesthetic agents (with the exception of α -chloralose), which may therefore affect sphincter motility indirectly.¹²²

(d) Physical factors

Temperature affects sphincter of Oddi activity in rabbits, cold being inhibitory and a rise to 40°C being stimulatory.⁸³ Increasing the blood pressure in dogs by infusing saline raises sphincter opening pressure, whereas hypotension produced by haemorrhage diminishes opening pressure.¹¹¹ That sphincter activity is influenced by the degree of gall bladder filling is well established.^{74 92 119} In the prairie dog, for example, distending the gall bladder increases sphincter activity and emptying it has the opposite effect, the so-called cholecystosphincter of Oddi reflex.⁷⁴ A relationship has recently been shown between sphincter of Oddi activity and the interdigestive or migrating myoelectric complex.^{95 123} Two groups of investigators have shown in the conscious opossum that phasic contractions are synchronous with spike potentials in the sphincter and that both exhibit cyclical changes that correlate with the MMC.^{95 123} Using a canine model, Mochinaga has demonstrated a relationship between gastroduodenal motor activity and bile flow.⁶⁸

(e) Intraluminal stimuli

Early investigators observed that introduction of acid into the stomach increased resistance to bile flow entering the duodenum in the anaesthetised dog, whereas alkali achieved the reverse.¹²⁴ In patients with previous cholecystectomy installation of dilute hydrochloric acid into the duodenum causes a transient increase in sphincter of Oddi resistance, which can be blocked with atropine.¹²⁵

Fifty years ago, Best and Hicken¹²⁶ inferred from cholangiographic evidence that cream and olive oil relax the human sphincter of Oddi, but Doubilet could not confirm this finding in patients after cholecystectomy.¹²⁵ A more extensive investigation of cholecystectomy patients showed that an egg yolk meal caused relaxation but olive oil did not; protein also caused slight relaxation of the sphincter, but carbohydrate had no effect.¹¹⁴ Recent work in the prairie dog has shown that intraduodenal infusions of acidified saline¹²⁷ and sodium oleate¹²⁸ decrease sphincter of Oddi activity, whereas protein infusions stimulate sphincter activity.¹²⁹ Exogenous CCK consistently increases sphincter of Oddi activity in this species.^{90 92} These conflicting data may be explained by evidence in rodents that CCK is not released after ingestion of fats but is released by protein.¹³⁰

Pathophysiology

DYSMOTILITY AND GALL STONES

In 1856 Meckel von Helmsbach proposed that mucus might form a nidus, but that stasis was necessary for cholesterol to 'adhere' to this and create a gall stone.¹¹ It has been argued that the presence of established calculi affects neither the physiology of biliary constituents (bile salts, cholesterol and phospholipids) nor the contractility of gall bladder muscle.¹³¹ Whether alterations in gall bladder contractility play an aetiological role in gall stone formation is controversial. One survey has shown increased post-prandial emptying of the gall bladder in patients with cholesterol stones.¹³² These authors suggested that such an increase in gall bladder emptying would be associated with a decreased bile acid pool and in turn precipitate lithiasis. These patients also had increased gall bladder sensitivity to CCK.¹³³ Another group found unchanged gall bladder sensitivity to CCK *in vivo* but altered contractility in response to CCK *in vitro*; contractility increased in early disease but decreased in advanced disease.¹³⁴ These data¹³²⁻¹³⁴ are, however, at variance to the majority of published studies on the correlation between altered gall bladder motility and gall stone formation.

Many clinical and experimental studies confirm decreased gall bladder emptying in the presence of gall stones.¹³⁵⁻¹⁴² In the prairie dog, prevention of stasis by periodic administration of CCK lowers the incidence of gall stones.¹³⁵ Increased resistance to flow in the cystic duct delays gall bladder emptying and predisposes to calculi.¹⁴³ Increased viscosity of gall bladder bile may result from hyperconcentration during delayed emptying.¹⁴⁴ Calculous gall bladders have diminished sensitivity to prostaglandin stimulation of smooth muscle contraction,¹⁴⁵ but prostaglandins are not the prime mediators of gall bladder emptying. Patients with gall stones have raised CCK concentration in their duodenal mucosa compared with normal controls.¹⁴⁶ This may be because of increased synthesis of CCK in order to promote gall bladder emptying if the gall bladder is less sensitive to CCK, or alternatively it may be because of a failure to release CCK which results in poor gall bladder emptying in response to the presence of food and acid in the duodenum. On balance, we favour the former hypothesis. During gall stone formation in the prairie dog, changes in gall bladder motility precede changes in bile salt pool size.¹⁴⁷ Dysmotility may reflect a diminished contractile response to CCK¹⁴⁸ rather than alterations in membrane excitation, excitation-contraction coupling or total content of contractile proteins in gall bladder muscle.

Thompson and colleagues¹³⁷ have described a group of gall stone patients whose gall bladders failed to contract with the normal endogenous release of CCK after a fat meal. They termed these patients 'non-contractors'. CCK-induced contraction of their gall bladder muscle strips were correlated with the preoperative contractility of the gall bladder in response to endogenous CCK. 'Non-contractors' were shown to have fewer CCK receptors in gall bladder muscle

than other gall stone patients whose gall bladders contracted normally to endogenous CCK. In the guinea pig too, experimental cholelithiasis is associated with decreased biliary motility owing to fewer CCK receptors.¹⁴⁹

After major abdominal operations reductions in bowel motility, CCK release and vagal activity could all lead to gall bladder hypotonicity and biliary stasis predisposing to gall stones.¹⁵⁰ Reduced motility of gall bladder and intestines alike may contribute to gall stone formation after truncal vagotomy, when increased resistance at the sphincter of Oddi⁸⁰ and gall bladder dilatation¹⁵¹ may both be factors. Patients receiving prolonged total parenteral nutrition are also at risk of rapid gall stone formation; bile stasis appears to be the major aetiological event.^{150 152} Interestingly, children on longterm total parenteral nutrition seldom develop gall stones unless other aetiological factors are also present – for example, necrotising enterocolitis or distal ileal resection resulting in reduced bile salt pool or biliary stasis.^{153 154} The frequency and severity of acute cholecystitis, both calculous and acalculous, in seriously ill patients after trauma or major surgery necessitate urgent ultrasonography and prompt cholecystectomy if the diagnosis is suspected.¹⁵⁵ Daily administration of CCK to patients on longterm total parenteral nutrition might prevent this complication.¹⁵⁶

One interpretation of the evidence that implicates altered biliary motility in the aetiology of gall stone formation is that gall bladder activity must be maintained in a tight narrow band between overactivity reducing the bile acid pool with consequent lithiasis,^{132–134} and underactivity causing stasis and gall stone precipitation.^{135–136} Furthermore, as argued earlier, a reduction in the rate of turnover of the enterohepatic circulation of bile acids is associated with reduced hepatic bile acid secretion, so on balance we support the view that decreased biliary motility rather than increased biliary motility is the aetiological event in cholelithiasis.

BILIARY MOTILITY AND AGEING

Boyden and Grantham investigated the effect of age on gall bladder emptying in 1926,¹⁵⁷ using oral cholecystography after a standard 'Boyden meal' (five egg yolks well stirred in half a pint of cream). The rate of gall bladder emptying decreased sharply between childhood and adulthood but remained constant thereafter. When cholecystograms were reviewed from subjects aged 60–83 years, a quarter of those without gall stones had evidence of delayed emptying.¹⁵⁸ In support, both fasting and corn oil-stimulated concentrations of CCK in plasma are higher in older than younger healthy volunteers, though ultrasonic estimates of gall bladder volume were similar.¹⁵⁹ The CCK content of upper small bowel mucosa increases progressively with age in normal human subjects¹⁴⁶ and guinea pigs,¹⁶⁰ although it is not known if this is the result of increased synthesis or decreased release of CCK. The *in vitro* response of rabbit gall bladder strips to CCK diminishes between six months and four years of age,¹⁶¹ and in the guinea pig *in vivo* there is an age related loss of gall bladder sensitivity

and contractility to exogenous CCK owing to a decrease in gall bladder CCK receptors.¹⁶² Although age lessens the sensitivity of gall bladder muscle to CCK, therefore, there is a compensatory increase in CCK release, which maintains near normal gall bladder emptying.

The mechanism that correlates the age related decrease in gall bladder emptying to increased compensatory CCK release is probably the bile salt inhibition of CCK release postulated by Gomez and colleagues.²⁰ Decreased gall bladder emptying results in less bile salts reaching the duodenum and therefore greater CCK release. In extreme youth the gall bladder response to CCK is different. Ultrasonography has been used to measure the contraction of both maternal and near term fetal human gall bladders in response to a standard maternal meal.¹⁶³ Maternal gall bladder size decreases, but fetal gall bladder size is unchanged. It is not known if maternal CCK can cross the placenta. Indeed, whether any derivatives of the maternal meal can reach CCK cells in the fetal duodenum in sufficient quantities is unknown, likewise nothing is known of the ontogeny of CCK physiology during embryonic development in man. In guinea pigs the magnitude of contractile response of gall bladder strips to various stimulants (including CCK) increases progressively from the preterm fetus to the mature adult.¹⁶⁴ These data indicate that cholinergic and CCK receptors are present and functional before birth, but the contractile power of gall bladder muscle continues to develop after birth. Certainly, in the guinea pig gall bladder CCK receptors decline in number with advancing age.¹⁶²

A possible aetiological factor in the biliary stasis of ageing is the presence of duodenal juxtapapillary diverticula.¹⁶⁵ The association between such diverticula and common bile duct stones is well documented,¹⁶⁵ perhaps dysfunction of the sphincter of Oddi allows reflux of duodenal contents into the lower common bile duct.¹⁶⁶ We have shown that the rate of development of experimental gall stones in the guinea pig correlates directly with age and can be prevented by administration of CCK to provoke biliary emptying.¹⁶⁷

CHOLECYSTECTOMY AND THE SPHINCTER OF ODDI

Nearly half a million cholecystectomies are performed each year in the United States,¹⁶⁸ yet very little is known about the effect of this operation on the sphincter of Oddi. Ruggero Oddi was the first to observe that cholecystectomy resulted in marked dilatation of the common bile duct in dogs:¹⁶⁹ 'La bile se recueille dans la vésicule biliaire ou dans les conduits biliares très dilatables des animaux qui manquent de cette dernière'. These findings were confirmed by Judd and Mann, who also found increased luminal pressure in the bile duct.¹⁷⁰ Subsequent work has also shown that the common bile duct dilates in animals after cholecystectomy,¹⁷¹ but autopsy and radiological studies in man do not confirm a clear cut effect.^{172 173} Patients with choledocholithiasis have recently been shown to have greater

TABLE Sphincter of Oddi dysfunction

	Structural	Functional	
	Biliary I	Biliary II	Biliary III
Presentation	1 Biliary type pain 2 Abnormal LFTs on 2 occasions 3 Delayed drainage of contrast on ERCP >45 min	1 Biliary type pain and 2 Abnormal LFTs on 2 occasions or 3 Delayed drainage on contrast on ERCP >45 min or 4 Dilated CBD >12 mm Necessary for diagnosis	1 Biliary type pain only
Manometry	Optional	1 Elevated SO basal pressure 2 Reduction of pressure or SO phasic wave amplitude with CCK-OP or amylnitrite	Mandatory 1 SO hypertonicity or spasm 2 Paradoxical response to CCK-OP 3 SO tachyoddia 4 Altered SO phasic wave sequence
Treatment	Operative sphincteroplasty	Endoscopic sphincterotomy	

LFTs=liver function tests; ERCP=endoscopic retrograde cholangiopancreatography; CBD=common bile duct; SO=sphincter of Oddi; CCK-OP=cholecystokinin octapeptide

common duct diameters than normal volunteers, and it appears that after cholecystectomy further dilatation of these ducts occurs in the absence of symptoms.¹⁷⁴

Recent studies have shown the presence of a cholecystosphincteric reflex suggesting that sphincter activity is mediated, at least in part, by the degree of gall bladder distension.^{74 119} Furthermore, in dogs CCK release is increased in response to fat stimulation after cholecystectomy.¹⁷⁵ This finding could reflect loss of bile salt inhibition of CCK release,²⁰ as bile salt flow will no longer surge when the gall bladder empties after a meal. In prairie dogs the sphincter of Oddi behaves differently after cholecystectomy, with altered responses to CCK and intraduodenal fat.¹²⁸

‘POST CHOLECYSTECTOMY SYNDROME’
Although cholecystectomy is a safe and effective operation, 20% of patients develop either new gastrointestinal symptoms or recurrence of the symptoms for which the operation was recommended.¹⁷⁶ This unfortunate outcome has been referred to as ‘the post cholecystectomy syndrome’, but it is unlikely that there is such a specific entity. Many non-biliary conditions can mimic the symptoms of biliary tract disease and should be considered in the differential diagnosis of such patients. These include pancreatitis, peptic ulcer, reflux oesophagitis, right sided colonic diverticulosis and the irritable bowel syndrome.¹⁷⁷ Common duct stones, retained gall bladder and traumatic stricture of the bile duct are obvious potential explanations for post cholecystectomy problems. Although a long cystic duct remnant is sometimes implicated,¹⁷⁶ the evidence is unconvincing unless stones are contained in the stump.¹⁷⁷ Some patients with post cholecystectomy symptoms may have motor dysfunction of the sphincter, including papillary stenosis and biliary dyskinesia.

PAPILLARY STENOSIS
Papillary stenosis has been defined as a narrowing of all or part of the sphincter of Oddi

segment.¹⁷⁸ This is a structural problem resulting from fibrosis of the sphincter. Aetiological factors include injury by impacted stones or operative instrumentation, infected bile and pancreatitis.¹⁷⁸⁻¹⁸¹

To distinguish organic stenosis from biliary dyskinesia, Hogan and Geenen have proposed a classification based on clinical, laboratory and radiological findings which recognises three groups of patients¹⁷⁸ (Table): group I patients have biliary pain, abnormal liver function tests on two or more occasions, delayed drainage of ERCP contrast beyond 45 minutes and a dilated common bile duct >12 mm in diameter. These patients are likely to have a structural problem, ie papillary stenosis, and manometry is optional. Group II patients have biliary pain but only one or two of the other criteria. As their lesion could be structural or functional, sphincter of Oddi manometry helps to separate the two. Raised baseline pressures which decrease with iv CCK-OP (20 ng/kg) or inhalation of amyl nitrite indicate a functional rather than a structural abnormality, but in either case endoscopic sphincterotomy may be beneficial.¹⁷⁸ Group III patients present only with biliary pain and probably have ‘true’ sphincter of Oddi dyskinesia; manometry is essential to define the abnormality, and again endoscopic sphincterotomy may be helpful.¹⁷⁸

Fibrosis and inflammation of the papilla of Vater have often been documented at operation and may be associated with biliary tract disease and/or recurrent acute pancreatitis.¹⁸²⁻¹⁸⁵ Symptoms do not, however, necessarily coincide with the severity of histological change.¹⁸³ In a prospective study of 28 patients with post-cholecystectomy pain, Moody found an abnormal papilla in 82%.¹⁸⁴ Anterior sphincteroplasty and transampullary septectomy gave long-term relief of pain or symptomatic improvement in 76% of patients,¹⁸⁶ and we too have found this operation beneficial.¹⁸⁵ Nonetheless, the extensive amount of collagen that is normally present within the papilla makes the histological diagnosis of fibrosis difficult,¹⁸² so that a clear cut differentiation from biliary dyskinesia is not always possible.

BILIARY DYSKINESIA

Biliary dyskinesia is defined as a primary disorder of the tonic or phasic motor activity of the sphincter of Oddi.¹⁷⁸ Long suspected as a source of abdominal pain after cholecystectomy, sphincter spasm was described by Parvel in 1932 and termed biliary dyskinesia by Ivy and Sandblom two years later.¹⁸⁷ In early radiographic and manometric studies of eight patients with T-tubes, McGowan and colleagues observed that morphine provoked a rapid rise in intrabiliary pressure associated (in one patient) with severe epigastric pain similar to that experienced before cholecystectomy.¹⁸⁸ Furthermore, unprovoked episodes of pain were also associated with a marked rise in intrabiliary pressure. These classical studies indicated a pivotal role for the sphincter of Oddi in raising intrabiliary pressure and causing abdominal pain. The hypothesis was soon supported by Colp's observation that sphincterotomy could often relieve post cholecystectomy pain¹⁸⁹ and by Dahl-Iverson's discovery that with an intact sphincter patients with presumed biliary dyskinesia could still experience episodic pain even with a T-tube to provide dependent drainage.¹⁹⁰

Attempts to identify biliary dyskinesia by pharmacological provocation of pain or pancreatic enzyme changes have had varying success. Nardi and Acosta introduced the morphine-neostigmine provocation test in which papillary contraction is stimulated by morphine and pancreatic secretion by neostigmine.¹⁹¹ In one series 16 of 23 patients with abdominal pain and a positive Nardi test had moderate to marked signs of papillary stenosis on endoscopic evaluation.¹⁹² Other investigators have found this test much less specific, either failing to confirm any correlation with papillary stenosis at operation¹⁹³ or finding positive tests in 60% of healthy controls and patients with irritable bowel syndrome.¹⁹⁴ An operative sphincteroplasty of the pancreatic duct, however, renders Nardi-positive patients Nardi-negative.¹⁸⁵

The development of transendoscopic papillary manometry has provided a method for direct assessment of sphincter of Oddi motility.⁷⁵ A spectrum of manometric abnormalities has been identified in patients with post-cholecystectomy pain by means of this technique.¹⁹⁵ High frequency of phasic contractions ('tachyoddia'), raising of baseline pressure, paradoxical response of the sphincter to CCK and altered direction of phasic waves have all been described.⁸¹⁻¹⁹⁵ The therapeutic implications of these changes have yet to be determined, but preliminary studies suggest that some patients with sphincter of Oddi dysfunction may benefit from endoscopic sphincterotomy.¹⁹⁶ If pancreatic duct obstruction contributes to the pain, however, an operative double sphincteroplasty seems likely to give a better result.¹⁸⁵

Conclusion

Before the advent of modern research techniques, knowledge of the physiology and pathophysiology of biliary motility was rudimentary. Now hormone and receptor assay, ultrasonography, cholecystography and endoscopic mano-

metry have generated important new data. Although primarily mediated through CCK, gall bladder emptying and refilling are the net result of a whole symphony of stimulatory and inhibitory agents. Opening of the sphincter of Oddi, once thought to be a simple passive relaxation, is a highly synchronised, dynamic and propulsive event. What is apparent from this review is that there is potential for many other hormonal, neurological, and pharmacological mechanisms in the regulation of biliary motility. Furthermore, recognition of pathophysiological mechanisms will lead to accurate diagnosis and treatment of symptomatic patients. More importantly, virtually nothing is understood of the molecular events that occur beyond the cell membrane within biliary smooth muscle once the events of gall bladder emptying have been provoked, and further research is required in this area.

Now that the treatment of biliary disorders is no longer the private estate of the surgeon, it behoves all who endeavour to treat patients with gall stones, acalculous cholecystitis, biliary dyskinesia and papillary stenosis to develop a better understanding of these complex physiological processes.

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