Progress report

Acalculous disease of the gall bladder

Cholecystectomy is a common operation in many countries of the world and gall stones are the overwhelming indication. Autopsy studies and sonographic screening in developed countries indicate that at least a quarter of the elderly female population possess gall stones, although the epidemic may have reached its peak.¹ The extreme prevalence of cholelithiasis diverts attention from the fact that the gall bladder can be host to a number of other conditions (Table), some of which are lethal.

Congenital anomalies

These are chiefly of importance to the surgeon seeking to identify the biliary anatomy at cholecystectomy. The gall bladder may be rudimentary, absent, duplicate (Fig. 1) or even triplicate. In complete agenesis of the gall bladder the bile duct has a greater risk of developing both gall stones and carcinoma.² The commonest abnormality in shape is the so-called Phrygian cap, a pseudodiverticulum of the fundus that may be mistaken on cholecystography for a pathological septum.³ True congenital diverticula and septa are much less frequently encountered. Giant cystic malformation of the gall bladder has recently been reported and could represent a variant of choledochal cyst.⁴

The gall bladder may retain its intrahepatic (fetal) position into adult life, again posing difficulties in identification at operation. Besides *situs inversus*, other ectopic situations are an attachment to the left lateral segment of the liver and a transverse position on the right side, when the gall bladder may receive both hepatic ducts and drain directly through the bile duct.²

Table *Acalculous conditions of the gall bladder*

Congenital	<ul style="list-style-type: none">– anomalies of number, shape and site– anomalies of cystic duct– mucosal heterotopia– abnormal mesentery (torsion)
Traumatic	<ul style="list-style-type: none">– blunt (rare)– penetrating– iatrogenic (needle puncture, chemical)
Inflammatory (=acalculous cholecystitis*)	<ul style="list-style-type: none">– primary (no predisposing cause)– secondary to operations, burns, trauma– specific (typhoid, staphylococcal, parasitic)– other (emphysematous, xanthogranulomatous, sclerosing, vasculitic, Crohn's)
Degenerative	<ul style="list-style-type: none">– cholesterosis
Neoplastic	<ul style="list-style-type: none">– adenomyosis (diverticulosis)– (pseudotumours)– adenoma– other benign tumours (rare)– carcinoma (adeno, squamous)– melanoma (primary, secondary)– metastatic carcinoma

*acalculous cholecystitis can be acute or chronic.

Fig. 1 Oral cholecystogram showing a double gall bladder (by courtesy of Dr J Virjee).

Variations in the 'normal' anatomy of the cystic artery and duct are 'too common to be considered anomalous. Heterotopic tissue in the gall bladder wall can be hepatic, pancreatic, intestinal, or gastric,^{5,6} exceptionally giving rise to peptic ulcer of the gall bladder.⁷

A 'floating' gall bladder is not uncommon in elderly patients with visceroptosis. The organ is suspended either by a long mesentery attached from the fundus to the neck or by a short mesentery comprising only the cystic duct and artery.^{8,9} Rarely a floating gall bladder undergoes torsion, either complete or partial and recurrent;¹⁰ the gall bladder can even 'float' into an epigastric hernia.¹¹ Torsion of the gall bladder typically occurs in elderly women, but children can also be affected.¹² It has been described in one moiety of a double gall bladder.¹³ The presentation mimics that of acute cholecystitis, and the correct diagnosis is hardly ever suspected before laparotomy. Classically, pain is of sudden onset and there is a tender mass in the right upper quadrant.^{8,10}

Traumatic conditions

Protected by the overlying liver and costal margin, the gall bladder is seldom involved in abdominal trauma. Penetrating wounds in the right

upper quadrant will sometimes broach the gall bladder, usually in association with injury to the liver, small bowel, or colon. Severe blunt trauma can occasionally disrupt the gall bladder, especially if it is distended – for example, after a meal; this can be an isolated injury or accompany damage to the adjacent viscera. Of 5670 abdominal injuries of one or other type, 109 (1.9%) involved the gall bladder, causing contusion, laceration, avulsion or rarely traumatic cholecystitis from intraluminal haemorrhage.¹⁴

The gall bladder can sustain inadvertent damage from needles used for liver biopsy or percutaneous transhepatic cholangiography. Nowadays, interventional radiologists are attempting diagnostic and therapeutic procedures on the gall bladder itself with increasing enthusiasm.¹⁵ Diagnostic manoeuvres involve inserting a skinny needle into the gall bladder under ultrasound or computed tomography control, either by direct percutaneous puncture or preferably across the liver and the nonserosal surface of its gall bladder fossa. To drain a distended and/or infected gall bladder, percutaneous cholecystostomy can be undertaken by dilating up the needle track or by passing a trocar straight into the lumen. In skilled hands the reported incidence of bile peritonitis has been remarkably low; indeed there were no such complications among some 50 diagnostic and therapeutic procedures in two recent series.^{15 16}

Another type of iatrogenic injury can result from the repeated infusion of chemotherapeutic agents through a catheter placed in the hepatic artery for the treatment of colorectal liver metastases.¹⁷ Initially there is an acute cholecystitis with mucosal necrosis, and these changes progress to chronic fibrosis. The rapidly increasing use of implantable pumps for the delivery of drugs such as fluoro-deoxyuridine will magnify this problem unless prophylactic cholecystectomy is adopted as a routine.¹⁸

Acute acalculous cholecystitis

Between six and 17% of gall bladders removed for acute cholecystitis contain no gall stones;^{19–22} the proportion may be increasing.²³ In Glenn's retrospective review of 139 such patients, about half had a predisposing cause and half did not.¹⁹ These predisposing causes included surgical operations (remote from the biliary tract), multiple injuries, burns, recent childbirth and severe sepsis. Thus acute acalculous cholecystitis is often encountered in the intensive care unit. An attack of calculous cholecystitis after an operation could just be coincidence, yet nearly half the postoperative cases are acalculous; among post-traumatic cases no less than 92% of patients have no gall stones.²⁴

Several aetiological mechanisms have been postulated for acute acalculous cholecystitis, leaving aside rare circumstances like torsion, trauma, and intra-arterial drug therapy. Multiple blood transfusions were implicated in young American soldiers wounded in Vietnam, because of the increased pigment load.²⁵ Likewise dehydration might increase bile viscosity, and both parenteral nutrition and assisted ventilation (with positive end expiratory pressure) can cause bile stasis.^{20 26} Under these circumstances normal constituents of bile such as lysolecithin and bile acids could damage the mucosa and initiate cholecystitis.²⁷ Repeated doses of opiates in postoperative or traumatised patients would lead to prolonged sphincter spasm and perhaps increase luminal pressure in the gall bladder

above systolic blood pressure.^{28 29} Ischaemia could also result from increased sympathetic tone or atheroma, many of these patients being elderly.³⁰ Previous vagotomy, primary papillitis and the presence of a long, tortuous cystic duct have also been incriminated in the aetiology of acalculous cholecystitis.³¹ In children, where 30% of gall bladder disease is acalculous, cystic duct obstruction could result from congenital narrowing or local inflammation;³² the duct may be compressed by enlarged lymph nodes.³³ One fatal case in a premature infant was attributed to parenteral nutrition.³⁴ Whatever the underlying cause circulating organisms may compound the infection;²⁸ the same bacterium can often be grown from bile and blood alike.^{25 29}

There are no specific clinical or histological differences between (acute) calculous and acalculous cholecystitis, though the proportion of men is higher in the absence of gall stones and the overall mortality is twice as high – for example, 9.6 v 4.3%.²³ In postoperative and post-traumatic patients gangrene and perforation of the gall bladder are common sequelae (in about 60% of cases) and explain the high mortality rates observed (32–47%).^{28 35 36} The classical signs of fever, tenderness and a mass are often not detected at an early stage in these critically ill patients. Gangrene is either focal or diffuse, when it can cause bizarre complications such as bleeding into the colon³⁷ or pulmonary bile embolism.³⁸

The diagnosis of acute acalculous cholecystitis requires a high index of clinical suspicion. There is usually a leucocytosis, and serum concentrations of bilirubin, liver enzymes and amylase may be increased;³⁹ indeed patients can be mildly jaundiced. When peritonitis supervenes, perforated stress ulcer is an alternative possibility.⁴⁰ Ultrasonography is the simplest investigation. It can be done at the bedside using a portable real time scanner. Positive findings include mural thickening, distension of the gall bladder, sludge within the lumen and the halo sign of subserosal oedema.⁴¹ Cholescintigraphy using technetium labelled iminodiacetic acid may be a more sensitive technique than ultrasound, however.^{22 30} Non-visualisation of the gall bladder despite good hepatic uptake and the entry of isotope into the small intestine is taken as positive evidence of cholecystitis. Moreover, increased pericholecystic activity (the 'rim' sign⁴²) can indicate the complication of gangrene, and exceptionally free peritoneal spill will diagnose perforation of the gall bladder.²² Indium labelled leucocytes offer an alternative method for diagnosing a 'hot' gall bladder in this disease.⁴³

The best treatment of acute acalculous cholecystitis (and arguably of the calculous variety) is prompt laparotomy and cholecystectomy.^{26 28 35 36} Cholecystostomy is a poorer option because of the risk of extensive gangrene; moreover, the tube may subsequently become blocked or extruded.⁴⁴ Nevertheless, cholecystostomy can be a life saving procedure when carried out under local anaesthetic in a desperately ill patient.^{45 46} It may be particularly appropriate in children, in whom gangrenous changes are uncommon.³³ As for prophylaxis, it has been suggested that the periodic administration of oral fat or intravenous cholecystokinin might overcome biliary stasis and prevent the development of acute acalculous cholecystitis among high risk patients in a surgical intensive care unit.^{20 26}

Chronic acalculous cholecystitis

Although some degree of chronic inflammation is an inevitable accompani-

ment of cholelithiasis, these pathological changes can occur in the absence of gall stones.⁴⁷ In two recent series, chronic cholecystitis was acalculous in 12–13% of cases.^{21,48} Postinflammatory stenosis or primary tortuosity of the cystic duct might inhibit normal emptying of the gall bladder.^{31,49,50} Gall bladder dysfunction is suggested by low concentrations of biliary lipids in duodenal juice.⁵¹ Such patients may have persistent pain in the right upper quadrant. They pose diagnostic difficulties because repeat ultrasound scans and oral cholecystograms are often normal. The two tests combined with scintigraphy, however, can give an overall sensitivity of 85%.⁴⁸ Reproduction of pain within 5–10 minutes of an iv injection of cholecystokinin (CCK) can also select a group of patients who will benefit from cholecystectomy.^{50,52} If the CCK provocation test is done during oral cholecystography, poor concentration and incomplete emptying of the gall bladder are observed.^{49,53}

Rare types of cholecystitis

Typhoid fever can cause either acute or chronic cholecystitis.¹⁹ Such patients may harbour salmonellae in the bile for the rest of their life and could be at increased risk of gall bladder carcinoma.⁵⁴ Acute dilatation (hydrops) of the gall bladder may develop in children with typhoid, leptospirosis, or other systemic infections and can settle with conservative treatment.⁵⁵ Staphylococci can rarely cause acute cholecystitis, presumably reaching the gall bladder *via* the bloodstream.⁵⁶

Acute emphysematous cholecystitis results from gas forming organisms, notably clostridia and coliforms. Typically it occurs in male diabetics, who develop sudden onset of pain and fever;^{57,58} there may be a mass, and toxicity is often severe. The gas filled gall bladder gives a classical appearance on plain abdominal radiograph (Fig. 2). The primary lesion in emphysematous cholecystitis may be occlusion of the cystic duct⁵⁷ or cystic artery,⁵⁸ infection being secondary.

Xanthogranulomatous cholecystitis is a rare condition in which the gall bladder is shrunken, nodular and chronically inflamed with foci of necrosis and haemorrhage.⁵⁹ Abundant histiocytes packed with lipids impart a yellow colour to its wall. Gall stones are usually present. The same condition is described in the kidney, again in association with chronic infection and lithiasis. Mass lesions can sometimes form pseudotumours.

The gall bladder is quite often affected in polyarteritis nodosa,⁶⁰ but acute cholecystitis is rare. Acute dilatation has been reported in mucocutaneous lymph node (Kawasaki) syndrome⁶¹ and Sjögren's disease,⁶² and chronic inflammation in systemic sclerosis.⁶³ The typical changes of Crohn's disease have been described in the gall bladder of a man with granulomatous enteritis.⁶⁴ Lastly, the cystic duct and the gall bladder are commonly involved in patients with sclerosing cholangitis.⁶⁵

Cholecystoses

In cholesterosis (cholesterolosis) of the gall bladder triglycerides and cholesterol esters are deposited within macrophages in the lamina propria and also in the epithelial cells.⁶⁶ These deposits sometimes project from the mucosa as tiny cholesterol polyps.⁵ Diffuse cholesterosis produces the

Fig. 2 Plain abdominal radiograph in a patient with acute emphysematous cholecystitis. The gall bladder is clearly outlined by gas in its wall.

'strawberry gall bladder', with yellow flecks of cholesterol highlighted against a red background of mildly inflamed mucosa. The polyps can break off and form a nidus for cholesterol gall stones, which are found in 10–15% of cases.⁶⁶ The aetiology is obscure but may reflect increased hepatic synthesis of cholesterol and/or its precursor, methyl sterols, and increased absorption from the gall bladder lumen and esterification in the wall; excess cholesterol (or free sterols) is present in the bile but not the blood.⁶⁷ Cholesterosis is not just the sequel of lithogenic bile: cholesterol gall stones frequently develop in its absence and the changes are irreversible with bile acid therapy.⁶⁶

Adenomyosis (adenomyomatosis) of the gall bladder is characterised by hyperplasia of the mucosa and especially the muscularis and by intramural diverticula or crypts (Rokitansky-Aschoff sinuses).⁶⁸ The localised form is sometimes termed adenomyoma, but it is not a true neoplasm; it consists of a sessile mass in the fundus, which bulges into the lumen and is often umbilicated.⁵ The segmental form is marked by a constricting ring or septum in the fundus or body, which separates the gall bladder into two compartments.⁶⁶ The diffuse form causes generalised thickening of the wall with

Fig. 3 Adenomyosis of the gall bladder (diffuse form). Oral cholecystogram (Fig. 3a) shows scalloping of the upper border of the gall bladder. Cholecystectomy specimen (Fig. 3b) shows a large diverticulum bulging from the upper surface; the diverticulum was packed with pigment stones.

structures resembling glands or cysts, hence the alternative names cholecystitis glandularis proliferans and diverticulosis.³ Pigment stones are commonly trapped in the diverticula. The aetiology of adenomyosis is unknown, but increased luminal pressure seems a plausible mechanism (as in colonic diverticulosis).⁶⁶ Muscular dysfunction, spasm and stenosis of the cystic duct have been incriminated.³

These common types of 'hyperplastic cholecystosis' may coexist with rarer types, such as neuromatosis, lipomatosis, and hyalocalcinosis (porcelain gall bladder).⁶⁹ They may be clinically silent or cause symptoms suggestive of gall stones, which coexist in up to 20% of cases.⁷⁰ Although adenomyosis or cholesterosis may be present in some 20% of cholecystectomy specimens,⁶⁶ their radiological detection rate is much lower. The mural thickening and diverticula may be visualised on ultrasound or even computed tomography scan,^{71 72} but oral cholecystography (with or without CCK) is probably superior (Fig. 3).^{68 70} Symptomatic patients generally benefit from cholecystectomy even in the absence of gall stones.⁴⁷

Fig. 4 Ultrasound scan of the gall bladder showing a large papillary carcinoma arising from a pre-existing adenoma.

Neoplasms

Pseudotumours include inflammatory polyps, cholesterol polyps, heterotopic nests and adenomyoma, the localised form of adenomyosis.⁵ Adenoma is the commonest type of true benign neoplasm.^{73 74} It can be either sessile or papillary and is usually solitary. Adenomatous gall bladder polyps have been described in Peutz-Jeghers syndrome.⁷⁵ Some 10% of adenomas are multiple, and a similar percentage show evidence of carcinoma *in situ*.⁷⁶ As in the intestinal tract, it is probably the larger adenomas that undergo malignant transformation (Fig. 4).⁷⁴ Intestinal metaplasia (especially goblet cells) can be found in large adenomas and may be a premalignant change, as it is in the stomach;⁷⁷ certainly some carcinomas of the gall bladder have a predominantly intestinal appearance.⁷⁸

Although adenomas are often incidental findings at operation or autopsy or on radiograph, they are commonly associated with gall stones and chronic cholecystitis.⁷⁶ They can also cause symptoms in their own right – for example, by breaking off and obstructing the cystic duct.⁷⁶ The probability of an adenoma-carcinoma sequence makes cholecystectomy advisable even for asymptomatic polyps.^{74 77 79} Other benign neoplasms of the gall bladder include fibroma, lipoma, myoma, myxoma, carcinoid, and haemangioma, but all are exceedingly rare.^{80 81}

Carcinoma of the gall bladder is the fifth commonest cancer of the digestive tract. A retrospective review in 1978 of over 6000 cases emphasised its strong aetiological link with cholelithiasis: three in four patients had gall stones and a similar percentage were women.⁸² More recent reports,^{83–86} including our own from Bristol,⁸⁷ confirm the prevalence of gall stones (60–92%) and the female sex and indicate the grim prognosis of gall bladder

cancer, with five year survival rates of 1–3%. Nearly all series show that cure is impossible once the tumour has breached the gall bladder wall, though there is one discrepant report.⁸⁸ Presumably gall bladders containing stones develop cancer as a result of irritative trauma and chronic inflammation. In experimental animals carcinoma can be induced by inserting a sterile glass rod into the gall bladder,⁸⁹ but also by implanting radium,⁸⁹ methylcholanthrene,⁹⁰ cholesterol pellets in association with oral dimethylnitrosamine,⁹¹ and paraffin pellets containing N-ethyl-N'-nitro-N-nitrosoguanidine.⁹²

The true incidence of cholelithiasis in gall bladder cancer may be even higher than the reported figures, because resection is not attempted in advanced cases.⁸⁷ Nevertheless it never reaches 100%, and in some countries it is much lower – for example, 34% in Hong Kong, where pyogenic and parasitic disease of the biliary tree is common.⁹³ Other potential predisposing causes are occupation carcinogens,⁹⁴ ulcerative colitis,^{95 96} and the typhoid carrier state.^{54 97}

Japanese workers have recently shown an association between carcinoma of the gall bladder and an anomalous connection of the bile duct with the pancreatic duct;^{98 99} the anomaly is also linked with choledochal cyst and cholangiocarcinoma. The aetiological mechanism in each case may be reflux of pancreatic juice into the biliary tree, and high amylase concentrations have been reported in the bile.¹⁰⁰ It now appears that there may be two variants,¹⁰⁰ although they both feature a long common channel with the ductal union outside the duodenal muscle and thus beyond the control of the sphincter of Boyden.¹⁰¹ When the bile duct joins the main pancreatic duct, it tends to become ectatic above a narrow distal segment and choledochal cyst eventuates.¹⁰⁰ When the pancreatic duct joins the bile duct, there seems to be an increased risk of gall bladder carcinoma; mucosal metaplasia is a frequent accompaniment.

Some 3% of gall bladder cancers are squamous.⁸² A mixed adeno-squamous pattern has also been described in animals⁹⁰ and man.¹⁰⁰ Other malignant tumours are extremely uncommon, though primary melanoma can occur at this site.¹⁰² Melanoma can also metastasise to the gall bladder from primary sites elsewhere.¹⁰³ The serosal surface of the gall bladder may become involved in a diffuse carcinomatosis, but intraluminal secondaries have occasionally been reported from a variety of other primaries including pancreas, lung, kidney, ovary, colon, liver, and breast.^{104 105}

R C N WILLIAMSON

*Department of Surgery,
Royal Postgraduate Medical School,
Hammersmith Hospital, London.*

Address for correspondence: Prof R C N Williamson, Department of Surgery, Royal Postgraduate Medical School, Hammersmith Hospital, DuCane Road, London W12 0HS

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