AN EVALUATION OF

ACALCULOUS BILIARY DISEASE

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To my family,

who are, who have been

and who will be.

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PRESENTATIONS

AND

PUBLICATIONS

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Parts of this work have been presented to learned societies during the period of study and these are listed below:-

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Cholecystokinin does not predict outcome in acalculous biliary pain. Presented to the Surgical Research Society. Leeds, July 1987.

Gallbladder motility in the presence of gallstones Presented to the Jubilee meeting of the British Society of Gastroenterology, London, September 1987.

Sphincter of Oddi motility in acalculous biliary pain. Presented to the Jubilee meeting of the British Society of Gastroenterology, London, September 1987.

Computer analysis of history in acalculous biliary pain. Presented to the Jubilee meeting of the British Society of Gastroenterology, London, September 1987.

Acalculous Biliary Pain:- The cholecystokinin provocation test; Gallbladder imaging. Lectures to the British Council Course on Advances in Pancreatico-biliary Surgery, Glasgow, October 1987.

Acalculous Biliary Pain: An alternative explanation? Surgical Research Society, Belfast, January 1988.

What is normal gallbladder emptying? Association of Surgeons Great Britain and Northern Ireland, Harrogate, April 1988.

Computer history analysis in acalculous biliary pain. Association of Departments of Surgery in Europe, Edinburgh, April 1988.

Some aspects of this work have been accepted for publication and these are detailed below:-

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Gut (In press)

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Sphincter of Oddi motility in acalculous biliary pain.
Gut (In press)

Sunderland GT, Knill-Jones RP, Crean GP, Carter DC.
Computer analysis of history in acalculous biliary pain.
Gut (In press)

Sunderland GT, Morran CG, Carter DC.

Acalculous Biliary Pain: An alternative explanation?

Br J Surg (In press)

DECLARATION

These studies were performed between August 1985 and October 1987 when I was a registrar in the University Department of Surgery, Glasgow Royal Infirmary.

I declare that I am the sole author of this thesis. The patient investigations and data collection were planned and carried out by myself except for dynamic radionuclide imaging which was performed by the staff of the Department of Nuclear Medicine under my supervision. Where assistance has been obtained from others such help has been freely acknowledged.

SUMMARY

SUMMARY

This thesis is based on the clinical and laboratory findings in 64 patients referred to the University Department of Surgery, Glasgow Royal Infirmary over a 2 year period. The patients were referred from surgeons and physicians in the West of Scotland on the basis of a diagnosis of acalculous biliary pain and were considered suitable for cholecystectomy.

Chapter 1 introduces the concept of acalculous biliary disease. This clinical condition is not clearly understood and treatment has been empirical. Specific questions about this condition are the aims of the present studies.

Chapter 2 reviews the literature available on gallbladder disease in the absence of stones. The possible aetiology of acalculous biliary pain is considered. The origin of pain from the biliary tree is examined and the literature reviewed suggests that qualitatively similar pain can be generated from all parts of the biliary tree. The diagnostic methods used to detect gallstones are discussed along with their role in acalculous biliary disease. There is a body of work available on the use of cholecystokinin in acalculous biliary disease and this is critically

examined together with the reports on cholecystectomy as a method of treatment for this condition. Lastly post cholecystectomy symptoms which have been reported to occur more frequently after surgery for acalculous biliary disease are examined in the light of published work.

Chapter 3 outlines the functional anatomy and physiology of the gallbladder, common bile duct and sphincter of Oddi. Recent work has suggested that the gallbladder may not be the only source of biliary pathology and this is discussed.

The patients examined and the methods used in the clinical part of this work are outlined in detail in Chapter 4. The methodology used in the experiments described in Chapters 5,6 and 7 is contained within this section.

Chapter 5 deals with the history presented by the patients with a diagnosis of acalculous biliary pain. Each patient had a further clinical history and a computer elicited history taken. Comparison is made between the two. The history profile of the patients with acalculous biliary disease is compared with that of patients with proven gallstones. One third of 64 patients gave a history typical of biliary origin on

extensive clinical history. Previous studies have elucidated the features necessary to diagnose gallstones in our population. The computer analyses showed agreement between patients with acalculous biliary pain and patients with gallstones in the features used to diagnose gallstones. There were two exceptions. The duration of the symptoms was longer (>2 years against <6 months) in the acalculous patients and a greater percentage (80% against 20%) of the gallstone patients described 'attacks' of pain.

Chapter 6 examines the cholecystokinin provocation test as a means of predicting outcome following cholecystectomy. Where pain develops with cholecystokinin it has been suggested that such patients will improve after cholecystectomy. Follow up of the 64 patients in the present study after cholecystectomy reveals no difference in outcome between the 9 patients who had positive CCK tests and the 43 who had negative CCK tests although follow up is relatively short (median 1 year).

Chapter 7 describes the findings when gallbladder emptying is examined quantitatively by dynamic radionuclide imaging in patients with acalculous biliary pain and a cohort of normal volunteers.

Gallbladder emptying was observed to be very variable (range 10-99%) in both patient and volunteer groups. Total emptying was assessed by the ejection fraction (EF) and the rate of emptying by the half life of gallbladder activity. Median ejection fraction and half life were 67% and 16 minutes for the patients and 64.5% and 12.6 minutes for the volunteers and did not differ significantly.

In Chapter 8 the findings in gallbladders removed from patients with acalculous biliary pain are presented. The gross and histological appearances have been examined and compared with gallbladders removed for gallstone disease and a group of otherwise normal gallbladders removed during the course of hepatic artery cannulation. The in vitro contractility and sensitivity to acetylcholine, histamine and cholecystokinin octapeptide in each of these groups of specimens has also been examined. The acalculous patients had the highest proportion of cholesterolosis but not significantly so. Histological changes and contractility were the same in the control and acalculous patients but histological changes were significantly greater and contractility significantly reduced in the gallstone patients. Patients with acalculous pain appeared

relatively resistant to acetylcholine and histamine but showed no alteration in sensitivity to CCK-8.

The results of the patient studies and examination of the gallbladders suggest that a local gallbladder abnormality is an unlikely cause for this condition. The contribution of sphincter of Oddi abnormalities is unknown and in Chapter 9 the findings of manometric assessment of sphincter function are presented. Manometry measurements were performed prior to cholecystectomy in 34 cases to determine the presence or absence of sphincter abnormalities. Abnormal sphincter manometry was found in 65% of the patients examined. The significance of these findings in relation to symptoms and patient management is discussed.

In Chapter 10 the overall results of the clinical and laboratory findings in patients with acalculous biliary pain are discussed. The clinical relevance of the present findings is examined in the light of previously published work. The possibility that sphincter of Oddi motility disorders represent an alternative aetiology for acalculous biliary pain is also discussed.

Chapter 11 sets out the conclusions drawn from the present studies and lays out plans for future work in this field.

Chapter 12 uses the findings from the present work as a basis for planning the future investigations of patients with acalculous biliary pain. A clinical algorithm is suggested for management of such patients.

A short appendix explains the principles behind the projection of diagnoses from the features present in a patient's history.

CHAPTER 1

INTRODUCTION

AND

AIMS

INTRODUCTION AND AIMS

Surgeons continue to be faced with patients who present a convincing history of biliary disease and yet have no gallstones. Despite improvements in the diagnostic accuracy of imaging techniques some of these patients may have gallstones which will still be missed or may be too small for adequate resolution. The natural history of these patients has not been examined. It is not known if patients who present with acalculous biliary pain are a subset of gallstone patients or if they have some other pathological process. The outcome from cholecystectomy has been reported to range from improvement in less than 50% of cases to improvement in 100% and the problem of selection for surgery remains. Cholecystectomy has been the standard treatment for this condition based on the premise that the gallbladder is the source of the symptoms. Aside from the evidence that cholecystectomy sometimes relieves the symptoms there is little evidence that the gallbladder is the source of the complaint. The commonly quoted finding of chronic cholecystitis on histological examination is of questionable significance. These changes appear to be common in reported series but their subjective nature

and lack of comparability make interpretation of such studies difficult. Histological changes do not necessarily correlate with symptoms even in the presence of gallstones. In the absence of mechanical irritation it is not clear why inflammatory changes should develop within the gallbladder wall. Pain and the symptoms associated with biliary disease have been shown to arise from all the components of the biliary tree under certain circumstances. Such symptoms may also arise as a result of pathology in other organs and the possibility that a gallbladder appears normal on investigation because it is normal cannot be ignored. Some reports have identified abnormalities of gallbladder emptying in response to food or cholecystokinin stimulation. These abnormalities have been associated with acalculous biliary pain and have been used to select patients for cholecystectomy. These methods of assessment have not found universal acceptance and the precise role of gallbladder emptying disorders is not clear. Some workers have reported a high incidence of symptom recurrence in patients with acalculous biliary pain after cholecystectomy. Indeed of all patients undergoing cholecystectomy this group has the greatest reported incidence of recurrent symptoms. The trite explanation for this may be that the

symptoms were not due to biliary disease and would not be improved by any operation on the biliary system. It has been more recently recognised that bile flow and gallbladder and sphincter of Oddi function have a complex innervation. Resection of a functioning gallbladder may well in itself induce problems in the biliary system which would manifest as recurrent symptoms.

As stated the source of biliary pain in the absence of gallstones has hitherto been believed to be the gallbladder. It has been recognised recently that abnormalities in sphincter of Oddi function are one cause of post cholecystectomy symptoms. It is not known if these abnormalities exist prior to cholecystectomy. If so then they may predispose to symptoms following removal of the gallbladder. Alternatively cholecystecomy may in some way lead to the development of these abnormalities. There are a number of unanswered questions concerning patients with acalculous biliary pain. The aim of the experiments to be described in this thesis was to examine a cohort of patients believed to have acalculous biliary disease who were being considered for cholecystectomy. We set out to determine whether:

1. the symptoms experienced by these patients were compatible with a history of biliary disease, whether there were features which might suggest an alternative explanation and whether any such features were unique to these patients.

2. the cholecystokinin provocation test could predict the outcome from cholecystectomy in these patients.

3. there was an abnormality of the gallbladder in vivo or in vitro which was unique to patients with acalculous biliary disease or shared with patients with gallstones.

4. it was possible that patients with acalculous biliary pain had some abnormality in the sphincter of Oddi which lead to their symptoms and would predispose to post cholecystecomy symptoms.

CHAPTER 2

HISTORICAL REVIEW

ACALCULOUS BILIARY DISEASE

A proportion of the patients who present with the signs and symptoms of gallbladder disease will have no demonstrable gallstones. When other gastrointestinal investigations prove normal it is these patients who may be described as having chronic acalculous biliary pain.

A number of terms such as "cholecystitis without stones", "acalculous cholecystitis" and "non-calculous gallbladder disease" have been used to describe a situation where the resected gallbladder shows signs of chronic inflammation yet does not contain gallstones. This situation has been recognised for many years and both acute and chronic cholecystitis are described in the absence of gallstones. These have quite distinct clinical presentations and may not be manifestations of a single disease process as in gallstone disease.

CHRONIC ACALCULOUS BILIARY PAIN

This broad term is largely undefined. At present a diagnosis of acalculous biliary pain is made by a process of exclusion. Criteria for the diagnosis are subjective and vary from surgeon to surgeon. A

proportion of patients with this diagnosis will have other conditions and the number who have true organic or functional biliary disease is not known. The histological changes associated with chronic cholecystitis such as oedema, leucocyte infiltration and Rokitansky Aschoff sinus formation can undoubtedly occur in the absence of gallstones [1-5]. Many surgeons have used the detection of such changes in the resected gallbladder as proof that the organ was responsible for the patients symptoms [4-10]. Such reliance on histological findings may be misplaced. Carmen and colleagues [11] in 1924 examined a consecutive series of gallbladders obtained from 5000 autopsies. On histological examination only 16 specimens were considered normal, the remainder were described as having features of chronic cholecystitis. Edlund and Zettergren [12] did not support this view when they compared histology in 21 'normal' gallbladders obtained at autopsy with specimens from gallstone patients. They could find no evidence that inflammatory changes occur 'normally' in the gallbladders of adults. Whether inflammatory changes are a natural consequence of ageing and can give rise to biliary symptoms sufficient to seek medical advice remains an unanswered question.

In the early part of this century it was clear that a proportion of patients in whom stones were not found at operation would nonetheless obtain relief following cholecystectomy. A number of large collected series of cholecystectomies were reported in the 50 years following the introduction of this procedure in 1882 and success rates in the absence of gallstones varied between 60 and 90% of cases [1-3,13-16]. Deaver and Bortz [3] reported their initial experience of 903 patients undergoing cholecystectomy. Of these 412 operations were performed in the absence of gallstones. They noted that 83% of the acalculous patients were cured or improved by operation compared with 77% of the patients with gallstones ($p < 0.05$, Chi square). They also observed that the mortality rate was significantly less in the acalculous patients and believed the operation had better results in the absence of stones. Ross [14] in a British series of 135 cases of which only 15 had no gallstones observed a 'cure' rate of 73% compared with 82.4% in patients with stones. When acute cases were excluded the 'cure' rate in the acalculous group fell to 60%. Several early writers [2,15,16] and later Bodvall [17] drew attention to a relatively high incidence of post cholecystectomy symptoms in these acalculous patients

compared to those in whom stones were present. Following the introduction of techniques to demonstrate gallstones pre operatively [18], elective operations on patients without gallstones became less common. Some surgeons continued to recognise acalculous cholecystitis however and a number of reports emphasised that careful patient selection would allow good results from cholecystectomy even in the absence of stones [19-21]. Selection of those patients without stones who will benefit from cholecystectomy has remained an elusive goal.

CLINICAL HISTORY OF BILIARY DISEASE

A priority for the diagnosis of acalculous biliary pain is a history of biliary disease. While this may seem obvious no good definition of a 'biliary history' exists and symptom overlap must exist between this condition and other gastrointestinal disorders. The symptoms presented by patients will vary even in the same condition and individual clinicians will place different emphasis on certain features in the history. This lack of precision continues to be a major confounder in the analysis of reports. In 1934, Mackey [19] examined the history in 149 patients with acalculous biliary pain and paid

special attention to the presence of 'biliary colic' which he defined as 'a pain of considerable severity originating in the epigastrium and radiating backward normally to the angle of the right scapula.' Even accepting the limitations of this broad definition, he showed that 76% of patients with this symptom improved after cholecystectomy compared to 58% of patients without it ($p < 0.05$ Chi square). It may be that the biliary colic patients had passed stones and were not truly 'acalculous'; however the observation stands. Other workers also noted this symptom as a 'good' prognostic factor when considering cholecystectomy in patients with acalculous biliary pain [15,16,22]. Mackey examined other symptoms such as flatulent dyspepsia and food avoidance with regard to outcome. Acalculous patients were not different from stone patients and the presence of these symptoms did not influence outcome after surgery. Despite the critical importance of a 'biliary history' in the diagnosis of acalculous biliary disease the majority of reports pay little attention to defining the history presented by these patients. In most cases the diagnosis is one of exclusion and is made eventually when symptoms, consistent with an origin in the biliary tract, persist in the face of negative gastrointestinal investigations [5-10,19-21,23-25].

Various other clinical conditions may generate symptoms which appear to arise from the biliary tree and up to 20% of patients have been excluded from reported studies when alternative diagnoses became manifest.

POSSIBLE AETIOLOGY OF ACALCULOUS BILIARY PAIN

The cause of acalculous biliary disease is not known. Ivy [26] believed that an unusually strong gallbladder contracting vigorously might be a source of symptoms. Others have observed impaired gallbladder contraction in patients with gallstones [27,28] and it has been implied that acalculous disease could well be associated with reduced motility [27,29,30]. The relationship of acalculous disease to gallstone formation is not clear. Initially it was believed that pain arising in acalculous gallbladders represented the earliest stage of cholelithiasis and that these patients would progress to stone formation [3,4,16].

If the explanation for the lack of calculi in acalculous biliary disease is the passage of gravel or stones too small to be detected by conventional techniques, then impaired contractility might be expected as in stone disease. Some small clinical

studies have examined gallbladder motility in acalculous patients and suggested improved outcome from cholecystectomy in patients with reduced gallbladder emptying [31,32]. The numbers however were too small and follow up too short to be conclusive. No studies have addressed directly the problem of impaired muscle contractility in patients suspected of acalculous biliary disease.

Faecal sieving which successfully detected occult stones in patients with pancreatitis [33] appears to have been neglected in patients with acalculous pain. The old diagnostic technique known as the Meltzer-Lyon test [34] which examined bile aspirated from the duodenum after induction of gallbladder contraction has been revived recently, although with conflicting results. Einarsson and colleagues [35] were unable to demonstrate any difference between bile samples from patients thought to have acalculous pain and control subjects. Moskvitz's group [36] have recently found both cholesterol and bilirubinate crystals in bile samples from patients with acalculous pain. In 28 patients with positive findings cholecystectomy successfully cured the patients' symptoms; in the ten patients without positive findings only five improved following

cholecystectomy. These workers felt that although positive findings predicted a good result from cholecystectomy, a negative finding did not exclude the presence of biliary disease. Other workers have also reported success with this technique in the detection of bile abnormalities in acalculous patients [37,38].

Cholesterol deposits in the gallbladder wall, cholesterolosis, is well recognised clinically, radiologically and histologically. Its significance in other forms of gallbladder disease is not known. Moynihan [2] described cholesterolosis as a condition demanding cholecystectomy and several authors have been impressed by the relief of symptoms obtained following removal of a 'strawberry' gallbladder [1,13,16]. This condition has been reported in as many as 26% of surgically removed gallbladders [39] although autopsy studies have suggested a lower prevalence of 12% [40]. Cholesterolosis has been observed in series of patients with acalculous biliary pain but is by no means a universal finding. Some believe that cholesterolosis alone causes no symptoms [39-41]. If this is so it is difficult to see why removal of such gallbladders should relieve symptoms of biliary

disease. Cholesterol deposits in the mucosa of the gallbladder may lead to an inflammatory reaction and thickening of the gallbladder wall and this could impair gallbladder function. There is however no direct evidence to support this hypothesis.

Pathological narrowing of the cystic duct was described by Cozzolino et al in 1963 [42] and Goldstein in 1967 [7]. Cozzolino and his colleagues reported 7 patients with this condition who had pain and symptoms reproduced during gallbladder contraction induced by cholecystokinin. Each patient improved after cholecystectomy. The term 'cystic duct syndrome' was used to describe this condition. The explanation for the patients' pain was that contraction of the gallbladder against the resistance of the narrowed cystic duct caused a rise in pressure within the gallbladder. Other small series of such patients have been reported [30,43,44] and some workers have described 'narrow' cystic ducts in a proportion of patients in their series [8,10,45]. It is not currently believed that this condition is a major cause of acalculous biliary disease.

Northfield's group [46,47] reported two studies on gallstone patients in 1980 in which they demonstrated increased gallbladder contraction by two methods in

patients with gallstones. They suggested that in patients with gallstones, gallbladder sensitivity to cholecystokinin was increased as the underlying mechanism. Lennon et al [48] have shown in vitro that diseased human gallbladders become more sensitive to histamine as the inflammatory changes within the gallbladder become more advanced. This was thought likely to be an effect of the damage to the gallbladder wall rather than a cause. Feeley et al [28] were unable to show such an alteration in sensitivity to cholecystokinin in vitro with increasing disease. They could however distinguish between the sensitivity of muscle in the wall and muscle in the cystic duct. Agonist sensitivity has not been examined in acalculous biliary disease. It remains possible that hyper- or hypo-sensitivity accounts in some way for the symptoms in these patients.

ORIGIN OF BILIARY SYMPTOMS FROM OUTWITH THE GALLBLADDER

The site of origin of pain from the extrahepatic biliary tree is difficult to localise. Like the main gastrointestinal tract it has only a limited response to perturbation and typical 'biliary pain' can arise from gallstones in the gallbladder or common duct,

from distension of the gallbladder, cystic duct or common bile duct, or from spasm of the sphincter of Oddi [49-51].

It is recognised that increases in common bile duct pressure cause pain in the right hypochondrium or epigastrium. Ivy [52] demonstrated in dogs that the threshold pressure for 'pain' on distension of the common bile duct was 21 mmHg, approximately equal to the maximal pressure induced by gallbladder contraction. Experiments in humans using T-tubes in the common bile duct have shown that soon after cholecystectomy rapid changes in pressure of between 39-78 mmHg will cause pain like 'biliary colic' [50,53]. In contrast slow increases up to 78 mmHg do not necessarily cause pain [50].

Recent work in animals [54] and humans [55] has shown that after cholecystectomy, morphine induced contraction of the sphincter of Oddi can cause common bile duct pressure to rise significantly. With the gallbladder present such changes may bedampenedby its relaxation. If the biliary control mechanism is disturbed so that gallbladder and sphincter of Oddi contract together, the resulting pressure within the biliary system will be sufficient to cause pain in some individuals. Westphal was reported by Ivy [54] to

have induced gallbladder contraction in the presence of pilocarpine which causes spasm of the sphincter of Oddi. Patients subjected to this developed biliary pain which was only relieved by relaxation of the sphincter of Oddi. In the presence of a common channel termination of common bile duct and pancreatic duct (approximately 60% of individuals) [41,56] closure of the sphincter of Oddi could allow transmission of such pressure to the pancreatic duct with consequent bile reflux. Alternatively if the sphincter were to relax fully in the face of a rapid or strong gallbladder contraction, the delivery of a bolus of concentrated bile to the duodenum may lead to marked distension and symptoms of pain and nausea [57].

ACUTE ACALCULOUS CHOLECYSTITIS

This is clinically a quite separate condition from chronic acalculous disease. Typically it is found in patients admitted to an intensive care unit following major trauma or burns [58,59]. There is an equal sex incidence. Diagnosis in ventilated patients may be very difficult such that patients present with advanced disease and even frank gangrene or perforation of the gallbladder. Such events are

associated with a high mortality of up to 60% [60]. Acute acalculous cholecystitis is recognised in patients other than in intensive care and it has been correlated with diseases which affect small blood vessels such as diabetes or collagen disorders [61].

The aetiology of this condition is not known but the common concurrence of major trauma or associated medical disorders has thrown suspicion on a local hypoperfusion [61]. Some workers have suggested that an increased opiate dosage can be found in patients who develop this condition compared to matched controls [62,63]. This observation combined with the recognition that prolonged fasting and parenteral nutrition lead to gallbladder stasis may provide an alternative explanation [64]. As a clinically distinct entity from the chronic symptom complex under discussion acute acalculous cholecystitis will not receive further attention in this review.

SITE OF ORIGIN OF BILIARY SYMPTOMS

The gallbladder has been considered the principal source of biliary symptoms for many years. Historically a diagnosis of gallbladder disease was suspected when patients complained of bloating and abdominal discomfort after eating fatty foods [22,45,65]. The association of constipation or headache with these symptoms increased the clinical suspicion [1,3]. In the early part of this century before cholecystography became available cholecystectomy would be considered for patients with these symptoms. When the gallbladder could be easily visualised it was apparent that feeding the patient would result in gradual emptying of the contrast into the bowel. This emptying was amenable to study using serial static films [11] or later by fluoroscopy [66]. Abnormalities of gallbladder emptying were observed and these emptying or movement disorders were associated with the symptom complex thought to be due to gallbladder disease [65,67]. While it was recognised that gallstones caused pain and led to the development of significant complications such as jaundice, empyema or liver abscess, the eventual outcome of these movement disorders or dyskinesias was not known. Some considered them to represent a

predisposition to gallstone disease [26] in keeping with the earlier belief that symptoms in the absence of stones was the first stage in the evolution of gallstones [1,3,4,14,16]. Cholecystectomy was often performed for these dyskinesias which were ascribed individual names such as vesicular hyperkinesia [68] or infundibulo-cervico dyskinesia [69].

The symptom complex thought to be due to gallbladder disease is well recognised but not defined clearly. Most clinicians would agree that right hypochondrial pain, fatty food intolerance, flatulent dyspepsia and vomiting occuring together would be a strong indication of biliary disturbance. The addition to these of obstructive jaundice would fix the pathology firmly in the biliary tract. The relation of such symptoms to biliary disease appears to have arisen largely from observation and has only been examined sparingly in surgical practice.

ORIGIN OF BILIARY PAIN

In 1925, Ogilvie [70] reported a small series of 6 patients who had had cholecystostomy for acute cholecystitis. In the convalescent period he distended the gallbladder remnant via the fistula and noted that 4 of the patients localised pain to the

gallbladder area i.e. right hypochondrium. One of the remaining patients described pain in the epigastric region and the other described pain between the shoulder blades at his back. This study suffered from the fact that apposition of the gallbladder serosa to the parietal peritoneum was likely. This was subsequently shown to cause localised right hypochondrial pain by stimulation of peritoneal nerve endings. Ivy and Oldberg [71] in the series of experiments from which they identified and isolated cholecystokinin (CCK), noted that one dog with an obstucted cystic duct began to salivate (suggesting nausea) and became distressed following the administration of CCK. Their interpretation of this observation was that the dog was experiencing pain as a result of the gallbladder contracting against a resistance leading to an increased intravesical pressure. This, they believed, accounted for the animals' nausea and distress. Examined retrospectively their interpretation is open to debate. It is recognised in man that bolus administration of CCK may itself induce nausea and pain unrelated to its direct effect upon the gallbladder [72]. It is also known that high doses of CCK may lead to contraction of the cystic duct muscle

which may induce functional obstruction of gallbladder emptying [28,73,74].

Schrager and Ivy [49] in 1928 reported on a series of dog experiments in which the gallbladder was distended using a balloon. They noted that distress and salivation which they interpreted as pain and nausea occured at a minimum pressure of 40mmHg. They also observed that respiratory inhibition was prominent prior to the development of other symptoms and at relatively low pressures. Zollinger [75] in the early 1930's examined the consequences of gallbladder distension in 9 patients at the time of operation. In some patients the surgery was performed under local anaesthesia but others were allowed to recover from anaesthesia sufficiently to answer questions. He found that gallbladder distension was accompanied by deep epigastric discomfort which did not radiate to the right hypochondrium or to the back. Two patients experienced no discomfort at all. If the distended gallbladder came into contact with the parietal peritoneum localised pain was experienced which could be abolished by infiltration of the abdominal wall with local anaesthetic.

In further dog experiments Schrager and Ivy [49] examined the effects of distending the common bile

duct. They used a T-tube apparatus and infused fluid into the non occluded biliary tree. From these experiments they concluded that the animals experienced nausea and pain which developed at pressures over 20 mmHg and was universally experienced at 100 mmHg. The symptoms experienced were in their opinion much more pronounced than those experienced with gallbladder distension to similiar pressures. Zollinger [75] also reported his experience with distension of the common bile duct in 3 patients. He found that pain was not experienced in the right upper quadrant or the back with this stimulus. Two of the three patients vomited during this examination. Further experiments in post operative patients using implanted electrodes in the common bile duct were reported by Zollinger and Walter [76] in 1936. In 8 patients faradic stimulation induced pain but only 4 patients experienced back pain and none had pain in the right hypochondrial region. This particular study was of limited value since faradic stimulation will cover a wide area of tissue. Stimulatation of the common bile duct and adjacent structures makes interpretation of the response difficult if not impossible.

Hicken and his colleagues [77] distended the common bile duct using an infusion system following cholecystectomy. By leaving a small catheter in the cystic duct or using a T-tube after common duct exploration, they examined the effects of a fluid load on the sphincter of Oddi breakthrough pressure. 'Normal' values were obtained at laparotomy prior to cholecystectomy and the studies were repeated in the convalescent phase. They claimed that sphincter breakthrough pressure was unaffected by cholecystectomy. More importantly they were unable to demonstrate pain in any of their patients unless intraductal pressure exceeded 30 mmHg. This is a higher level than would normally be experienced in the biliary system. Hicken et al suggested that inflammation within the biliary tree might account for pain being experienced at more normal levels of pressure. This study suffered from a number of methodological problems. In particular the measurement of control data under general anaesthetic is open to critisism. If anaesthesia induced some effect on the sphincter which was reproduced by cholecystectomy then this technique would fail to reveal the change. Secondly the use of breakthrough pressure may not have been sensitive enough to detect any small change which had taken place.

Doran [78] in 1966 examined 56 patients with a small foley catheter left through the cystic duct stump after cholecystectomy. This allowed local dilatation of the common bile duct without giving a fluid load and increasing pressure on the sphincter of Oddi. The technique had the disadvantage that inflation of the balloon would lead to biliary obstruction but inflation times were brief and unlikely to lead to changes in liver function. Patients were studied on the twelfth post operative day prior to cholangiography. Doran took great care to avoid stimulation of the parietal peritoneum and found that slow injection of 2-5 mls of air into the balloon of the foley catheter led to pain in 40 patients. Five patients required a greater volume of air before pain was experienced and 11 patients did not develop pain despite the balloon being inflated up to 'a considerable tension'! Of the 45 patients with pain 18 felt pain only in the epigastrium and 10 only at the right costal margin. In 6 patients pain was felt in the back in addition to the main pain and 5 patients experienced only back pain. He concluded from this study that the site to which pain was referred was associated with the rather sporadic sensory innervation of the common bile duct and that right sided abdominal pain was not necessarily

evidence of local peritonitis. Back pain similiarly did not imply retroperitoneal spread of the inflammatory process as had previously been believed [79].

Layne and Bergh [50] in 1940 also used a hydrostatic infusion via a T-tube to increase common bile duct pressure in a similar manner to Hicken et al. They observed that distension of the common bile duct by infusion of fluid under pressure induced a 'spasm' in the sphincter of Oddi. This was sufficient to actively restrict flow from the reservoir until a relatively high inflow pressure was achieved. If the pressure was reduced again this spasm persisted as a marked resistance to flow. During episodes of spasm some patients experienced right hypochondrial pain which was not relieved by reducing the pressure and only disappeared when glyceryl trinitrate was administered to abolish the spasm. Twenty of 30 patients examined developed pain which was primarily located in the epigastric region but radiated to the right upper quadrant. In addition 11 of these 29 patients had pain which subsequently radiated to the right subscapular region. Only one patient experienced no pain with increased pressure in the common bile duct. Other workers observed that in some

patients with post cholecystectomy pain, a small amount of morphine, known to contract the sphincter of Oddi, would induce an attack of 'biliary colic'. Administration of morphine has also been associated with a rise in common bile duct pressure to 39-62mmHg [51,55,77].

Available evidence supports the concept that distension or spasm within the components of the extrahepatic biliary tree generates pain which may be qualitatively similar. Clinically precise identification of the source of the pain is impossible. It is particularly difficult to divorce the side effects of common bile duct pressure studies from intrinsic disturbance of the sphincter of Oddi. Doran's work was an attempt in this direction and suggested that common duct distension alone can cause biliary pain although the possible obstructive element in this technique cannot be ignored. The situation was further complicated by a recent observation from Basso and his colleagues [53] who studied patients presenting acutely with a diagnosis of biliary colic. They were careful to exclude patients with cholecystitis by rejecting patients with pyrexia or leucocytosis. The administration of caerulin was effective in relieving the pain of

biliary colic. Caerulin is a potent CCK analogue which in normal circumstances will contract the gallbladder and relax the sphincter of Oddi. If biliary colic is due to contraction of the gallbladder against a resistance it is difficult to see why further contraction of the gallbladder should have relieved the patients' pain. Basso et al performed further experiments in post operative patients with T-tubes and demonstrated that caerulin apparently increases the compliance of the common bile duct. In effect they found it difficult to achieve the pressure threshold at which pain was experienced before giving caerulin. This was almost certainly due to relaxation of the sphincter of Oddi. This study suggested that during an episode of biliary colic the pain was arising from the common duct and could be relieved by relaxation of the sphincter of Oddi.

It is no longer reasonable to believe that biliary pain arises solely as a result of gallbladder disorders. There is evidence to incriminate all parts of the biliary tree in the production of such pain. When acute gallbladder inflammation is present local peritoneal irritation will lead to prominent right upper quadrant pain. Outwith this situation, however,

it is not clear why pain should be experienced on the right hand side. The extrahepatic biliary tree is formed from midline structures and most patients appear to experience midline pain with distension although some have radiation to the right side. It is known that the sphincter of Oddi is embryologically distinct from the bowel and the biliary tree and it is richly supplied by separate nerve fibres [80,81]. Right upper quadrant pain has been observed by Hicken [77], Layne & Bergh [50] and Basso et al [53] associated with sphincter spasm and relieved by glyceryl trinitrate and caerulin. The available evidence suggests that the sphincter of Oddi may play an important role in the genesis of biliary pain.

OTHER BILIARY SYMPTOMS

Other symptoms commonly associated with biliary disease are largely those which are found in gallstone disease. They may not be appropriate in patients with acalculous biliary disease but are important in the presentation of a 'typical' biliary history. Intolerance to dairy foods or meats with a high fat content is a common symptom reported in patients with gallbladder disease [82,83]. These foods are likely to provide the most potent stimulation of

the biliary tract via endogenous cholecystokinin and consequently may be most likely to precipitate pain and nausea. Fatty food intolerance is by no means unique to biliary disease and is recognised to occur in pancreatic disease [84] although in this condition steatorrhoea is a prominent feature. Dyspeptic symptoms related to fat ingestion have also been observed in patients with the irritable bowel syndrome [85].

Flatulent dyspepsia or excessive belching or burping associated with symptoms of acid regurgitation, has often been attributed to gallstone disease. The logic behind such an association is not clear. Such symptoms are common in patients with hiatus hernia [86] and the concurrence of gallstone disease and hiatus hernia is well recognised [87]. Both conditions become more common with advancing age and it seems reasonable to propose that the association is fortuitous. Price [88] in a study published in 1963 examined patients presenting with upper abdominal symptoms before the results of investigations were known. He found that the frequency of dyspeptic symptoms was the same in patients who were shown to have gallstones and patients who had other complaints. Other workers have observed that

extirpation of the gallbladder, while relieving the patients' pain, rarely has a major influence on dyspeptic symptoms [15,19]. Data from Rhind and Watson [89] in 1968 may contradict this view. In 32 patients with mainly 'dyspeptic' symptoms and no hiatus hernia who had a simple cholecystectomy 19 (59%) were cured of these symptoms. Only 3 such patients were unchanged. Where a hiatus hernia was present only 2 of 11 patients were cured although a further 6 were improved. Dyspeptic symptoms alone are not a good indicator of biliary disturbance and are certainly not pathognomonic [90]. They are however commonly present in patients with gallbladder disease and cannot be disregarded.

OTHER FACTORS ASSOCIATED WITH GALLBLADDER DISEASE

It is an accepted fact that women are in general three times more likely to develop gallstone disease than men [82]. The obvious physiological differences are the hormone changes experienced by women. It is known that the gallbladder increases its residual volume and becomes 'sluggish' in pregnancy [91,92]. Such changes have been implicated in gallstone formation [64,93]. There is no evidence to suggest that bile in women is different from that of men but it is

recognised that obesity, commoner in women, may be associated with alterations in bile biochemistry [94]. At least one clinical report has suggested that gallbladder motility is different in women [29]. In vitro work has suggested that there is a non specific direct depressive effect from progestogens on smooth muscle motility and this effect can be demonstrated on gallbladder muscle [95]. Some workers have challenged the view that gallbladder motility alters throughout the menstrual cycle [96] but there is agreement that emptying is significantly reduced in all stages of pregnancy [96,97]. The 'fair, fat, fertile, female and forty' aphorism may well have some validity in that these patients have lithogenic bile, opportunities for gallbladder stasis and time to develop gallstones and symptoms.

Gallstones are likely to develop with advancing age but there are no good explanations for this phenomenon. Contractility of the gallbladder in women appears to become impaired with age in some studies [98,99]. Khalil and colleagues [100] have examined the effects of ageing on gallbladder contraction in male and female volunteers. Using ultrasound scanning to assess gallbladder volume they stimulated gallbladder emptying with a meal of corn

oil. They found no difference in gallbladder emptying between young and old subjects but noted that older people had significantly greater plasma levels of CCK. They suggested that this indicated a decreased sensitivity to CCK in older gallbladders but another interpretation may be that some difference in gastric emptying accounts for their findings. Western diet is undoubtedly implicated in gallstone formation [101]. Prolonged exposure to this diet and relative gallbladder stasis due to altered eating habits may combine in the elderly to predispose to gallstone formation.

DIAGNOSIS OF BILIARY DISEASE

The majority of diagnostic techniques employed in biliary disease concentrate on the detection of gallstones within the gallbladder. A number have some value in acalculous disease as they may be used both clinically and experimentally to obtain information on function as well as structure of the biliary tree. The earliest reported demonstration of gallstones in the gallbladder prior to surgery has been attributed to Whittaker in 1882 [102]. He passed a needle into a patient's gallbladder and was able to feel the end 'grate' on the hard gallstone. It is not recorded how the patient fared thereafter. Before this time gallbladder surgery was confined to emergency procedures with the diagnosis based on the patients' history and clinical presentation. The finding of gallstones within the gallbladder at operation confirmed the diagnosis. In many cases no stones were found and histological changes in the wall of the gallbladder were also accepted as proof of disease. In the early part of this century as cholecystectomy became an increasingly common elective procedure there was no effective technique to detect the presence of gallstones preoperatively and surgery was performed on the basis of symptoms alone. The

introduction of X-rays allowed attempts at preoperative diagnosis. A variety of signs were proposed which when present on a plain abdominal radiograph were thought to be consistent with gallbladder stones. These were not found universally of value. Beck was credited by Carman et al [11] with detection of the first gallbladder shadow on plain X-ray. Other workers subsequently described deviation of the duodenal shadow [103], deformation of the antrum [104] and cardiac regurgitation [105] citing each finding as indirect evidence of gallbladder disease. Confirmation of gallbladder disease on such evidence was commonly recorded at surgery due possibly to the frequency with which gallstones existed in the population. Histological changes were also accepted as proof of gallbladder disease and the pathologist was usually able to find the changes of cholecystitis in the most innocuous gallbladder [2]. Carman and colleagues [11] in 1924 reviewed the Mayo clinic experience with plain abdominal films in the diagnosis of gallstones. In a review of 343 cases a plain film correctly diagnosed significant gallbladder disease as assessed by histological changes or stones in 53% but diagnosed correctly only 38% of 226 cases where stones were found at operation.

In 1917, Meltzer [106] described paralysis of the duodenal musculature in dogs following the direct application of a strong magnesium sulphate solution to the mucosa. This paralysis was accompanied by drainage of bile from the common duct and contraction of the gallbladder. Lyon [107] adapted this principle for use as a clinical test which he described in 1919 as useful in the diagnosis of biliary disease. A tube was passed into the first part of the duodenum and 50-100 millilitres (mls) of 20-40% magnesium sulphate ($Mg\ SO_4$) introduced along the tube. After 3-5 minutes duodenal content was aspirated. Recovery of the magnesium sulphate was followed by a yellowish increasingly bile stained fluid. This was thought to be the contents of the common bile duct or 'A' bile. There was then a sudden change to a dark brown 'B' bile thought to arise from the gallbladder. Lastly the fluid obtained became lighter and this 'C' bile was thought to be hepatic bile secreted by the liver. The specimens obtained were examined bacteriologically, cytologically and biochemically. Absence of the 'B' bile or abnormalities therein were claimed to be evidence of gallbladder disease and Lyon was enthusiastic in his support for this test. In 1922 Cutler and Newton [34] reviewed the use of this test and found both supporters and opponents in the

surgical literature. They reported their own experience with the test. Although in a group of 14 patients with absent 'B' bile 10 had gallstones (71%) and one had a common bile duct stricture they concluded that the test was difficult to perform properly and could not be relied upon for diagnostic purposes. Recent studies have employed variations on the Meltzer-Lyon test to examine gallbladder bile in patients suspected of having acalculous biliary disease. Of 4 studies published in the last 2 years only one group has failed to detect abnormalities of the bile in some of these patients [35]. The others have found crystals of cholesterol or bilirubinate, bacterial contamination or leucocyte infiltration in approximately 50% of patients examined [36-38]. In these selected groups of patients in whom conventional investigations have not been of value this test may be of benefit in detecting early stone disease.

The description by Graham and Cole in 1924 [18] of the use of intravenous tetraiodophthalein sodium salts to opacify the gallbladder revolutionised the preoperative diagnosis of gallstones. Deaver and Bortz [3] in 1927 observed that prior to this test, positive preoperative evidence of gallbladder disease

was found in less than 5% of cases on X-ray while cholecystography was correct in 95% of cases. Despite improvements in the technique and the equipment used there has remained approximately a 5% false negative rate with this test [108]. Although one recent study suggests an accuracy of 100% in diagnosisng gallbladder pathology [109]. Oral and intravenous cholecystography remained the mainstay of gallbladder investigations for nearly 50 years although they were very dependent on the function of both the liver and gallbladder and were of little value in the jaundiced patient [108]. Opacification combined with fluoroscopy and induced gallbladder emptying led to the concept of gallbladder movement disorders or dyskinesias in some patients [66]. In order to examine gallbladder mechanical function, contraction was induced by the ingestion of a fatty meal. This introduced a further complicating factor by being greatly dependent on gastric emptying [110]. No other method was practical however at that time. Although cholecystokinin was used experimentally from 1932 it was not available for general clinical use until 1960 [111].

In the late 1960's and early 1970's ultrasonography, originally developed for obstetric use [112], was employed in the diagnosis of gallstone

disease [113,114]. Ultrasound examination of the gallbladder became commonplace initially using the 'grey scale' B mode and more recently the 'real time' scanner mode. Early reports suggested a false negative rate of about 25% and a false positive rate of 8% for gallstones [113]. These figures have improved and at the present time ultrasound has a false positive rate of 1% and false negative rate of <2% [90,109]. The non invasive nature of ultrasound makes it ideal for initial evaluation of the biliary tract and repeated examination is possible. It is unaffected by liver function and is valuable in examination of the jaundiced patient. Interpretation of images requires considerable experience and there remains a degree of subjectivity in reporting sonograms. As a result ultrasonography has been subject to marked interobserver variation. Ultrasound measurement of size is very accurate and does not suffer from the magnification effect noted with conventional X-rays. This allows accurate assessment of the bile duct calibre and stones can sometimes be detected in the duct. The measuring accuracy of ultrasound has been used in the experimental setting and shown to be reliable in the determination of gallbladder volume and emptying [96,100,115,116]. The major drawback to this particular application is the

requirement for skilled operators and dedicated computing facilities [117].

The introduction of ^{99m} Technetium (Tc) labelled compounds initially pyridoxylidene glutamate [118] and hydroxy indole diamino acid (HIDA) [119] allowed radionuclide gallbladder imaging to become a practical clinical procedure. Newer radiopharmaceuticals such as ^{99m} Technetium DISIDA (2,6 diisopropyl phenyl carbomoyl methyl imminodiacetic acid) have further improved this technique. The diagnostic value of HIDA scanning has to date been principally in the acute phase of cholecystitis with reported specificity of up to 100% [118-120]. Failure of the gallbladder to fill, strongly suggests cystic duct obstruction resulting from gallbladder inflammation. Simple radionuclide imaging is of unproven value in the chronic situation and has not been shown to be reliable in the detection of calculi [121]. Jamieson and his colleagues [122] in a recent report of 2 years experience of HIDA scanning in practice have confirmed a useful clinical role in the acute phase of gallbladder disease with an accuracy rate of 96% and only 4% false positives. In the chronic situation they felt that there was a limited place

for radionuclide imaging in detection of acalculous biliary disease. Dynamic radionuclide imaging has also been employed in quantification of gallbladder emptying [27,29,31,123]. This relatively simple technique can be standardized and uses the equipment already available to make a standard scan [73,123,124]. Observer interpretation can be minimised and scans can be repeated if necessary with good reproducibility [29,115]. This technique has been used succesfully in several studies of gallbladder motility.

Endoscopic retrograde cholangiopancreatography (ERCP) may be used in some situations to diagnose gallbladder disease. This invasive procedure is generally used as a second line investigation only after patients have undergone negative preliminary investigations. ERCP will rarely show lesions of the gallbladder undetected by other imaging techniques. It is occasionally useful if small stones have been missed or if all stones have passed from the gallbladder. ERCP has the advantage of allowing direct visualisation of the common bile duct along with the pancreatic duct system [125]. In addition to these features manometry can be performed to give information on the function of the sphincter of

Oddi [126,127]. The added ability of ERCP to allow operative intervention at the same examination has made this an invaluable investigation in the management of benign and malignant biliary disease.

Other imaging techniques such as intravenous cholangiography (IVC) and percutaneous transhepatic cholangiography (PTC) are rarely used to detect gallbladder disease and are more commonly employed in gross extrahepatic biliary obstruction. Computerised axial tomography (CAT) scanning [128] and magnetic resonance (MR) imaging [129] can undoubtedly detect gallstones within the gallbladder but have little clinical value in this context at present.

CHOLECYSTOKININ AND ACALCULOUS BILIARY DISEASE

In a series of experiments including cross circulation studies in dogs, Ivy and Oldberg first discovered and isolated from the duodenal mucosa a substance which caused contraction of the gallbladder [71]. They termed this substance cholecystokinin (CCK). Following initial purification they administered bolus doses to volunteers including themselves [130]. With X-ray fluoroscopy they observed wide differences in the effect of this hormone on human gallbladder emptying. They also noted that some individuals experienced pain described as typical of gallbladder colic. At this time the hormone preparation was given as a bolus injection, usually in a dose of 1 Ivy dog unit (IDU) per kilogram, over a period ranging from 30 seconds to 3 minutes. A dog unit was the quantity of dried material which would increase the intragallbladder pressure of a dog by 1 centimetre of water within 3 minutes when injected intravenously. In one animal experiment in which the cystic duct was obstructed, administration of CCK caused the dog to salivate and become distressed [71]. This was interpreted by Ivy as the development of pain and nausea following CCK. Ivy's enthusiasm for the use of CCK in clinical practice received a boost

when 17 years after experiencing discomfort on injection of CCK he underwent cholecystectomy for gallstones [26]. He took this to mean that the pain he experienced during CCK induced contraction of his gallbladder indicated an abnormality of motility which subsequently led to the development of gallstones. Cholecystokinin did not become commercially available until the late 1950's when Jorpes and Mutt developed a method of purifying the extract [131-133]. Torsoli and his colleagues [111] evaluated the purified preparation and noted, as had Ivy, that some volunteers experienced pain, not unlike biliary colic, on injection of CCK. They suggested that CCK would be clinically useful for induction of gallbladder contraction during fluoroscopy, and raised the possibility that it might prove of value in the evaluation of acalculous biliary disease or gallbladder dyskinesia.

BIOCHEMISTRY OF CHOLECYSTOKININ

Since the earliest studies it has been clear that the introduction of the products of digestion, particularly fat, into the duodenal lumen led to the release of CCK from the duodenal mucosa [71,134]. Plasma levels of CCK have been measured by

radio-immunoassay and shown to rise following a meal [135,136]. The plasma changes noted are in phase with contraction of the gallbladder and relaxation of the sphincter of Oddi. Further when physiological levels of CCK are achieved by low dose intravenous infusion, active gallbladder contraction may be observed [116]. The half life of CCK in the bloodstream is short at between 2.5 and 3.3 minutes [47,136] in common with most peptide hormones, and physiological levels can only be achieved by continuous infusions.

The active part of the CCK molecule is the C-terminal octapeptide chain and the biological activity of this segment depends upon the sulphate group attached to the tyrosine residue (Figure 1). In vitro animal studies have shown that loss of this sulphate group reduces the activity of CCK by about 150 times [134]. Cholecystokinin is thought to act via cell membrane receptors and its effect on muscle is a direct one, independent of cholinergic or adrenergic mechanisms [137]. The contractile effect on gastric smooth muscle is not dependent on extracellular calcium [138] and Lennon and his colleagues [48] showed in vitro that human gallbladders will respond to CCK in the presence of antihistamines. Amer and McKinney [139] have proposed that CCK stimulates

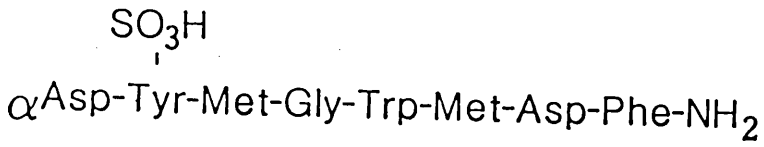


Figure 1 Structure of cholecystokinin octapeptide (CCK-8). This represents the C-terminal end of the cholecystokinin molecule and is responsible for contraction of the gallbladder. Note the sulphated tyrosine residue in position 2. Similiarities between this amino acid sequence and the terminal end of gastrin account for the weak cholecystokinetic activity of this hormone.

phosphodiesterase activity. This leads to a decrease in the levels of intracellular cyclic AMP which is generally accepted to be the mediator controlling contraction in many forms of smooth muscle [140,141]. CCK is recognised to contract all gastro-intestinal smooth muscle on direct exposure. This includes muscle from the sphincter of Oddi [142] and muscle from the lower oesophageal sphincter [143] in animals. In the intact animal both these structures relax when exposed to CCK in the bloodstream but after nerve conduction has been blocked by a neurotoxin such as tetrodotoxin, contraction is observed. This suggests a nervous control of these sphincters which can override the direct response to CCK in these sphincter zones.

CHOLECYSTOKININ PREPARATIONS

The different preparations of CCK available and used in practice has made comparison of work in this field difficult. Cholecystokinin like most gastro-intestinal hormones exists in a number of forms. A linear polypeptide of 33 amino acid residues (CCK-33) is considered to be the physiologically active hormone with a 39 residue polypeptide, possibly a pro-hormone (CCK-39), being less active.

On a molar basis the C-terminal octapeptide (CCK-8) is 8-10 times more active in-vitro than any of the larger molecules [134]. The extraction from porcine duodenum and separation method described by Jorpes and Mutt [131] yields a number of fractions with cholecystokinetic activity. One preparation based principally on the larger molecules CCK-33 and CCK-39 was marketed in this country by Kabi-Vitrum. This was relatively expensive (£15-20 per patient) and has recently been withdrawn for commercial reasons. Another fraction is marketed as a British preparation called Pancreozymin (Boots). This remains readily available (<£5 per patient). Oliver and Harvey [144] have analysed both preparations and have shown that the biological activity of Pancreozymin relies largely on smaller peptide fragments and that this preparation contains immunoreactive forms of CCK with little biological activity. This may be due to loss of the sulphate group in the active portion of the larger molecules as discussed above. In the same study they examined both the in-vivo and in-vitro behaviour of the Boots and the Kabi-Vitrum preparations, concluding that both were equally effective in causing contraction of the gallbladder. There has been confusion over the dosage of CCK which may be expressed in dog units (IDU) or Crick Harper

Raper units (CHRU). These expressions are equivalent for CCK but differ for secretin. Some workers have used purified CCK-8 (Sincalide, Squibb) to induce gallbladder contraction [145-147]. This is considerably more expensive (£85-100 per patient) and at present cholecystokinin octapeptide is not licensed for clinical use in this country.

Caerulin is a decapeptide structurally similiar to CCK-8 isolated from the skin of toads. It is slightly less potent than CCK-8 but shares similiar in-vivo and in-vitro characteristics [134,148]. Like CCK-8 it is not available for general clinical use in this country although there are reports of such use in Europe [53,148,149].

CHOLECYSTOKININ AND GALLBLADDER IMAGING

It has been suggested that the pain induced by CCK parallels the onset of gallbladder contraction [24] but Dunn et al [67] and others [5,10] who have imaged the gallbladder during CCK administration noted that pain and reproduction of symptoms are not always related to gallbladder emptying. This might be interpreted as support for an extra-biliary explanation of the pain but does suggest that the pain may not be due solely to gallbladder contraction. If gallbladder

contraction is the aim of CCK administration it seems sensible to confirm that this is actually achieved.

Early studies relied on the use of X-ray films and fluoroscopy to detect gallbladder contraction but these techniques are principally qualitative in nature. Ultrasonography [116,135,136] and Technetium HIDA scanning [32,47,123] have allowed quantitative interpretation of gallbladder emptying in response to CCK. Attempts have been made to use these techniques to refine identification of patients with acalculous gallbladder disease [31,115] and to predict those who will benefit from surgery. Published results have suggested that patients with poor gallbladder function will benefit from cholecystectomy but only small numbers of patients have been studied to date.

DEVELOPMENT OF CHOLECYSTECTOMY AS A TREATMENT FOR GALLBLADDER DISEASE

In the 17th century it was known that the gallbladder could be excised from dogs allowing the animals to survive. Van der Wiel was reported to have removed gallstones from a living patient in 1840 following incision of a pointing abscess the seat of which was an empyema of the gallbladder [102]. Kocher [150] was the first to report success with cholecystostomy for the

treatment of gallstones in 1878 and four years later Langenbuch was credited with the first successful cholecystectomy [19,150].

At that time cholecystostomy was the more favoured procedure as biliary surgery was only undertaken in the face of some dramatic complication such as empyema of the gallbladder or acute gangrenous cholecystitis. Cholecystectomy was in widespread use by the turn of this century but considered largely for the emergency situation and used only when complications of gallstones developed [151]. Early studies of the results following cholecystectomy concentrated on mortality rate which in these reports was around 10% [19]. Cholecystectomy was often performed in elderly patients who were acutely unwell and today this would be recognised as a high risk group for surgery. Hotz [152] in 1923 was among the earliest authors to advocate elective operation in young people once the diagnosis had been made. In this situation mortality could be reduced to about 4% and the expectation of a successful result was said to be better.

OUTCOME FOLLOWING CHOLECYSTECTOMY

The introduction of cholecystography [18] allowed detection of gallstones prior to the development of complications and furthered the practice of elective surgery for cholelithiasis. Improvements in the understanding of physiology and biochemistry coupled with advancing anaesthetic skill led to cholecystectomy becoming a much safer procedure and in 1931, Graham [153] reported a reduction in mortality from 6% to 0.4% for this procedure. As the mortality rates reduced more emphasis was placed on the outcome from surgery. Deaver [3], Hartmann [4] and Judd [16] were among surgeons who published early figures suggesting that when the excised gallbladder did not contain stones expectation of a good symptomatic result was greater than if stones were present. It was believed by these authors that the acalculous condition was the earliest stage of cholelithiasis and that by the time gallstones developed other secondary conditions existed which would perpetuate the symptoms post operatively. Lahey [1] was among workers who took the opposing view and suggested that clinical outcome was superior in gallstone disease. They believed that many stoneless gallbladders were not responsible for the patients' symptoms [14,15,17,19]. Under these

circumstances cholecystectomy could not hope to influence the patients' complaints. Judd and Priestley [22] later suggested that the results were equivalent irrespective of the presence or absence of stones at cholecystectomy. Mackey [19] in a review in 1934, summarised much of the published data and from an analysis of more than 6000 reported cholecystectomies observed that 'nearly 90%' of cases of cholelithiasis and 'rather over 80%' of cholecystitis without stone, were cured or improved by surgery. In his own retrospective series of 149 cases of cholecystitis without stone treated by cholecystectomy at the Barnes Hospital, St Louis, 8 patients died as a result of the surgery. Of those surviving 31% were declared cured and 31% improved. Cholecystectomy failed to relieve the symptoms in 37% of his patients. Mackey also observed that 18 patients with cholesterolosis all improved after cholecystectomy. He introduced the idea of selecting preoperatively the 37% of patients who failed to obtain relief from surgery. He tried to define this subgroup of patients retrospectively by careful examination of the history, cholecystographic and histopathological findings. No clear picture emerges of the non responders although he emphasised the need for a typical history, which included pain, if the

patient were to do well. He concluded that the results of surgery for cholecystitis without stone were relatively unpredictable in the individual case and were not as good as in the presence of gross organic disease.

In the late 1930's and 1940's cholecystectomy was the elective operation of choice for proven symptomatic gallstone disease [154]. It was still commonly practised however in the absence of stones. The indications for such operations would be a history considered by the surgeon to represent biliary disease and perhaps the finding of some abnormality in the oral cholecystogram. A number of conditions were described and apart from non filling most centered around failure of the gallbladder to contract satisfactorily after a fatty meal [66,155]. Others claimed to see 'spasm' of the gallbladder in response to a fatty stimulus [156]. Movement disorders or dyskinesias were considered by some surgeons sufficient indication for laparotomy and cholecystectomy [65,68,69]. Analysis of the results of these operations revealed that cholecystectomy in the absence of stones, for 'dubious' symptoms and with no obvious evidence of gross pathology was often attended by a poor outcome [157]. Farrar in 1966 [65]

commented on the reaction to these results in North America which persisted until that time stating that 'the only universally accepted cause for biliary tract pain is a demonstrable gallstone'. At the present time it is accepted that symptomatic 'cure' will be achieved in 80-85% of patients with proven gallstones [158]. Reports vary however and Bodvall [17] reported a large series from Sweden in 1964 with only a 51% complete symptomatic 'cure' in all patients with gallstones.

PAIN INDUCED BY CHOLECYSTOKININ AND OUTCOME FROM CHOLECYSTECTOMY IN PATIENTS WITHOUT GALLSTONES

Clinical reports of the value of CCK in practice initially highlighted its use in the identification of patients suspected of having pathologically narrow cystic ducts [7,42,45]. Subsequently a series of reports on small numbers of patients suggested that intravenous CCK combined with cineradiography of the opacified gallbladder was useful in selecting symptomatic patients without gallstones who would benefit from cholecystectomy [8-10,24]. A test was positive when abnormalities of gallbladder contraction were demonstrated. In addition the reproduction of symptoms was regarded as a basis for

a positive test even in the face of normal gallbladder contraction.

Nathan and his colleagues [5] using CCK obtained from the Karolinska Institute reported in 1970 on the combined results of two series of CCK cholecystograms. A total of 141 patients with biliary symptoms but no demonstrable gallstones and 142 normal controls were examined. Each subject received 75 IDU intravenously over 15-30 seconds. In the patient group, 57% developed pain after injection of CCK and of these two-thirds had reproduction of their symptoms. Of the normal controls, 10% developed pain. Cholecystectomy was performed in 79 patients who were considered positive and 77 had the diagnosis 'confirmed' by microscopy. Follow up of 70 of these patients showed substantial improvement in 94%. Eight patients with normal gallbladder emptying and no pain on CCK injection had cholecystectomy. The indications for surgery and outcome in these patients is not clear although 6 were classified as false negatives when histology showed the changes of chronic cholecystitis. Nathan's group were of the opinion that CCK cholecystography was of value in detecting patients who would benefit from cholecystectomy.

Dunn and his coworkers [67] in 1974 performed CCK cholecystography in 79 patients who had normal oral cholecystograms despite typical gallbladder pain, and in 44 normal volunteers. It was their view that previous studies had unacceptable bias in the interpretation of CCK cholecystograms. In this study three independent radiologists reported the cholecystograms 'blind' and the findings were related to the patients' ultimate outcome. The CCK preparation was the same as in Nathan's study although the 75 IDU dose was given over 45 seconds. The patient group was arbitrarily divided into two groups. In one group of 44 patients with intermittent pain, labelled as biliary colic, 65% developed pain with CCK. In the group whose pain was continuous, described as 'dyspepsia', significantly fewer (44%) had their pain reproduced by intravenous CCK. Twelve of the 44 normal volunteers developed pain consistent with biliary colic on administration of the CCK which was not significantly different from those labelled as dyspepsia. Twenty nine patients came to cholecystectomy because of continuation of their symptoms and two were found to have small gallstones on opening the gallbladder. Symptoms were reproduced by CCK in 20 of the 29 patients although the CCK cholecystogram was reported as normal in 11 cases. In

the group of 9 patients who experienced no symptoms with CCK, 3 were thought to have abnormal gallbladder contractions on cholecystography. Chronic cholecystitis was found in the majority of gallbladders examined and only 2 from the positive group and 2 from the negative group were considered normal. Following cholecystectomy 17 of the 20 patients whose symptoms were reproduced by CCK and 6 of the 9 patients who did not respond to CCK were improved. Dunn and his colleagues concluded from this study that CCK cholecystography was not valuable in identifying those patients who would improve following cholecystectomy.

In 1984 Lennard and his coworkers [25] published the results of a series of 42 patients in whom they performed CCK provocation without imaging of the gallbladder. The Kabi-Vitrum preparation was used in a dose of 1 IDU/Kg given over 5 minutes. A placebo injection of normal saline was also used as a control. In this study the patients' pain was given a numerical score using a pain questionnaire. The pain before CCK was compared specifically with the pain experienced during a positive test. If there was no difference between the two scores cholecystectomy was performed. There was no difference in pre-test scores

between patients who developed pain with CCK and those who did not. All of the 26 patients offered surgery showed improvement with resolution of symptoms. Of the 16 patients with a negative CCK test, 10 were shown to have alternative disorders to explain their symptoms. Of the remaining 6 patients, 5 improved spontaneously. These workers were strongly in favour of the CCK test and advocated its use in any patient with persisting pain and negative upper gastro-intestinal investigations.

Although the CCK test has appeared to show good discrimination in some papers, a common finding in papers which support the prognostic ability of CCK provocation is that patients with negative tests have not been operated on (Table 1). Selection for surgery has been based mainly on the results of CCK provocation on the assumption that this identifies biliary pathology. Those authors who have operated on CCK negative patients on the basis of continued symptoms have failed to show any difference in outcome between CCK positive and CCK negative patients and have not felt CCK provocation to be a useful aid to clinical practice (Table 2). Byrne and his colleagues [159] have performed recently a prospective study using a bolus dose of Pancreozymin

Table 1 Analysis of reports supporting the use of CCK to predict outcome after cholecystectomy.

	*POSITIVE CCK TEST	SURGERY PERFORMED	NEGATIVE CCK TEST	SURGERY PERFORMED
Cozzolino et al 1963 [42]	7	7	-	-
McFarland & Currin 1969 [43]	9	9	7	0
Nathan et al 1970 [5]	79	77	62	8
Valberg et al 1971 [6]	13	12	-	-
Goldstein et al 1972 [7]	26	26	14	0
Nora et al 1974 [8]	10	10	9	0
Freeman et al 1975 [10]	17	17	9	0
Griffen et al 1980 [9]	16	13	10	0
Sykes 1982 [24]	15	15	1	0
Lennard et al 1984 [25]	26	26	15	0

* A positive test may mean either abnormal radiological contraction of the gallbladder or reproduction of symptoms. Cozzolino et al refer solely to patients said to have pathological narrowing of the cystic duct at subsequent operation.

Table 2 Analysis of reports which have not found CCK of value in predicting the outcome from cholecystectomy.

	*POSITIVE CCK TEST	SURGERY PERFORMED	NEGATIVE CCK TEST	SURGERY PERFORMED
Dunn et al 1974 [67]	43	12	31	17
Reid et al 1975 [23]	4	3	4	4
Madsen et al 1975 [160]	5	5	4	4
Davis et al 1982 [115]	8	7	2	2
Thornell 1985 [161]	-	-	6	6
Byrne et al 1985 [159]	32	21	16	3

* A positive test may mean either abnormal radiological contraction of the gallbladder or reproduction of symptoms.

(1 IDU/kg in 90 seconds) during cholecystography. They examined 48 patients with a typical history of biliary pain and negative ultrasound and conventional cholecystography. Cholecystectomy was performed in 24 patients. At a mean follow up of 3 years they showed no difference in outcome between patients who had radiological abnormalities or symptom reproduction with CCK and those with normal tests. They have further shown no difference in outcome between patients who had cholecystectomy and those managed conservatively.

The use of CCK has been proposed as a method of provoking pain in patients who appear to have acalculous biliary pain. It has been suggested that reproduction of such pain predicts a good outcome from cholecystectomy. There is a lack of convincing evidence to support this view. Selection of patients with cholecystectomy offered only to those who developed pain has biased many studies. There is evidence to suggest that CCK in conjunction with an imaging technique will detect abnormalities in gallbladder contraction although the significance of these abnormalities is not clear. It is still not possible to predict the outcome from cholecystectomy in the individual patient with acalculous biliary pain.

POST CHOLECYSTECTOMY BILIARY PAIN

Early workers recognised that cholecystectomy was not always associated with relief of pain and symptoms [2,4,13,15,19,22]. At that time it was considered that such symptoms were due to an extrabiliary cause and that for example cure of a duodenal ulcer could not be expected following cholecystectomy. Although this may have been true in some cases a number of patients patients developed pain due to retained common bile duct stones and others to complications such as a duct stricture following surgery. A commonly held idea was that the cystic duct remnant was the seat of gallstone recurrence and a number of patients had further surgery for the 'cystic duct stump syndrome' [56,162]. In 1950, Pribram [163] drew attention to some of the likely functions of the gallbladder and the consequences of its removal, based on his experience of 1370 patients. In addition to the recognised function of storage and concentration of bile, he regarded the gallbladder as a pressure reservoir which damped or absorbed changes in pressure within the biliary tree. It was his contention that removal of a functioning gallbladder may lead to symptoms because of the loss of capacitance within the system.

He observed that patients with narrow common bile ducts after cholecystectomy developed pain with only small increases in pressure. Patients with dilated ducts could tolerate considerable increases before experiencing pain. He suggested that removal of the gallbladder could induce a variety of abnormalities in the sphincter of Oddi ranging from tonic spasm to total paralysis. The association of low tolerance to pressure changes and altered sphincter behaviour could he believed account for post cholecystectomy symptoms. Naunyn in 1900 [164] measured common bile duct pressure before and after cholecystectomy and reported an increase of 25 mmHg. Recent work by Tanaka [55] has confirmed an increase in bile duct pressure following cholecystectomy although this is a modest 5 mmHg. They have also shown that induced spasm of the sphincter of Oddi results in further pressure increases within the duct. Hicken et al in 1951 [77] addressed the question 'does removal of the gallbladder produce spasm within the sphincter of Oddi?'. They were unable to demonstrate changes in sphincter resistance after cholecystectomy by measuring 'breakthrough' pressure using T-tubes in the common bile duct. A small number of patients were examined up to 10 years after cholecystectomy and these did not show any change with this method. Their

experimental technique was less than ideal in some respects and has been discussed in an earlier section. It may not have been sensitive enough to detect any disturbance which existed. Burnett and Shields [165] studied a group of 80 patients from the Western Infirmary, Glasgow in 1958. At a mean of 12 months after cholecystectomy for gallstones they found that 75% of patients were cured of all symptoms by cholecystectomy. They were not impressed by the concept of post cholecystectomy biliary motility disorders and of the 20 patients with persistent complaints only 2 had symptoms which could be directly related to biliary pathology. Bodval in 1964 [17] and Bodval and Overgaard in 1967 [166] reported the late results of a large careful follow up of post cholecystectomy patients. They studied 1930 cases over a five year period and actively followed up 98.4%. Post cholecystectomy symptoms were most common in young women with a prolonged history of a great number of attacks of pain and who had a functioning non calculous gallbladder. In this group of patients they reported that 64% continued to have symptoms after surgery. In patients whose gallbladder demonstrated little or no histological abnormality, 86% obtained no relief from surgery. In a study of 800 patients, Stephani et al in 1974 [167] noted post

cholecystectomy symptoms in 31%. These were mainly mild (27%) and of these patients only 4 had biliary disorders overlooked at the original surgery. Severe symptoms were experienced by 32 patients (4%) and 26 of this group had either common bile duct stones or 'stenosis' of the sphincter of Oddi. They also observed that symptoms occured more often in patients who had a functioning gallbladder removed. Blumgart et al [168] in 1977 reviewed 52 symptomatic patients after cholecystectomy using ERCP. Common bile duct calculi were present in 19 of the 52 patients and 3 had common bile duct strictures. Inspissated bile was found in 2 patients, 5 patients had pancreatic abnormalities and one was considered to have papillary stenosis. Consequently they were able to identify biliary/pancreatic pathology in 30 of 48 patients with post cholecystectomy symptoms. They were unconvinced of the presence of sphincter motility disorders in any patients as a cause for their symptoms. Removal of the pressure reservoir in the biliary tree may well result in some post cholecystectomy changes as suggested by Pribram. That these are related in some way to sphincter of Oddi function is a reasonable assumption but there is no evidence that changes occur in the sphincter after cholecystectomy. If such changes occur symptoms

arising from them are likely to be mild. Severe post cholecystectomy symptoms probably result from some gross pathology in the biliary tree.

CHAPTER 3

ANATOMY AND PHYSIOLOGY OF THE EXTRAHEPATIC BILIARY TREE

THE EXTRA HEPATIC BILIARY TREE

The anatomy of the extrahepatic biliary tree is illustrated in Figure 2. In some species the gallbladder is absent. In such cases the choledochoduodenal sphincter (sphincter of Oddi) is also absent and teleologically one does not occur without the other. In man the wall of the gallbladder and cystic duct contain a defined smooth muscle layer [169] and within the wall of the common bile duct occasional smooth muscle cells can be demonstrated [169,170]. The sphincter of Oddi is made up of smooth muscle fibres which are distinct from both the common bile duct and the duodenal musculature. In man only the gallbladder and the sphincter of Oddi are considered capable of independent active contraction.

GALLBLADDER

The gallbladder is a blind fibromuscular sac of variable size ranging from 60-150 mm in length and from 50-150 mls volume. It is lined with a simple columnar epithelium projected into folds to increase the absorptive function. There is only a small amount of muscle normally present within the wall of the gallbladder. It receives both sympathetic and

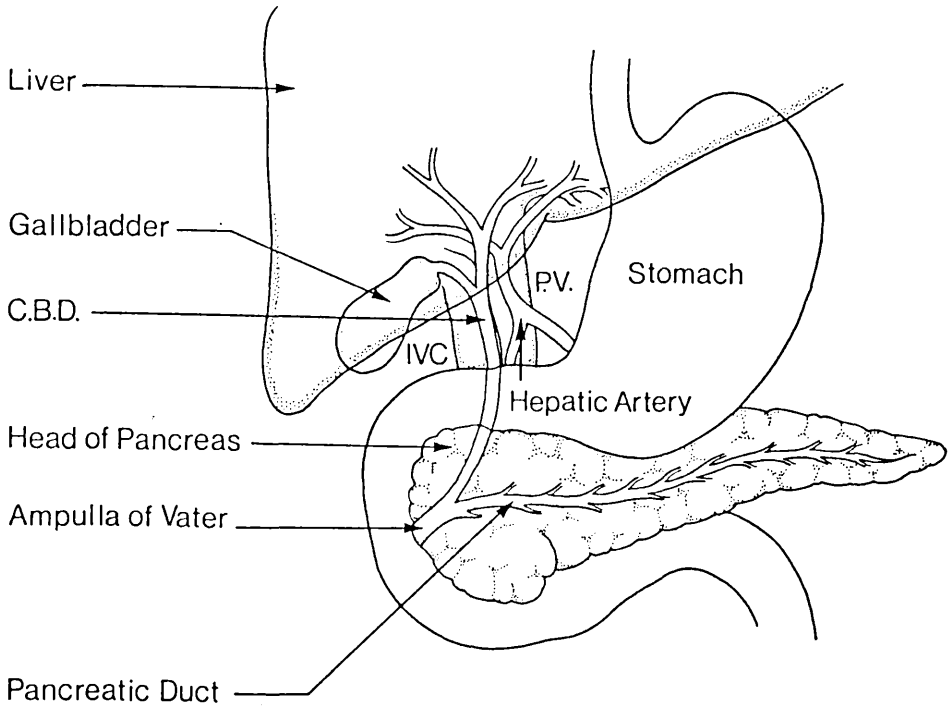


Figure 2 Schematic anatomy of the gallbladder and extrahepatic biliary tree. Reproduced by kind permission of J McDonald, Department of Medical Illustration, Glasgow Royal Infirmary.

parasympathetic nerve supplies. Its sympathetic supply emanated from the cell bodies in the coeliac ganglion along the hepatic and cystic arteries and its parasympathetic supply comes from the hepatic branch of the left (anterior) vagal trunk which passes along the lesser omentum.

The function of the gallbladder is to store and concentrate bile produced by the liver in preparation for release into the duodenum when food is ingested [171]. The advantage of such a mechanism is not clear but it may be that fat and fat soluble vitamins which should constitute low percentages of the food intake of the 'hunter gatherers' are best extracted and absorbed by this system. The large absorption area of the gallbladder serves to reduce the water content of stored bile and is capable of absorbing cholesterol and other large molecules. It is also able to secrete cholesterol although the significance of this observation is not clear [172]. There are no glands within the gallbladder but mucus is produced by the mucosa. This is recognised to occur normally [173] but excessive production has been implicated in the formation of gallstones [174]. Other workers have shown no difference in mucus content between bile samples from patients with gallstones

and those without [175]. The storage function of the gallbladder was thought previously to be regulated solely by local gastrointestinal hormones such as cholecystokinin. Studies of the effect of exogenous cholecystokinin have confirmed that it induces gallbladder contraction [5,67,116]. In addition some workers have suggested that a further agent can induce gallbladder contraction [176]. The evidence is not convincing and this work has not been confirmed. Some of the recognised gastrointestinal hormones have cholecystokinetic activity (gastrin, secretin) although all are weaker than cholecystokinin proper [134,177]. Somatostatin has been shown to reduce gallbladder contraction in pigs [178] and pancreatic polypeptide relaxes gallbladder muscle in vitro [179]. In man relaxation and gallbladder filling are probably passive procedures induced by a combination of absence of stimulation, hepatic secretion pressure and resistance of the sphincter of Oddi. There is evidence to suggest that parasympathetic innervation has some role to play in gallbladder activity. This work largely centres around examination of gallbladder motility after truncal vagotomy. Some workers have demonstrated impaired activity post vagotomy [180] although this has not been a universal finding [181].

Recent work [182,183] has suggested that gallbladder volume is proportional to sphincter of Oddi resistance. Observation of gallbladder volume throughout the interdigestive activity of the duodenum has demonstrated cyclical changes in the fasting state. Periodically, associated with a burst of duodenal activity, a proportion of gallbladder content is emptied and replaced with hepatic bile. This may represent a kind of 'housekeeping' activity and could be important in the prevention of stasis and gallstone formation [184]. This mechanism may be lost or reduced in prolonged fasting [64] or under the influence of systemic hormones like progestogens [95,96].

COMMON BILE DUCT

The common bile duct is formed by the confluence of the right and left hepatic ducts and is normally 7-8 cm long with a maximum diameter of 0.5 mm [185]. The common bile duct is lined by a single layer of columnar epithelium and has only scattered bundles of smooth muscle. These run longitudinally and obliquely forming an incomplete layer around the wall of the duct. Bile flow has been estimated at 0.1ml/kg/30 minutes in dogs with biliary fistulae [186]

and T-tube studies would suggest a figure of the same order in man. In dogs active peristalsis can be demonstrated in the common bile duct but this has not been shown in man. In vitro experiments on strips of common bile duct from man have confirmed its ability to develop tension [170,187]. It is likely that muscle activity results in altered compliance of the duct wall in the manner of the large veins adapting to volume changes. Such a change in compliance would allow flow rates to be maintained at low pressures and allow a degree of capacitance at higher pressures. It has been observed that discontinuity of the common bile duct restored with prosthetic material may result in typical obstructive appearances within the liver and an elevation in alkaline phoshatase even when an adequate channel is maintained [170]. The explanation for this is not clear but it may be related to a loss of compliance or might suggest a role for the common bile duct in control of the sphincter of Oddi. Our knowledge of bile duct physiology is incomplete and many questions remain unanswered concerning the function of this important structure.

SPHINCTER OF ODDI

Oddi first described a distinctly separate muscular sphincter at the choledochoduodenal junction in 1882 [188]. Anatomical and embryological studies have confirmed this muscle to be distinct from the duodenal muscle and to have a separate origin from the bile ducts [80,81]. Sphincter muscle is thought to arise from the neural crest. Three separate regions have been described, a main sphincter region surrounding the common channel of the bile duct and the pancreatic duct and separate bands of muscle around the distal end of each duct (Figure 3). Although the commonest arrangement of ducts is to come together at the sphincter a number of variations are recognised and the ducts may enter separately [56].

The introduction of low flow manometric systems to measure pressure within the sphincter and biliary tree at ERCP [126,127] together with animal studies [54,183,184] have considerably improved our understanding of sphincter function [189]. The normal response of the sphincter is to 'open' such that an increased bile flow can take place when food is presented to the duodenum. This is thought to be mediated by cholecystokinin and can be demonstrated in vivo in response to intravenous administration of

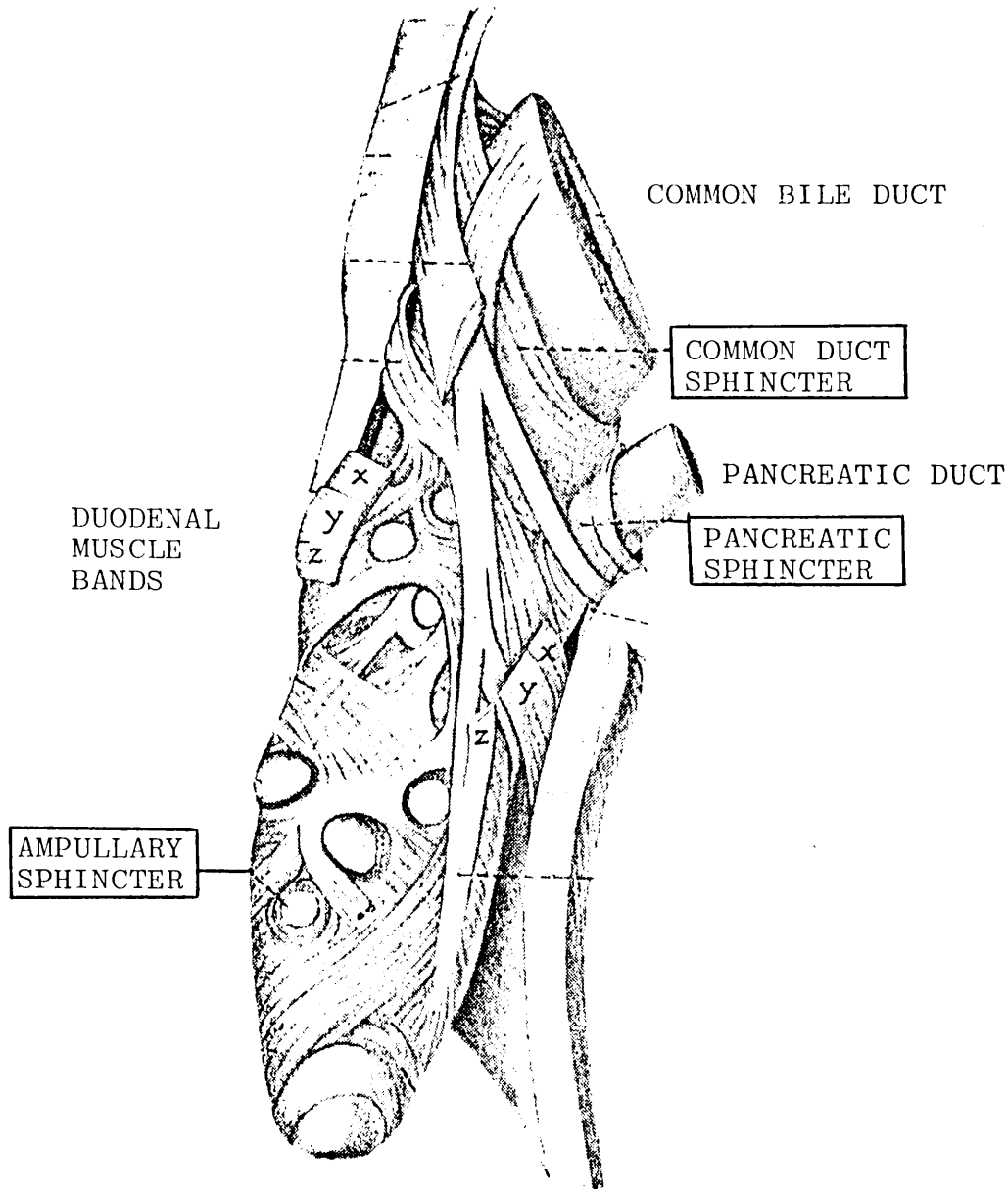


Figure 3 Anatomy of the sphincter of Oddi in man. Drawing derived from macerated specimen by EA Boyden[80]. The overall length of the sphincter is between 6 and 10 millimetres and this illustration shows the three main parts outlined. Reproduced by kind permission of Surgery, Gynecology and Obstetrics.

this hormone. The reduction in sphincter resistance is neurally mediated [142]. Post ganglionic neurones which may employ the peptide neurotransmitter substance 'P' have been implicated in this mechanism. Examination of patients with impaired post ganglionic function, such as occurs in Chagas disease [190], has demonstrated increased sphincter pressure. This finding provides further support for the mechanism proposed. In man response to cholecystokinin is accompanied by a reduction in electromechanical activity of the sphincter [189] but experiments in some animal models have suggested that cholecystokinin induces increased muscle activity leading to a 'pumping' action by the sphincter zone [54,191]. Although this 'pumping' does not appear to happen in man, Toouli [189] and others [192,193] have demonstrated propagation of activity within the sphincter zone. They have suggested that normally, contraction begins at the ductal end of the sphincter and progresses towards the duodenum. This in effect expels any luminal content into the duodenum. In man this activity is largely abolished when cholecystokinin is administered [189,193].

SUMMARY

The extrahepatic biliary tree consists of a gallbladder joining the common bile duct via a cystic duct and a sphincter of Oddi which appears to control bile flow within the system. In the fasting state the sphincter is closed directing hepatic bile into the gallbladder which gradually fills under secretion pressure. Periodically in phase with the interdigestive migrating motor complex of the small bowel sphincter pressure falls and a variable degree of partial gallbladder emptying occurs. Following ingestion of food and the introduction of partially digested food and acid into the duodenum, cholecystokinin is released from the duodenal mucosa. This induces a reduction of sphincter pressure and in addition contracts the gallbladder resulting in delivery of a bolus of concentrated bile into the duodenum. There is some clinical work to suggest that this is not an all or none reaction but that 'metered' amounts of gastric contents passed at intervals through the pylorus, results in a pulsatile delivery of bile to match the food bolus [194].

CHAPTER 4

PATIENTS AND CLINICAL METHODS

ACALCULOUS BILIARY PAIN PATIENTS

In July and August of 1985, 24 consultant surgeons and 48 consultant physicians in the West of Scotland were invited to refer, for pre-operative investigation, patients with a clinical diagnosis of acalculous biliary pain. These patients were required to meet certain criteria before referral. A history consistent with a biliary origin was of primary importance. Oral cholecystography and ultrasound investigations should have been negative for gallstones or other pathology. Upper gastrointestinal endoscopy or barium meal should have been performed and reported as normal. The referring consultant should have considered the patient a candidate for cholecystectomy.

Between 1st September 1985 and 31st August 1987, 72 patients in this category were referred to the University Department of Surgery, Glasgow Royal Infirmary. These patients had the investigations listed above but in addition many other investigations had been performed prior to referral (Table 3). They were asked to attend initially as outpatients and informed consent was obtained for the study investigations

Table 3 Investigations performed prior to referral in 72 patients complaining of right hypochondrial pain.

INVESTIGATIONS	NUMBER
Ultrasonography	81
Oral cholecystography	78
Endoscopy	55
Barium meal	44
Intravenous urogram	9
Barium enema	11
ERCP	8
Intravenous cholangiogram	4
Tc HIDA scintiscan	2
Laparotomy	3
Laparoscopy	1

from each patient. The study protocol was submitted and approved by the local Ethical Committee.

Full details of the methods used are given in this and subsequent chapters. In summary each patient was reinterviewed at first contact and an extended clinical history taken. Following this and at the same visit each patient was 'interrogated' using the computer administered Glasgow Dyspepsia (GLADYS) system. A McGill pain questionnaire was used to quantify the patient's subjective impression of their pain as a baseline measurement. A double blind cholecystokinin provocation test was also carried out at the initial visit. The response was assessed using a second McGill pain questionnaire. Patients were allowed home the same morning following a 30 minute observation period (Figure 4).

On a separate occasion patients were asked to return to the Department of Nuclear Medicine for a dynamic radionuclide scan which involved a second administration of cholecystokinin. Where possible patients were subsequently admitted for endoscopic retrograde cholangio-pancreatography (ERCP) and manometric assessment of sphincter of Oddi motility.

STUDY PROTOCOL

VISIT I :-Diagnosis of acalculous biliary pain
Negative US/OC/Upper GI investigations

University Department of Surgery - Outpatients

Re-interview: Clinical history - Diagnosis recorded

Computer 'interrogation' - GLADYS

Cholecystokinin provocation test

Home

VISIT II :-Department of Nuclear Medicine - Outpatient

Dynamic HIDA scan

Home

VISIT III :-Glasgow Royal Infirmary - Inpatient

ERCP

Sphincter of Oddi manometry

Return to referring clinician

?Cholecystectomy

VISIT IV :-Follow up

Figure 4 Protocol for patients referred with acalculous biliary pain. The time from first referral to completion of the protocol investigations varied from 1-6 months.

Following this pre-operative assessment patients were returned to the care of the referring consultant. The decision to proceed to cholecystectomy was made by the clinician in charge in consultation with the patient. No attempt was made to influence the surgeon's decision and the results of our investigations were not revealed to the surgeon at that time. Follow up was performed in all patients by a combination of out patient clinic visits and telephone calls directly to the patient. Each patient was reviewed at 1 month, 3 months, 6 months and 1 year from initial contact or cholecystectomy. Of the 72 patients referred, 64 have completed the preliminary investigations, except ERCP, and this thesis is based on the evaluation of these 64 patients.

CLINICAL HISTORY - ACALCULOUS BILIARY PAIN

Patients were all interviewed by myself. A full clinical history of their complaints was obtained with specific reference to onset of symptoms, symptom duration, site and radiation of pain, precipitating and relieving factors and associated symptoms. Based on this extended history, I recorded an opinion as to the likely diagnosis. A note was also made of the

investigations performed to date. If biliary disease was not thought probable then the best alternative diagnosis was recorded. Likely diagnoses were confined to biliary disease (GB), duodenal ulcer (DU), reflux or hiatus hernia symptoms (HH), irritable bowel syndrome (IBS), anxiety and extra gastrointestinal pathology as these have been shown to be the most common sources of confusion with acalculous biliary pain [25,67,78].

THE MCGILL PAIN QUESTIONNAIRE

The pain questionnaire used in this study was essentially that described by Melzack [195] in 1975 (Figures 5 & 6). It was designed to provide a quantitative measure of pain at a point in time and allows comparison of pain at different times. Three major values could be derived:

1. The present pain intensity (PPI) represented a number/word combination (Figure 5) chosen at the time of presentation of the questionnaire.

2. The number of words chosen from the list (NWC) (Figure 6)

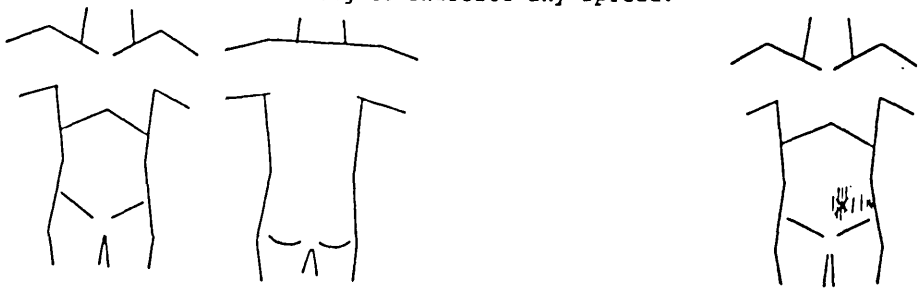
3. The pain rating index (PRI). Words were arranged in ascending order of severity (Figure 6). Each

QUESTIONNAIRE FOR PATIENTS PRESENTING WITH UPPER ABDOMINAL PAIN

WHERE IS YOUR PAIN ?

1. Fill in the site of your pain with an X for the most painful area and use shading to indicate any spread.

e.g.



2. HOW STRONG IS YOUR PAIN ?

People agree that the following words represent pain of increasing intensity.

0	1	2	3	4	5
NONE	MILD	DISCOMFORTING	DISTRESSING	HORRIBLE	EXCRUCIATING

To answer each question write the number of the best word in the blank space.

1.Which describes your pain right now ? ----------

2.Which describes it at its worst ? ----------

3.Which describes it at its least ? ----------

4.Which describes the worst toothache you ever had ? ----------

5.Which describes the worst headache you ever had ? ----------

6.Which describes the worst stomach-ache you ever had ? ----------

3. HOW DOES YOUR PAIN CHANGE WITH TIME ?

1.Which word or words would you use to describe the pattern of your pain ?

1	2	3
Continuous	Rhythmic	Brief
Steady	Periodic	Momentary
Constant	Intermittent	Transient

2.What kind of things relieve your pain ?

3.What kind of things increase your pain ?

Figure 5 Pain questionnaire presented to patients. Page 1 determines the subjective appreciation of pain in terms of its distribution, intensity and behaviour. Scores can be made in each of these categories but were not used in the CCK provocation test.

Some of these words describe your pain. Circle only those words that best describe it. Leave out any that are not suitable. Use only the best single word in each appropriate category.

1	2	3	4	5
FLICKERING	JUMPING	PRICKING	SHARP	PINCHING
QUIVERING	FLASHING	BORING	CUTTING	PRESSING
PULSING	SHOOTING	DRILLING	LACERATING	GNAWING
THROBBING		STABBING		CRAMPING
BEATING		LANCINATING		
POUNDING				

6	7	8	9	10
TUGGING	HOT	TINGLING	DULL	TENDER
PULLING	BURNING	ITCHY	SORE	TAUT
WRENCHING	SCALDING	SMARTING	HURTING	RASPING
	SEARING	STINGING	ACHING	SPLITTING
			HEAVY	

11	12	13	14	15
TIRING	SICKENING	FEARFUL	PUNISHING	WRETCHED
EXHAUSTING	SUFFOCATING	FRIGHTFUL	GRUELLING	BLINDING
		TERRIFYING	CRUEL	
			VICIOUS	
			KILLING	

16	17	18	19	20
ANNOYING	SPREADING	TIGHT	COOL	NAGGING
TROUBLESOME	RADIATING	NUMB	COLD	NAUSEATING
MISERABLE	PENETRATING	DRAWING	FREEZING	AGONISING
INTENSE	PIERCING	SQUEEZING		DREADFUL
UNBEARABLE		TEARING		TORTURING

Figure 6 Page 2 of the pain questionnaire. Each word in each category has been ranked from previous studies performed by Melzack in the development of this questionnaire. A numerical assessment of the patients' pain can be made from the number of words chosen to describe a pain and the total rank of those words

word chosen was ranked and had a value from its position in the list. The total rank score was the pain rating index. This has been shown to correlate closely with the number of words chosen [195].

The pictorial representation of the patients pain was useful for the clinician but could not be given a numerical value. In this study the present pain intensity was not valid since pre-CCK patients usually had no pain. The method of Lennard et al [25] was employed and the questionnaire was administered before and during the cholecystokinin provocation test if pain was experienced.

COMPUTER INTERROGATION

GENERAL DESCRIPTION

A formal objective 'interrogation' was carried out using the Glasgow Dyspepsia (GLADYS) interview which is a computer administered questionnaire. This interactive computer system operates on an Apple II microcomputer and collects data by writing questions for the patient on a visual display unit and obtaining answers via a modified keyboard (Figure 7). The software programme was developed and evaluated in

Figure 7 Photograph of patient using computer interrogation system. A - Visual display unit

B - Floppy disk drives

C - Mask for keyboard

the Diagnostic Methodology Research Unit at the Southern General Hospital, Glasgow. The keyboard was modified by the use of a simple mask which covered all the keys except the number keys 1-8. These were clearly redefined to allow the answers shown in Figure 8. The qualifications on YES and NO allowed patients a degree of flexibility in their answers and have been shown to improve acceptability and reliability of the system [196]. As each key is pressed the appropriate statement e.g. 1 - <Certainly No> is presented on the VDU for confirmation. Evaluation of this system has shown it to be a valid and reproducible method of obtaining patient data with a high level of acceptability to both patients and medical staff [196-198]. Previous work has demonstrated the importance of precise wording of questions and the interview has been carefully worded and structured [199]. The GLADYS computer interview is designed to adapt to an individual's verbal intelligence by altering the speed at which questions are printed on the screen. Questions are displayed at either 10 characters per second (cps) or 15 cps. This is based on a decision algorithm which initially determines the speed of response to the questions and has been shown to assess patients accurately [196,199]. In addition the structure of the interview is such

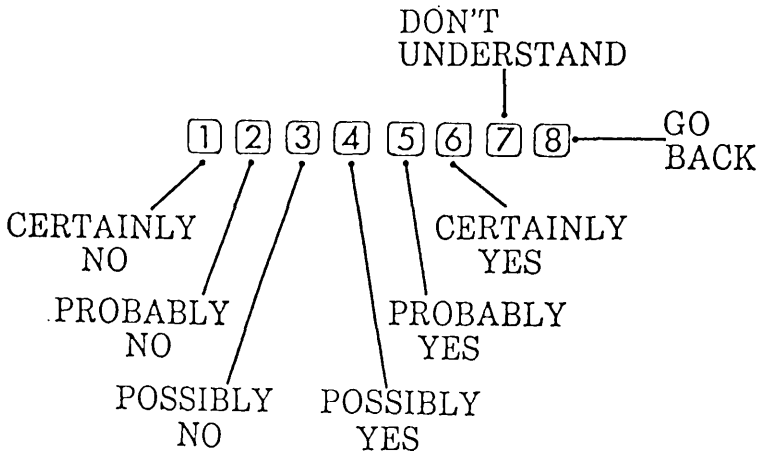


Figure 8 Copy of the mask used to cover the keyboard of the Apple II computer during the GLADYS interrogation. A cutout section surrounding the first eight number keys allowed them to be redifined as shown. Patients found this easy to use and staff had no difficulty with this system.

that branching occurs in response to key questions. This allows specific lines of questioning to be pursued or abandoned depending on the answers to previous questions. For example if patients deny vomiting, questions on the frequency and nature of vomiting are not asked. There are inbuilt consistency checks which effectively ask the same question twice in slightly altered forms and the system incorporates simple psychological assessment as well as questions directed at dyspeptic symptoms [197].

PATIENT INTERVIEWS

Before the computer system was established in the Department of Surgery the interview was conducted verbally using a questionnaire which follows the same question pathway as the computer. This specifically asks questions with the same wording as the computer and the history branches in the same manner. Data was then entered into the program at the Southern General Hospital by an assistant who was not medically qualified and who did not know the patients. The assistant answered the computer interview questions with the answers given at the verbal interview. Twenty six patients had their interviews conducted using the questionnaire and the remaining thirty

eight were interviewed directly by the computer system.

DATA PROCESSING

At the end of the computer interview the patients' answers in numerical form were transferred from memory to floppy disc. It was possible to identify each individual data set using a unique number and the date of interview. These were stored separately and confidentiality was assured. Without the GLADYS scoring program it was difficult to identify any particular item of information and relate it to an individual patient. The data was secure and not decodable easily by any third party. All information held in computer files was registered under the Data Protection Act 1987 [200] as research material.

INDIVIDUAL ANALYSIS

Following each interview the scoring program was executed. This reads an individual data set and weights the contribution of the presence or absence of each symptom with regard to the broad diagnostic groups known to the system (Table 4). The scoring program takes each answer in turn and scores that symptom's presence or absence as a contribution

Table 4 Disease classifications known to the GLADYS computer system. Each classification can be subdivided into a number of specific disease conditions as shown for duodenal ulcer disease.

Simple oesophageal disease
Severe oesophageal disease
Duodenal ulcer disease *
Gastric ulcer disease
Irritable bowel syndrome
Organic bowel disease
Gallstones
Alcohol-caused
Gastric cancer
Non-organic

* This category includes Duodenitis
Duodenal ulcer
Scar of duodenal ulcer
Pyloric/antral ulcer
Gastric outlet obstruction

towards a diagnosis. In this way a total score for each condition was amassed and the likelihood of a condition being present was calculated from the history elicited at the interview. A fuller explanation of the scoring system is given in the appendix. A list of categories within which the diagnosis may lie was generated along with the appropriate probabilities for each patient (Figure 9).

GROUP ANALYSIS

The collected data from all interviews was transferred to the Glasgow University ICL 2988 mainframe computer via a 300 baud Nightingale Modem. Transfer was effected via British Telecom using the Data Highway Communications Program (Data Highway Software Limited, London). Data Highway has an X-modem inbuilt error checking system to minimise data corruption in transit. Once established the mainframe file was checked manually for errors using the ECCE text editor. The only errors encountered were missing lines of data which were easily replaced. There was no evidence of individual character corruption on repeated sampling. In all 64 complete data sets were transferred by this method to

PATIENT'S IDENTIFICATION: 555586 DATE OF COMPUTER INTERVIEW: 10-11-86

****

DIAGNOSTIC STATEMENTS APPROPRIATE SUGGESTED ACTIONS (If not already taken)

7 Possibly Cholelithiasis : Refer to Hospital for Cholecystogram
9 Possibly Duodenal Ulcer Disease : Refer to Hospital for Barium Meal

****

DISEASE	P	ODDS
Cholelithiasis	.4329	1 TO ONE AGAINST
Insufficient evidence	.342	2 TO ONE AGAINST
Duodenal Ulcer Disease	.3306	2 TO ONE AGAINST
Nervous Dyspepsia	.0648	14 TO ONE AGAINST
Irritable Bowel Syndrome	.0165	60 TO ONE AGAINST
Gastric Ulcer Disease	.0102	97 TO ONE AGAINST
Organic Bowel Disease	<.01	158 TO ONE AGAINST
Progressive Alcohol Problem	<.01	403 TO ONE AGAINST
Simple Oesophageal Disease	<.01	700 TO ONE AGAINST
Severe Oesophageal Disease	<.01	3761 TO ONE AGAINST
Gastric Carcinoma	<.01	9999 TO ONE AGAINST

SEX = MALE MAIN SYMPTOM = PAIN/ACHE/DISCOMFORT
AGE = 23 LENGTH OF HISTORY = 1 - 2 YEARS

Figure 9 Copy of the printout generated by the Apple II computer after a GLADYS interview. Note that this system is designed for use by general practitioners. A high probability of any disorder triggers a series of suggested actions for the management of these patients. This was not appropriate for patients with acalculous biliary pain.

the mainframe computer. Analysis of the data obtained from all computer interviews was performed using the statistical programmes for the social sciences package (SPSSx) on the Glasgow University ICL 2988 mainframe computer. Programs for the data handling and statistical interpretation were written by Dr. Robin Knill-Jones and Fiona Marchbanks (DMRU) and have been used previously in analyses of this type of data [201].

CHOLECYSTOKININ PROVOCATION TEST

Patients attended the University Department of Surgery in the mornings having fasted from midnight the night before. Each patient was given the McGill Pain Questionnaire [25,195] and 10 minutes were allowed to complete this form. Two identical 60ml syringes (Plastipak, Becton Dickinson) were prepared immediately before the study began. One contained 50 mls of 0.9% saline solution (Travenol) and the other 100 Crick Harper Raper Units (CHRU) of cholecystokinin (CCK)(Pancreozymin, Boots) dissolved in 50 mls of 0.9% saline. Both syringes were given to another member of staff who coded one 'A' and the other 'B'. Patients were told before the test began that either or neither of the infusions might cause

them abdominal discomfort. The nature of the discomfort was not discussed and it was stressed that its non-development was not a failure of the test. Patients were asked to report any symptoms experienced during the test and in particular to report immediately any pain.

A venflon catheter (Viggo Products, Sweden) was introduced into an antecubital vein and venous access confirmed by withdrawal of 2 mls of blood which was discarded. The patient was asked to choose syringe A or B as the first infusion and the chosen syringe connected to the venflon via a 100 cm manometer line (Lectro-cath, Vygon). Infusion was started at a rate equivalent to 0.05 CHRU / kg.minute of the CCK syringe and continued for 20 minutes or until the patient developed pain, whichever occurred first. Infusion was controlled by an infusion pump (Treonic IP3, Vickers Medical). Preliminary experiments showed this to have an error of $\leq$ 1% at the infusion rates used. At the end of the first infusion the pump was stopped and the syringes exchanged. Cannula position was checked by withdrawal of blood and patency maintained with 2 mls of heparinised saline (Hepsal, CP pharmaceuticals). After a period of 10-20 minutes the second infusion was begun. If pain was

experienced at any time the infusion was stopped immediately and the patient asked to complete as far as possible a second McGill Pain Questionnaire. At the end of each provocation test the intravenous line was removed and the patients observed for 30 minutes, to ensure no ill-effects before being allowed to return home.

RADIONUCLIDE IMAGING

The majority of studies were performed on an outpatient basis although some patients were examined during a hospital stay. No female patient was pregnant at the time of scanning and scans were performed at menstruation where possible. Note was made of any patients taking oral contraceptives at the time of the study. Following an overnight fast patients attended the Department of Nuclear Medicine. Each was weighed and intravenous access established, where possible in an antecubital vein, using a 14 gauge Venflon cannula (Viggo). With the subject sitting comfortably 80 MBq of ^{99m} Technetium DISIDA (2,6 diisopropyl phenyl carbamoyl methyl iminodiacetic acid)(E.I. du Pont de Nemours & Company) was administered intravenously and a note made of the time of injection. Blood was withdrawn to

confirm position in the vein and the venflon flushed with heparinised saline (Hepsal, CP pharmaceuticals). After injection of radiopharmaceutical subjects lay supine under the gamma camera and the right upper quadrant of the abdomen was imaged (Figures 10 & 11). Scanning was performed using a small field gamma camera (IGE Portacamera IIc) fitted with a high resolution low energy collimator. This was interfaced to a Link Analytical MAPS 2000 computer and the acquired images stored on 8 megabyte CDC "Lark" cartridge discs. Initially liver activity was used as an aid to positioning but when the gallbladder was visualised this was centered in the field. The camera was positioned to demonstrate as far as possible separation of the gallbladder image from that of the bile ducts. The gallbladder was identified as a region of interest and 1 minute counts made of this region every 5 minutes until activity reached a plateau (Figure 11). The time to peak activity (TTP) was noted in each case.

DYNAMIC IMAGING

Once peak activity was maintained over 2 successive 1 minute intervals, an infusion of cholecystokinin (Pancreozymin, Boots) was begun. This was

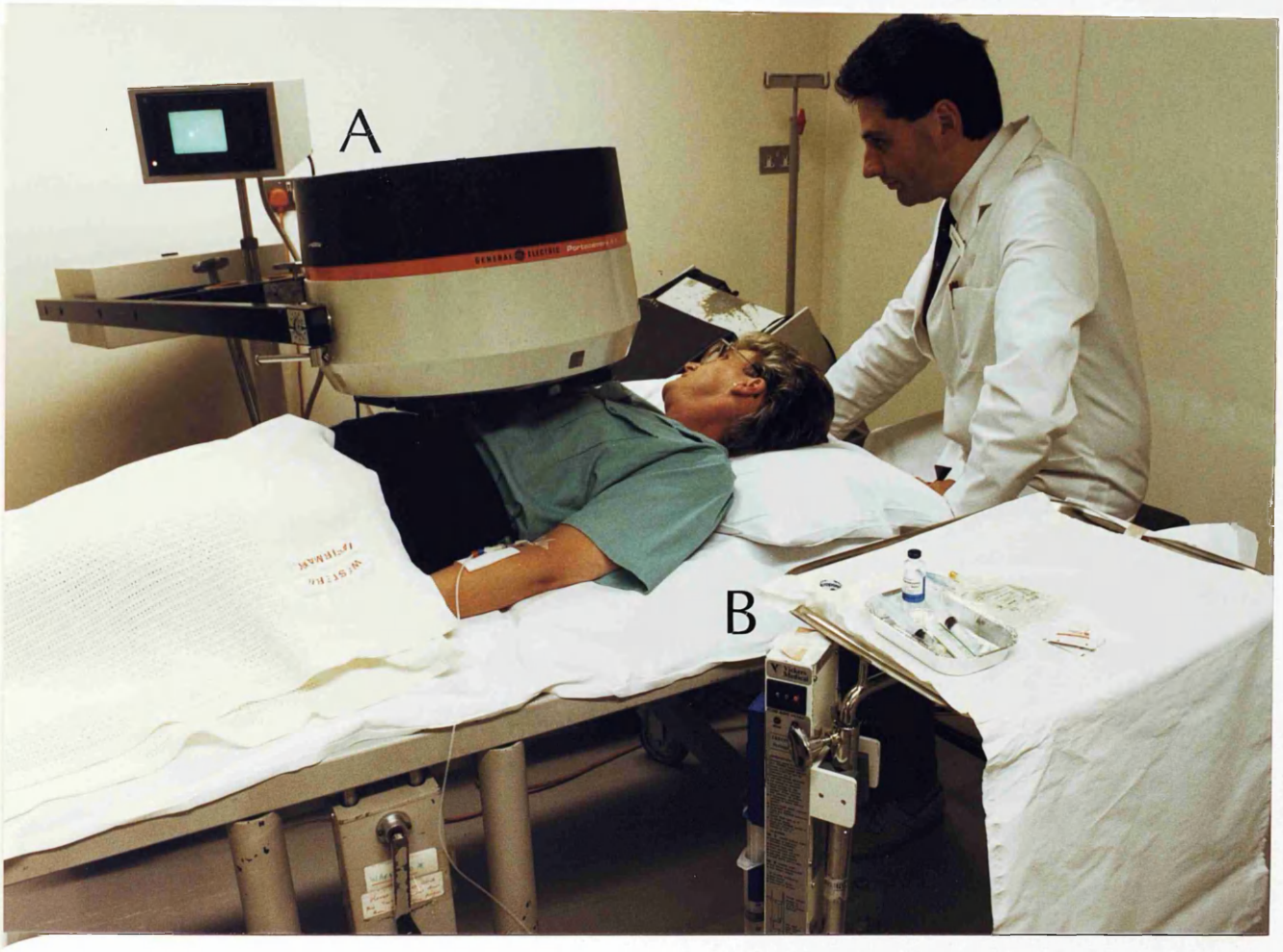


Figure 10 Photograph of patient having DISIDA imaging. A - Gamma camera
B - Cholecystokinin infusion

Figure 11 Photograph of image obtained by the gamma camera on DISIDA imaging showing liver and biliary tree. The gallbladder imaged is outlined by the white line as a region of interest.

administered through the venflon cannula via a 1 metre extension catheter (Lectro-cath, Vygon) using a Travenol infusion pump as in the CCK provocation test. Cholecystokinin was reconstituted immediately before use in 0.9% saline for injection to a total volume of 20 millilitres. The pump was set to deliver CCK at a dose of 0.05 CHRU / kg.min. Infusion was continued for 20 minutes to achieve a total dose of 1 CHRU / kg. Beginning from the start of cholecystokinin infusion, images were acquired over 1 minute intervals continuously for the next 45 minutes. Patients were asked to describe any symptoms experienced during infusion and if pain developed the infusion was discontinued immediately.

ANALYSIS OF IMAGES

Following acquisition of the study, the dynamic images were replayed rapidly to determine any movement of the gallbladder image within the field and to gauge its maximum size. Any movement was corrected by moving the relevant frames back into alignment, by reference to a fixed outline drawn around the gallbladder on an early image. Five to ten frames were then summed around the largest gallbladder image (usually near the beginning of the

study). Image contrast was increased to show the full extent of the gallbladder region and the position of activity in bile ducts and duodenum. A region of interest was drawn around the gallbladder image using a trackerball system to position the cursor. A separate annular region of interest was defined for liver background around the gallbladder taking care to exclude cystic duct or any segments where high activity had been noted to appear during replay of the study. Activity-time curves were generated from these two regions and the background curve subtracted, in proportion to the area of each region of interest, to give the curve of net gallbladder activity with time (Figure 12). Any departure from a smooth curve was examined on the appropriate frames to ensure that no movement had occured and that the images were properly aligned. Frames were also examined for the intrusion of high activity in ducts or duodenum into the regions of interest.

The time to initial decrease in gallbladder activity i.e. lag time from beginning of CCK infusion to gallbladder contraction was determined from the derived curves. From the maximum and minimum points on the net gallbladder activity-time curve the ejection fraction (EF) was calculated and expressed

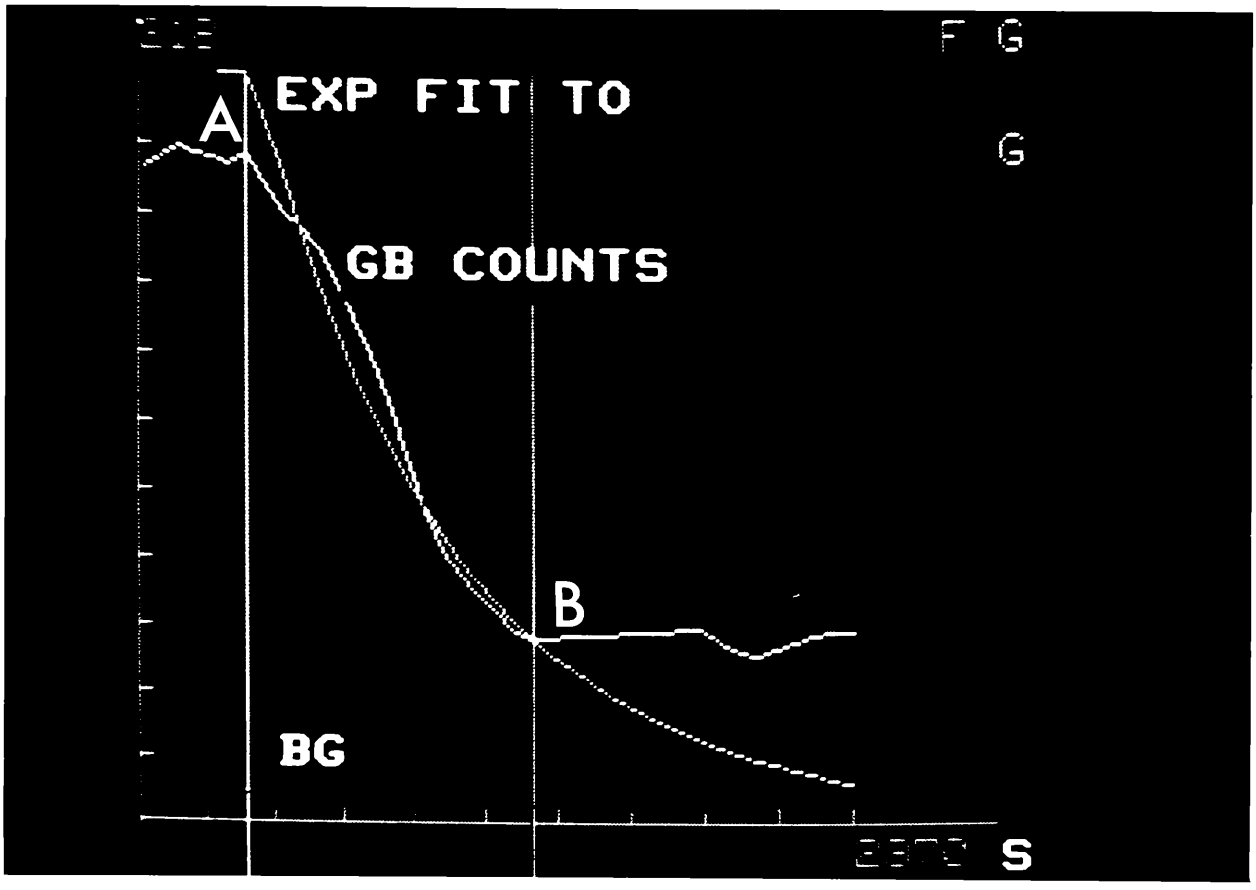


Figure 12 Activity time curve from a gallbladder region of interest in one patient. The Y-axis represents percentage activity and the X-axis time. Ejection fraction (EF) is calculated between points A and B. Note that although the gallbladder activity falls rapidly and then levels off we have used the steep part of the curve to fit the exponential. The decay constant of the computer generated exponential is the half life of CCK stimulated gallbladder emptying ($T_{1/2}$).

as a percentage of maximum activity. A single exponential fit was made to the initial steeply falling part of the gallbladder curve and the time constant of this exponential used to calculate the half life ($T_{1/2}$) of ejection (Figure 12). This was expressed in minutes.

STATISTICAL ANALYSIS

Clinical details and derived results were expressed as median and interquartile range values. Group values were compared by contingency tables and Chi squared analysis or Mann Whitney test where appropriate. The Kruskal Wallis test was used for initial comparison of more than two groups. If this suggested a difference the Mann Whitney test was used to determine the direction and magnitude of the difference. Differences were accepted as statistically significant when the probability that such a difference arose by chance was less than 1 in 20 ($p < 0.05$).

CHAPTER 5

ANALYSIS OF THE HISTORY

OBTAINED FROM

PATIENTS WITH ACALCULOUS BILIARY PAIN

INTRODUCTION

Pain located in the right upper abdomen has been shown to be useful in the diagnosis of acute cholecystitis [202]. Its value in the chronic situation is less certain. Some workers have suggested that chronic right hypochondrial pain is 'never' due to gallbladder disease [204] despite the use of such a symptom as a major diagnostic feature by most surgeons. The patient's symptoms play an important part in determining subsequent management and it is important to clarify the presenting complaints. It has been shown that the presence of a particular disease can be predicted statistically from the symptoms presented. In order that the diagnosis reached is accurate it is neccessary to obtain as full a history as possible from the patient. Recent reports on the outcome from acalculous biliary disease have stated simply that the patients presented a history of biliary pain without giving further details [5,25,37,67].

We have formally examined the history presented by a group of patients with a clinical diagnosis of acalculous biliary pain. The history obtained from an extended clinical interview was compared with that obtained using an interactive computer administered

questionnaire. The symptoms elicited by the computer program from the patients with acalculous biliary pain were also compared with the symptom profile of patients shown subsequently to have gallstones.

PATIENTS & METHODS

The detailed method of clinical and computer history taking in 64 patients referred with acalculous biliary pain is presented in Chapter 4. Previous studies on outpatients attending the Southern General Hospital, Glasgow [199,201] used a structured questionnaire to obtain the clinical details and symptoms experienced by 1176 patients. These patients were all referred by their general practitioners with upper gastrointestinal symptoms. All 1176 have been carefully followed up and each has had a firm diagnosis made from the categories described in Chapter 4. Gallstones were diagnosed by oral cholecystography or ultrasonography and confirmed at laparotomy in 57 (5%) of the 1176 patients. This information was used to construct a database from which the GLADYS diagnostic weights were derived (see Appendix). From this pool of information features present in the history have been identified which give a high probability of gastro-intestinal disease. In particular 7 features are independently useful in the diagnosis of gallstones (Table 5). When all of these features are present there is a probability of >90% that the patient has gallstone disease. A probability value can be calculated using specific

Table 5 Features important in the history for a diagnosis of gallstones in our population. The relative weight gives an idea of the importance of each feature (see Appendix). The higher the number the greater is the contribution to the diagnosis.

FEATURE		RELATIVE WEIGHT
SEX	Female	+53
	Male	-91
AGE	Age < 25	-121
	> 25	+17
LENGTH OF HISTORY	<6 months	+83
	>12 months	-52
EMERGENCY HELP SOUGHT	No	-93
	Yes	+148
PAIN RIGHT HYPOCHONDRIUM	No	-88
	Yes	+128
PAIN RADIATION	No	-74
	R. shoulder	+253
ATTACKS OF PAIN*	No	-175
	Yes	+218

* When attacks of pain are present the weight can be further increased by the presence of other features such as jaundice.

features for all of the disorders known to the system and the diagnosis or diagnoses which best fit the symptoms can be determined. A probability of <50% has been chosen arbitrarily as a level below which diagnoses are not considered useful. We have compared the incidence of the gallstone predictive features in 64 patients with acalculous biliary disease to their incidence in 57 patients with proven gallstones.

RESULTS

Clinical details and symptom information were available from verbal and computer interview with 64 patients who had acalculous biliary pain. Similiar information was available from computer interview with 57 patients who had proven gallstones (Table 6).

ACALCULOUS PATIENTS - INDIVIDUAL ANALYSES

The clinical diagnoses thought most likely at first contact with the acalculous pain patients are shown in Table 7. Also shown are the number of patients placed in each of these diagnostic categories by the computer predicted probabilities. The frequency of occurence of the most common computer diagnoses are shown for all 64 patients in Figure 13.

ALL PATIENTS - GROUP ANALYSIS

The features used by GLADYS to predict biliary disease ie gallstones are shown in Table 5. Acalculous patients differed in two categories from patients with gallstones (Figure 14). They had a significantly longer duration of symptoms (mean 2 years vs 6 months, Chi square 24.2, 2df, $p<0.001$) and a lower incidence of 'attacks' of pain (10% vs

Table 6 Details of patients with acalculous biliary pain and patients with gallstones

	ACALCULOUS	GALLSTONES	
n	64	57	
AGE (mean±SEM)	43±4	48±2.2	NS°
MALE	7	12	
FEMALE	57	45	NS¶

° p = 0.4 Mann Whitney

¶ Chi square = 2.33, 1df

Table 7 Principal clinical and computer diagnosis at first patient contact. Computer diagnoses are only those placed first on the probability listing (see Chapter 4).

	SURGEON	COMPUTER	X^2
Biliary disease	22	2	19.69°
Duodenal ulcer	13	6	3.02
Reflux/Hiatus hernia	5	3	0.57
Irritable bowel syndrome	16	9	2.43
Anxiety	5	1	2.79
Non GI pathology	3	-	-
*Insufficient evidence	-	37	-

° 1df, $p < 0.001$

* This category was unique to the computer.

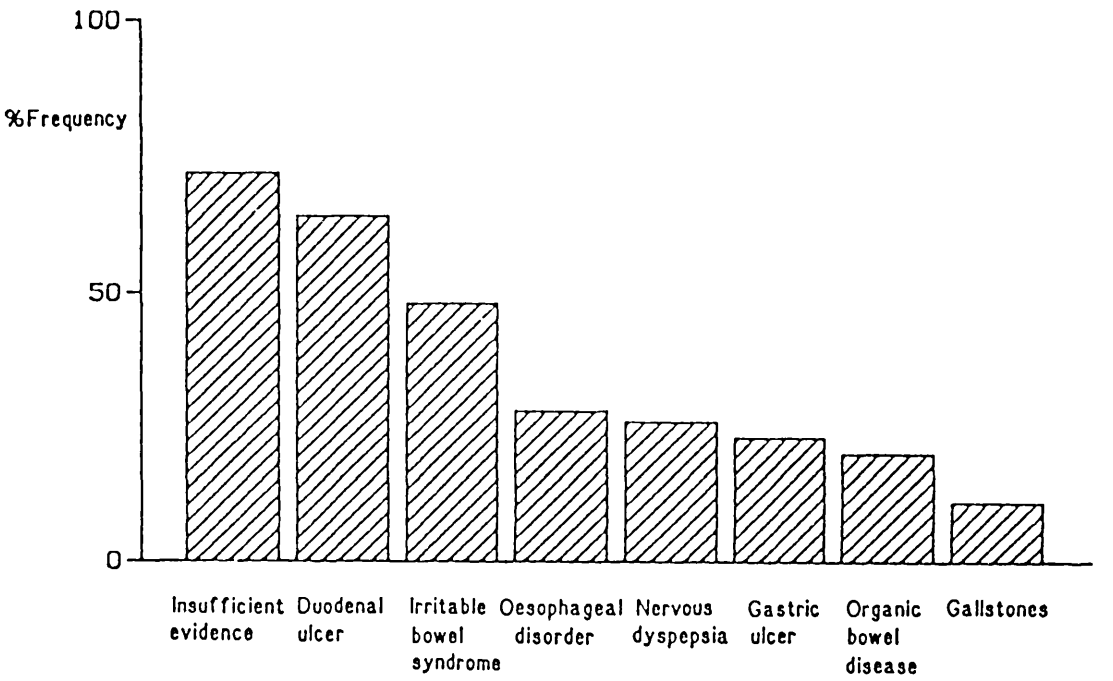
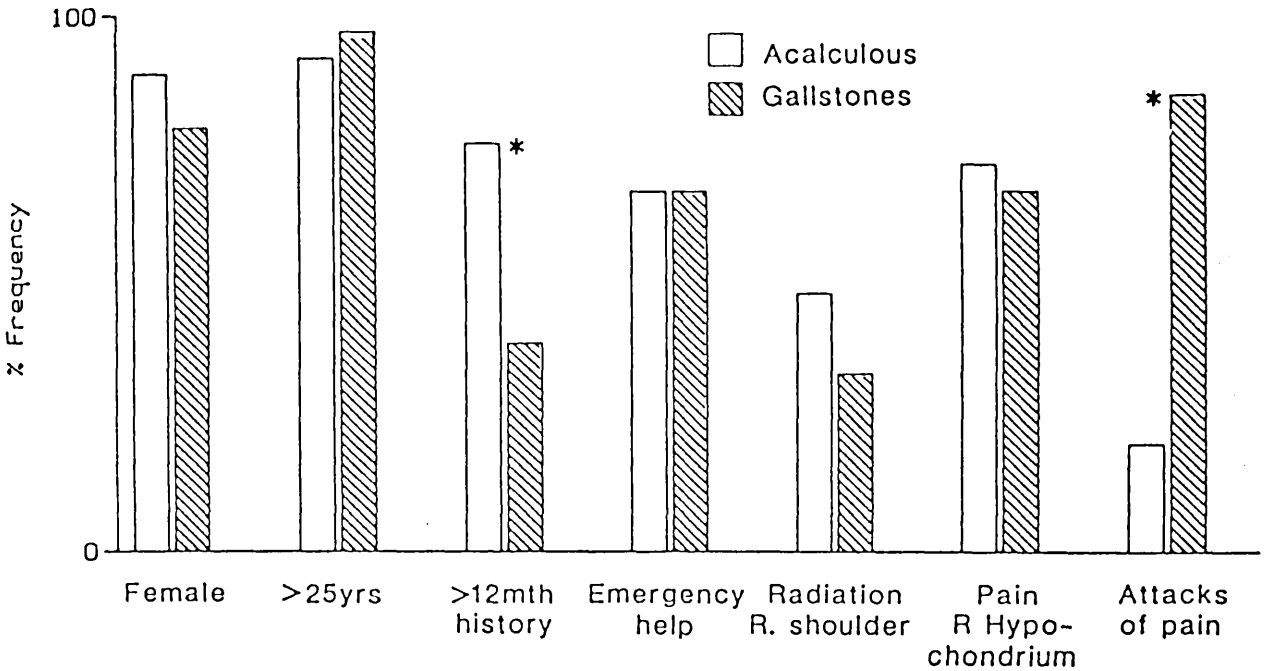


Figure 13 Frequency distribution of the most commonly predicted GLADYS diagnoses in 64 patients with acalculous biliary pain. A diagnosis was only considered when the predicted probability exceeded 50%.



* p < 0.01 Chi squared

Figure 14 Incidence of features independently useful for the diagnosis of gallstones (Table 5). Analysis of relationship between patient variables and the diagnosis of acalculous biliary pain (n=64) or gallstones (n=57).

70%, Chi square 52, 1df, $p<0.001$). The two groups of patients otherwise had similiar symptom profiles when specific features were compared but some features commonly present in the irritable bowel syndrome were more prominent in the patients with acalculous biliary pain (Table 8).

Table 8 Features which showed a different incidence between patients with acalculous biliary pain and patients with gallstones and are associated with the irritable bowel syndrome.

SYMPTOM	ACALCULOUS PATIENTS (% Frequency)	GALLSTONE PATIENTS (% Frequency)	
Daily pain	33	10	$p<0.02$
Bloating	77	28	$p<0.001$
Nausea	74	22	$p<0.001$
Vomiting	46	21	$p<0.02$
Early repletion	56	33	$p<0.05$

Chi square test.

DISCUSSION

The patient's history is important in the diagnosis of any disease but it is particularly important in the diagnosis of acalculous biliary disease. In the face of negative investigations many patients have proceeded to cholecystectomy solely on the basis of a history consistent with gallbladder disease. Previous workers have examined the history in these patients in an attempt to predict outcome after cholecystectomy [15,16,19,22]. Certain features in the history have been associated with a better [19,22] or poorer [17] result and these have been discussed previously. The predictive value of the history alone has been poor although the results achieved by one group have suggested that careful selection on this basis may be as effective as any other selection method [20,21]. In this study a group of patients referred by consultant clinicians with a diagnosis of acalculous biliary pain has been critically examined using two methods. We have taken an extended clinical history from each patient seeking particular symptoms and alternative diagnoses. We have also employed a computer administered questionnaire to elicit individual and group symptom profiles from the patients. The extended clinical history lasted up to

30 minutes and was informal in the sense that no questionnaire was followed. Specifically patients were asked about bowel habit and duodenal ulcer symptoms and attention was paid to social and domestic circumstances.

There is no agreed definition on what constitutes a history of biliary disease. Each patient was believed by the referring surgeon to have biliary symptoms sufficient to consider cholecystectomy yet only 34% were thought to give a convincing biliary history at the extended interview. This lack of agreement observed within this study confirms the different opinions which may exist between clinicians. The high frequency with which other diagnoses feature is not surprising. Symptoms which may be associated with duodenal ulcer and irritable bowel syndrome are not uncommon within the general population [204] and after biliary disease these were the next most common clinical diagnoses made at the extended interview. This was despite previously normal upper gastrointestinal investigations in all of these patients and the fact that a number had previous trials of medical treatment. Acid reflux and hiatus hernia symptoms are commonly associated with gallbladder disease. In some of the cases referred

however it was felt that these features were sufficiently dominant to be the patient's primary problem. A diagnosis of anxiety did not exclude biliary disease but was made in those cases where the organic symptoms appeared relatively insignificant. The importance of the different clinical diagnoses made in 64 patients believed to have acalculous biliary pain is open to debate. A different diagnosis will be reached simply by placing different emphasis on the same symptoms. The correct interpretation of a patient's history can only be determined by subsequent investigation and ultimate outcome. At the time of referral the clinician involved was sufficiently convinced of a diagnosis of acalculous biliary disease to plan cholecystectomy as the treatment for the patient. This intention to treat has been used as the basis for evaluation of these patients.

The GLADYS computer interview was used as a more objective interpretation of the patients' symptoms. There was a significant difference between the number of patients thought by the clinician to have biliary disease when compared with the computer prediction. This difference may be interpreted to suggest that gallbladder disease is very uncommon in these

patients. It is more likely however that the criteria required by GLADYS for a clear diagnosis of gallstones are not often met by patients with acalculous biliary pain. These patients by definition do not have gallstones. As a result their symptoms may not be exactly the same as gallstone patients. There were no significant differences between the clinician and the computer in the numbers of patients given other diagnoses with the exception of the 'insufficient evidence' category. This category is placed first when the computer program fails to reach a clear diagnostic score for any of the categories within its database. This may mean that the information available is incomplete or it may suggest that the patients' symptoms are due to a condition not known to the computer system. The classification of 58% of acalculous biliary pain patients within this category suggests that use of the individual analyses may have been inappropriate in this group of patients. These were highly selected patients and certainly form a subgroup of the general population in which the prevalence of gallstone disease is much lower. This means that the starting predictive score for any condition requires to be greatly altered in these patients before GLADYS can provide useful information (Appendix). More work is required in the

transfer of this program between patient populations before this question can be satisfactorily answered.

GROUP ANALYSES

The GLADYS interview was useful in its ability to obtain information from each individual in a fashion which makes it possible to compile the data from all the patients examined. This enabled the features these patients have in common to be determined. Comparison of the features independently important for a diagnosis of gallstones shows that these occur with the same frequency in both groups with two notable exceptions. The prolonged history and relative paucity of 'attacks' in the acalculous patients might be explained by the absence of gallstones. These features are important indicants for the diagnosis of gallstones by the computer system and their absence may partly explain the low number of patients diagnosed as biliary disease. The features common to gallstone patients such as age, sex and distribution of pain explains why these patients are believed to have biliary pain. Clinicians use these key features in reaching a diagnosis and the persistence of these features would be favoured by most surgeons as suggesting a

diagnosis of biliary disease. The fallibility of standard imaging techniques in the detection of gallstones and cholecystopathies is well recognised [65,90,108,109,205]. Negative investigations do not necessarily exclude biliary disease and many surgeons offer cholecystectomy on these grounds. Many of the acalculous patients have symptoms which could be derived from other conditions such as duodenal ulcer or irritable bowel syndrome. All of the patients had at least one negative investigation for duodenal ulcer and although this by no means excludes this diagnosis, endoscopy and barium meal are possibly more reliable in the diagnosis of duodenal ulcer than oral cholecystography and ultrasonography are in the diagnosis of gallstones. There are no definitive tests for irritable bowel syndrome although it can be positively predicted in the face of sufficient symptoms [206]. Features of irritable bowel syndrome were more common in the acalculous patients but relatively few had sufficient evidence for the computer to predict either duodenal ulcer or irritable bowel syndrome unequivocally. It is certain that the acalculous patients contain a mixture of pathological entities. Nonetheless they have in common with gallstone patients the majority of the

symptoms considered important in a diagnosis of gallbladder disease.

This analysis of the history has not been an attempt to predict outcome. Rather the symptoms offered by these patients have been established in an effort to better describe the condition. The important features are undoubtedly the right sided nature of the pain and its common radiation to the shoulder. The patients are most often women in their middle years and in these respects they are similar to gallstone patients. There are a number of other features however such as the presence of nausea and vomiting which are less common among gallstone patients. There are also features in the history of gallstone patients which are notably absent in patients with acalculous biliary pain. As far as can be ascertained the group of patients examined is similar in age and sex to other reported series of patients with acalculous biliary disease [20,21,25,37]. There is no reason to suspect that the group composition differs in any major respect from other series. From the history alone it cannot be said conclusively that a patient does or does not have biliary disease.

CONCLUSIONS

This study has shown that patients believed to have acalculous biliary pain share some of the features and complaints with patients who have symptomatic gallstones. There are differences between the two groups and patients with acalculous pain have a longer duration of symptoms and less "attacks" of pain than those patients with gallstones. Examination of the incidence of symptoms which have been associated with the irritable bowel syndrome shows that patients with acalculous pain have some of these significantly more often than gallstone patients. Patients diagnosed as having acalculous biliary disease on the basis of the history give symptoms which could arise from other gastrointestinal conditions.

CHAPTER 6

PREDICTION OF OUTCOME IN ACALCULOUS BILIARY PAIN USING THE CHOLECYSTOKININ PROVOCATION TEST

INTRODUCTION

Following the isolation of cholecystokinin from animals, Ivy [26] was able to confirm its ability to cause contraction of the gallbladder in man. It was also recognised that such contraction was sometimes accompanied by pain in certain individuals. This pain has been described as 'like biliary colic' by some authors [52,111,130] and it has been proposed that its occurrence suggests an abnormality of the gallbladder or of its contraction [5,25,42,111,]. On this basis a CCK provocation test has been used in patients suspected of acalculous biliary disease. Several workers have claimed that when pain is experienced with CCK administration an excellent result can be expected from cholecystectomy [5,7,9]. One recent study reported a succesful outcome after cholecystectomy in each of 26 patients who developed pain with CCK [25]. Such accurate prediction of outcome has not been the universal experience in published work and a number of authors have found the CCK test to have no useful predictive value [67,159-161]. In this study the value of CCK provocation in predicting the outcome following cholecystectomy was examined in patients with a clinical diagnosis of acalculous biliary pain.

PATIENTS AND METHODS

The methods employed in the administration of CCK as a provocation test have been described in detail in Chapter 4. A formal double blind CCK test was performed on one occasion only at initial contact in 64 patients. Ten patients who were subsequently shown to have an alternative explanation for their pain were excluded and in 54 patients follow-up was performed. A CCK test was regarded as positive when pain was experienced during CCK infusion and not with the saline. The pain characteristics were assessed by the McGill pain scores before and after CCK. Pain experienced during the test was only accepted as being the same as the presenting pain when the difference between the numerical values of the two McGill scores was less than an arbitrary value of 20%

FOLLOW UP

Each patient was reassessed at intervals of 1 month, 3 months, 6 months and 1 year from initial contact or cholecystectomy. Follow up was by means of attendance at out patient clinics or directly by telephone call to the patient. At each visit the patient was assessed, as far as possible by the same individual (GTS), using a modified Visick grading (Table 9) [207].

Table 9 Modified Visick grading system used for assessment of patients at follow up.

GRADE	DEFINITION
I	no symptoms
II	mild symptoms easily controlled. Patient satisfied
III	original symptoms persist unaltered
IV	symptoms worse, increased severity or frequency

RESULTS

Pain consistent with the presenting complaint was reproduced in 10 of the 64 patients during the infusion of CCK. This was considered a positive result. Two patients developed pain with both CCK and saline infusions and the test was considered negative. Of the remaining 52 patients 48 experienced only 'wind', mild discomfort or no symptoms. Pain was experienced in four patients but there was marked disparity between this and the presenting pain as assessed by the McGill pain questionnaire (Table 10).

Patients who were positive responders to the provocation test were not different from those who had a negative result in respect of age, pre test word scores or duration of symptoms (Table 11). Of the initial 64 patients examined, 10 were subsequently rediagnosed and have been excluded from analysis of outcome (Table 12). In 5 of these cases cholecystectomy has been performed. In four patients laparotomy was undertaken for a diagnosis of acalculous biliary pain. One patient was found to have primary hypoparathyroidism during the course of her hospital stay. In another patient a prepyloric ulcer was found at laparotomy and one patient had a gallstone in the gallbladder at operation. A further

patient had a renal stone diagnosed post operatively. The fifth patient was diagnosed as having chronic pancreatitis at ERCP. With no predisposing factors to explain his pancreatitis it was felt that cholecystectomy was indicated for this condition.Cholecystectomy has been performed in 29 of the 64 patients. Five of the 29 patients have been excluded from follow-up analysis.

All patients have been followed up. To date the median follow up is 12 months (range 6-24) from first contact or cholecystectomy where appropriate (Table 13). 80% of patients who have had cholecystectomy were cassified within Visick grade I or II at this time (Figure 15). There was no significant difference in outcome between patients who were positive to CCK and those who were negative. Those patients who have not had cholecystectomy have not improved to the same extent (Table 14). Only 50% were classed as Visick I or II over the same period (Figure 16). The gross and histological features and in vitro characteristics of the gallbladders removed are described in Chapter 8.

Table 10 McGill scores in patients with pain on injection of CCK considered to have negative provocation tests.

PATIENT No	PRE TEST SCORES		TEST SCORES	
	NWC	PRI	NWC	PRI
10	5	11	1	2
19	4	8	1	1
27	8	18	3	6
72	7	12	3	8

NWC - Number of words chosen.

PRI - Pain rating index.

Table 11 Comparison of positive and negative responders to CCK provocation.

	POSITIVE CCK TEST	NEGATIVE CCK TEST	
n	10	54	
M:F	1:9	4:50	
AGE (years)	42 (29-61)	40.5 (30-48)	NS†
Pre test word scores			
NWC	7 (3-13)	6 (4-8)	NS°
Rank (PRI)	15 (7-32)	14.5 (9-20)	NS/
Duration of symptoms (months)	48 (24-76)	30 (12-60)	NS§

Results are median and inter quartile range.

Mann Whitney test.

† p=0.54 ° p=0.63 / p=0.73 § p=0.16

Table 12 Patients excluded when another condition was found which could account for their symptoms.

A. CHOLECYSTECTOMY NOT PERFORMED

SEX	AGE	CCK TEST	DIAGNOSIS
Female	34	NEGATIVE	Duodenal ulcer
Female	57	NEGATIVE	Duodenal ulcer
Female	23	NEGATIVE	Acquired megacolon
Female	31	NEGATIVE	Redundant dilated colon
Female	51	NEGATIVE	Crohn's disease

B. CHOLECYSTECTOMY PERFORMED

SEX	AGE	CCK TEST	DIAGNOSIS
Female	56	POSITIVE	1° hyperparathyroidism
Female	32	NEGATIVE	Gallstone Hartmann's pouch
Female	30	NEGATIVE	Renal stone
Female	46	NEGATIVE	Prepyloric ulcer
Male	67	NEGATIVE	Chronic pancreatitis

Table 13 Follow up data in patients who have had cholecystectomy. Follow up from date of operation.

A. Cholecystokinin test - NEGATIVE

	MONTHS					
	1	3	6	12	18	24
Visick° Grade						
I	15	16	15	11	7	2
II	3	2	1	1	2	-
III	-	-	1	1	-	-
IV	-	-	-	-	-	-
TOTAL	18	18	17	13	9	2

B. Cholecystokinin test - POSITIVE

	MONTHS					
	1	3	6	12	18	24
Visick° Grade						
I	3	4	4	2	1	-
II	3	2	1	1	-	-
III	-	-	1	1	-	-
IV	-	-	-	-	-	-
TOTAL	6	6	6	4	1	-

°Modified Visick Grade

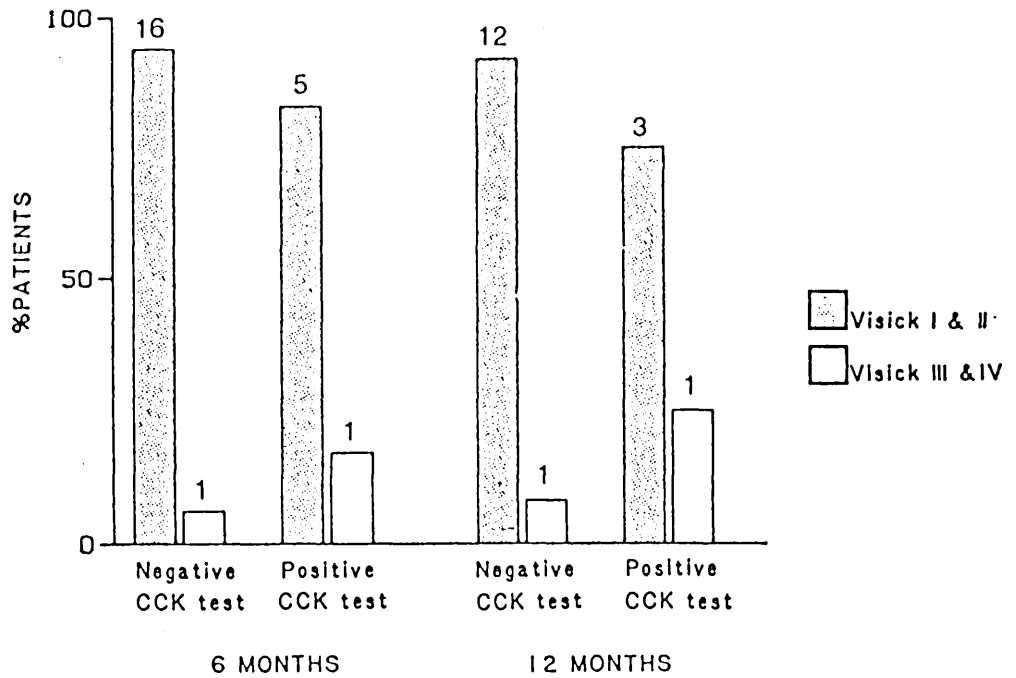


Figure 15 Outcome following cholecystectomy. Percentage of patients classified as Visick grades I and II or III and IV at 6 months and 12 months following operation. Total numbers in each group are shown at the top of each column. There is no difference between patients positive to CCK provocation and those negative. Visick grades are maintained with no evidence of deterioration at 12 months.

Table 14 Follow up data in patients who have not had cholecystectomy performed. Follow up from first contact.

A. Cholecystokinin test - NEGATIVE

	MONTHS					
	1	3	6	12	18	24
Visick° Grade						
I	1	2	3	3	3	2
II	1	5	7	7	3	1
III	23	19	15	8	1	-
IV	2	1	2	2	-	-
TOTAL	27	27	27	20	7	3

B. Cholecystokinin test - POSITIVE

	MONTHS					
	1	3	6	12	18	24
Visick° Grade						
I	-	-	-	-	-	-
II	-	1	1	1	-	-
III	3	2	2	1	-	-
IV	-	-	-	-	-	-
TOTAL	3	3	3	2	-	-

°Modified Visick Grade

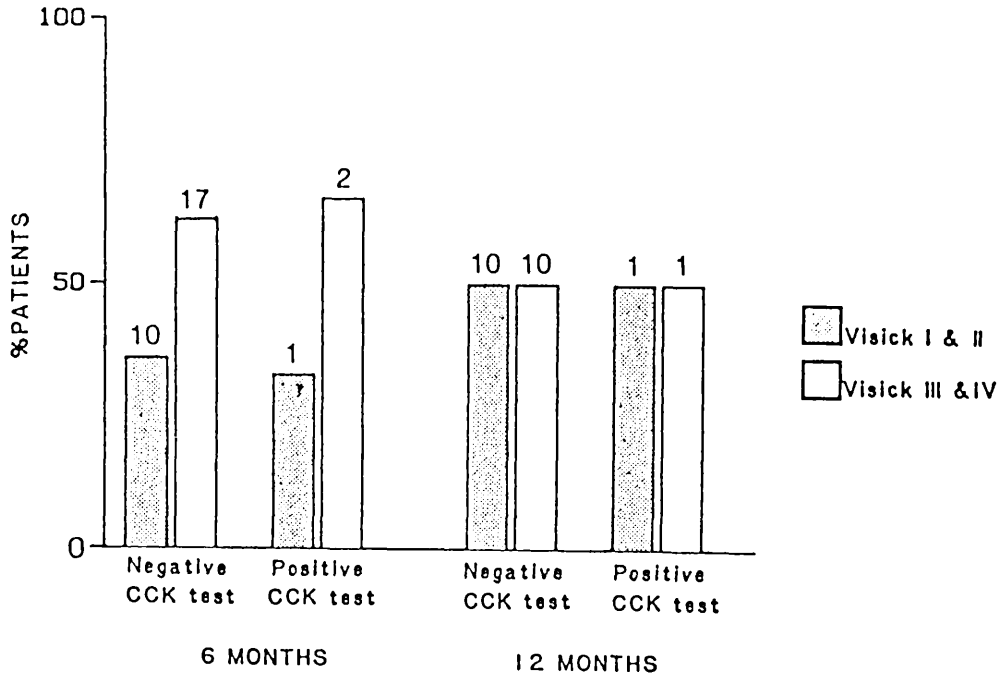


Figure 16 Percentage of patients classified as Visick grades I and II or III and IV at 6 months and 12 months from initial contact in patients who have not had cholecystectomy. Total numbers in each group are shown at the top of each column. The number of patients in the CCK positive group are too small for useful comparison. There is the suggestion of a trend towards spontaneous improvement in patients whether positive or negative to CCK provocation.

DISCUSSION

Many workers have used an 'abnormal' response to CCK administration as an indication for cholecystectomy. An abnormal response may be pain induced by the CCK or anomalies in gallbladder emptying seen using an imaging technique. Results have appeared favourable and it is currently believed that CCK provocation is useful in selecting patients for cholecystectomy [25,205,208]. With the possible exception of the very rare cystic duct stenosis, there is no evidence that CCK administration can detect gallbladder disease. There is good evidence that CCK injection, particularly when given as a bolus dose, can cause pain in normal individuals [73,111,130]. Further the common finding of histological changes in the wall of an excised gallbladder means that histology is not a reliable end point for studies in acalculous biliary pain. It has long been recognised that a pathology report of chronic cholecystitis does not implicate the gallbladder as the source of the patients symptoms [2,11,19,209].

Previous investigations of the CCK provocation test have suffered from methodological problems which this study has attempted to avoid. The methods used by

others could have led to errors in the interpretation of the results of their studies. As described in Chapter 2 the use of an intravenous bolus of CCK may lead to over diagnosis and confusion with normal individuals. For this reason an infusion of CCK was used in these examinations. It is probable that the relatively low number of positive tests experienced was due to this and was perhaps a truer reflection of the incidence of pain accompanying CCK administration. In most reports the result of a CCK test has been based on the patient's affirmation that the pain induced by the test was equivalent to the presenting pain. Lennard et al [25] attempted to be more objective in assessment of the patients' pain. They used the McGill pain questionnaire to quantify the presenting pain. The numerical values obtained were then compared with the values obtained during a CCK test. This technique has been emulated in the present study and the McGill questionnaire has been found to have a number of shortcomings. It was designed to quantify a defined pain and to detect differences in its intensity. In this respect it works well in for example assessment of an analgesic technique. In the context of the CCK test it is difficult to be certain that numerical values obtained at different times represent qualitatively

the same pain. Where substantial differences were detected these could be clearly demonstrated but the statistical statement that scores were not different does not mean that they were the same. As used this questionnaire takes little account of the quality and distribution of the pain. The use of the McGill questionnaire in the interpretation of the CCK provocation test may well have been misleading. A further critiscism of previous studies of acalculous biliary pain is the prediliction for surgery only in patients who are positive to CCK provocation. This lends an unacceptable bias to these reports and makes interpretation of the predictive ability of CCK impossible. Our results are comparable with those of other workers who have performed cholecystectomy regardless of the result of CCK provocation [23,67,160,161] and with others who have selected patients on clinical grounds alone [20,21].

The results of this study have suggested that the patient who is negative to the CCK provocation test has as good a chance of symptomatic response to cholecystectomy as the patient who is positive. There appears to be a tendency to symptomatic improvement with time among patients not yet operated on and this would confirm the findings of other workers [25,67] but

50% of these patients remain in the Visick III and IV category at 12 months. The high repsonse rates to cholecystectomy witnessed in the present and other studies may represent a substantial placebo effect. The 3 year follow up reported by Byrne et al [159] would support this although in those of our patients followed to 2 years there is no evidence of deterioration of symptom scores. CCK provocation does not predict the outcome from cholecystectomy in patients with acalculous biliary pain.

CONCLUSION

In this study the result of the cholecystokinin provocation test failed to distinguish those patients with acalculous biliary pain who had symptomatic benefit from cholecystectomy. Outcome as assessed by modified Visick grading was the same in those patients who had a positive test and in those patients who had a negative result at a mean follow-up of 12 months from cholecystectomy. The group of patients who had cholecystectomy showed greater overall improvement than those who did not.

CHAPTER 7

IN VIVO GALLBLADDER CONTRACTION

IN PATIENTS WITH

ACALCULOUS BILIARY PAIN

INTRODUCTION

The induction of pain by injection of cholecystokinin is not a reliable method of detecting gallbladder dysfunction. Using oral cholecystography several workers have reported abnormalities of gallbladder contraction and these have been associated with acalculous biliary disease [5,37,65,67]. Imaging of the gallbladder and quantification of gallbladder emptying in response to stimulation are desirable features in investigating motility disorders. Both of these demands can be met by ultrasonography and radionuclide imaging of the gallbladder. Ultrasonography has the disadvantage of requiring skilled operators and dedicated computing facilities. The equipment required for a standard diagnostic radionuclide examination can also be used to perform dynamic studies. This recognised technique is simple and safe and has been used by a number of authors to examine gallbladder behaviour in different patient populations [29,123,210]. In this study dynamic radionuclide imaging in conjunction with CCK induced gallbladder contraction has been used to determine gallbladder motility. The responses in a group of normal asymptomatic volunteers were compared with the responses of patients with acalculous biliary pain.

PATIENTS AND METHODS

PATIENTS

All 64 patients referred with acalculous biliary pain were invited to have dynamic radionuclide imaging as part of the investigation protocol described in Chapter 4. One patient declined the invitation and two patients had had scans performed prior to referral. These were not repeated and 61 patients had dynamic scans performed.

VOLUNTEERS

For comparison with the patient group dynamic DISIDA scans were performed in 16 normal volunteers. Subjects were drawn from laboratory and nursing staff in the University Department of Surgery. All were in good health and gave no history of recent upper abdominal pain or symptoms referrable to the biliary tract. None had previously had a radionuclide study performed and all gave informed consent for the study. Local ethical committee and ARSAC permission was obtained for these examinations.

The detailed methodology for scanning both volunteers and patients was the same and has been described in Chapter 4.

RESULTS

Dynamic radionuclide imaging was performed in 61 patients and 16 volunteers. Of the 61 patients examined, 10 have been excluded due to the finding of an alternative condition to explain their symptoms. (Chapter 6) In addition to these exclusions 5 scans could not be analysed. Of these equipment failure led to loss of the study in 3 cases and one patient had non filling of the gallbladder. In the fifth case the patient experienced pain during the administration of CCK which was so severe that the examination was aborted. Although one further patient developed pain during the administration of CCK she was able to continue the study. Satisfactory scans were thus available for analysis in 46 patients with a diagnosis of acalculous biliary pain and 16 healthy volunteers (Table 15). No volunteers developed pain during CCK infusion.

Ten subjects (3 volunteers and 7 patients) had studies repeated (Table 16). One patient had a non filling gallbladder on both occasions. EF was reproducible within 20% in 7 of the 9 individuals with gallbladder images in whom there was a mean difference of 6.8%. There was a greater variability

Table 15 Details of subjects having evaluable dynamic DISIDA scans.

	VOLUNTEERS	PATIENTS	
n	16	46	
M	4	3	
F	12	43	
AGE (years)	34.2 (27-38)	43 (30-60)	$p<0.05$†

† Mann Whitney test

Table 16 Percentage ejection fraction (EF) and $T_{1/2}$ derived from repeated examinations in 3 healthy volunteers (V) and 7 patients (P) with acalculous biliary pain.

SUBJECT	EF(1) %	EF(2) %	$T_{1/2}(1)$ (minutes)	$T_{1/2}(2)$ (minutes)
V1	84	24	7.2	117
V2	64	36	12	42
V3	48	48	36	36
P1	72	59	14	26
P2	99	97	3.4	6.9
P3	17	31	74	41
P4	14	20	167	128
P5	36	38	59	69
P6	69	80	6.4	8.4
P7*	-	-	-	-

* Non filling gallbladder.

in the $T_{1/2}$ between studies. Good qualitative reproducibility was seen in 8 examinations and examples are shown in Figure 17. Two volunteers were poorly comparable.

The values derived for ejection fraction (EF), half life of gallbladder emptying (T1/2) and the time to peak filling (TTP) are shown in Table 17 for each group. Examination of the derived parameters suggested an inverse exponential relationship between EF and $T_{1/2}$ (Figure 18). Replotting of the logarithm of EF against $T_{1/2}$ confirmed a linear relationship (Figure 19). There was no difference between volunteers and patients with a diagnosis of acalculous biliary pain in gallbladder emptying assessed by this technique.

Nine of the 46 patients responded with pain during cholecystokinin provocation tests (Chapter 6) although only two experienced pain during the dynamic scan. There was no difference in gallbladder emptying between patients who were positive to CCK and those who were negative (Table 18). Cholecystectomy was performed in 16 of the 46 patients and Table 19 shows the outcome from cholecystectomy related to emptying characteristics.

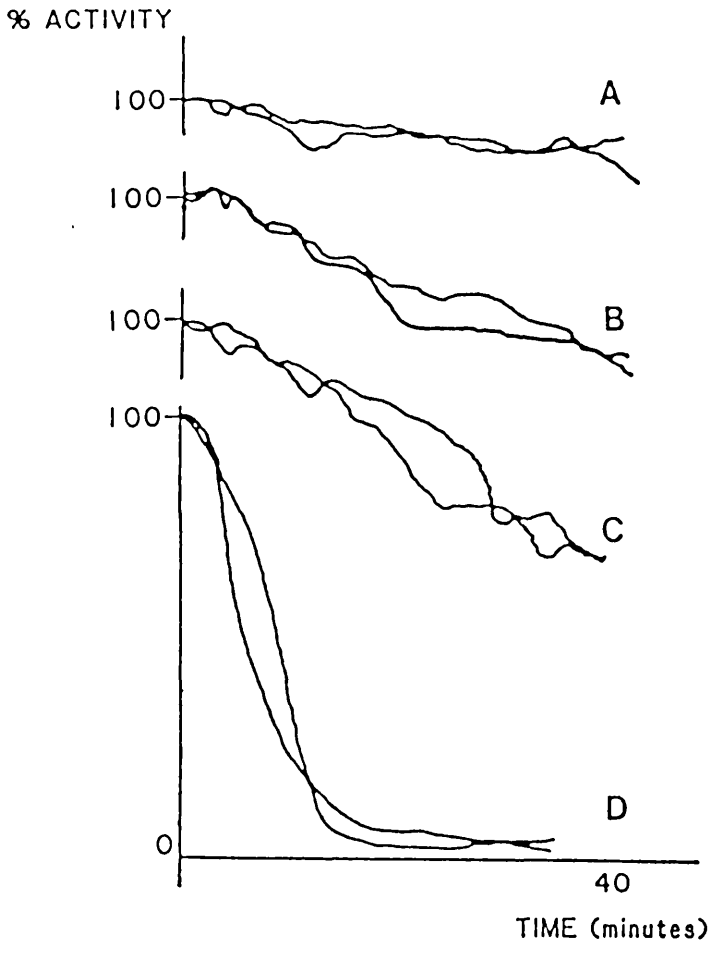


Figure 17 Illustration of reproducibility in 4 DISIDA studies. Examples of duplicate studies performed at different times in four subjects using the same vertical and horizontal scales. These scans showed the closest qualitative and quantitative reproducibility in the derived values for these individuals.

Table 17 Derived values of subjects having dynamic DISIDA scans.

	VOLUNTEERS	PATIENTS	
n	16	46	
EF (%)	64.5 (45-78)	67 (45-86)	NS†
$T_{1/2}$ (minutes)	12.6 (8.7-36)	16 (6-25)	NS°
TTP (minutes)	42.5 (25-64)	55 (40-70)	NS¶

Results are median and interquartile range

Mann Whitney test

†p = 0.73

°p = 0.44

¶p = 0.06

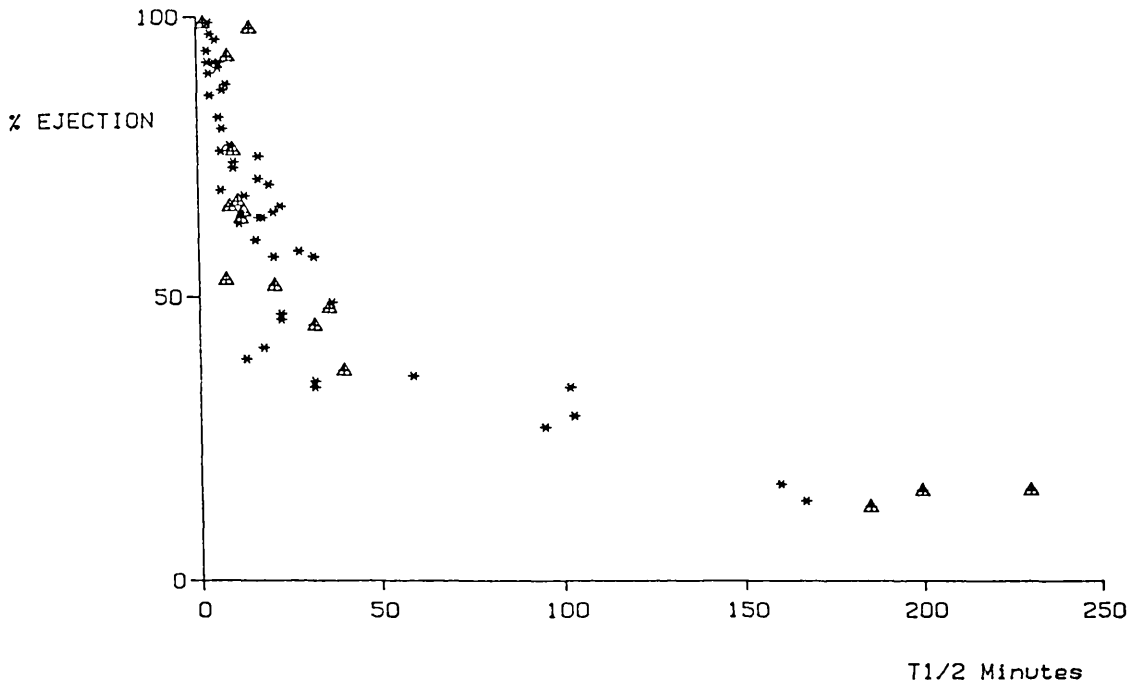


Figure 18 Scatter plot of ejection fraction and half life of gallbladder emptying for all studies performed. Patients *; Volunteers ⚠. The exponential distribution suggests an inverse relation between the two values.

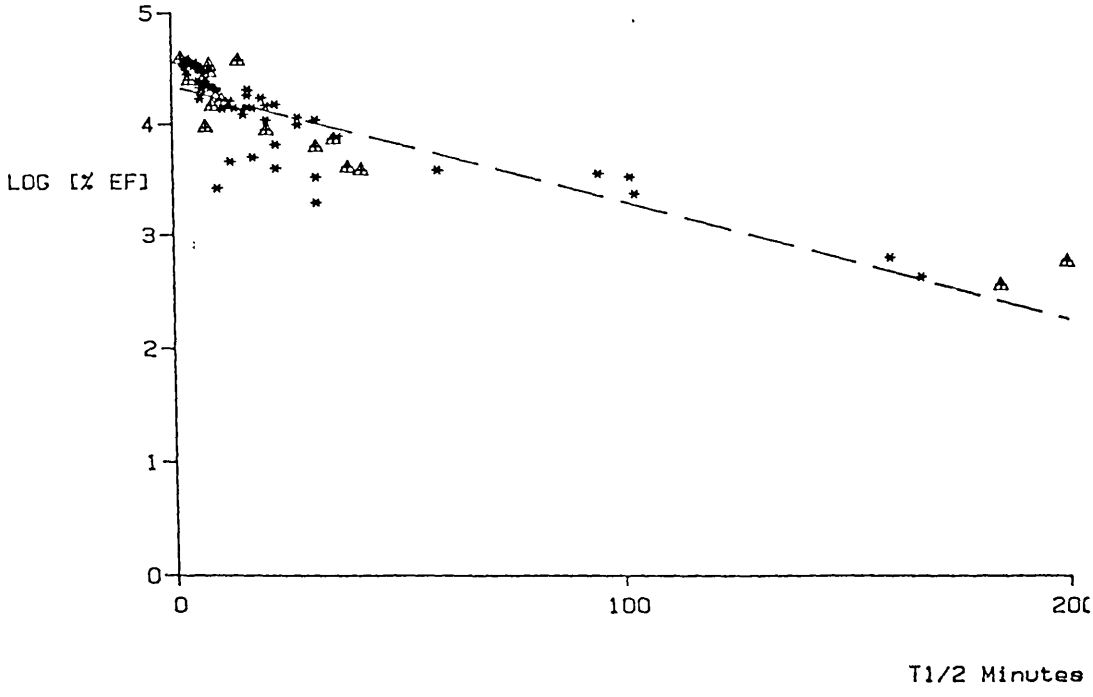


Figure 19 Scatter plot of the logarithm of percentage ejection fraction against the half life of gallbladder emptying. There is a linear relationship when the values are plotted in this way suggesting interdependence ($r = 0.904$, $p < 0.01$, 56df). Patients *; Volunteers ⚠.

Table 18 Gallbladder emptying characteristics in patients with positive and negative CCK tests.

	CCK TEST POSITIVE	CCK TEST NEGATIVE	
n	9	37	
EF(%)	73 (51-83)	66 (40-86)	NS†
$T_{1/2}$ (minutes)	17 (6.2-22)	14.5 (6.3-31)	NS°
TTP (minutes)	57.5 (51-70)	50 (40-70)	NS¶

Results are median and inter quartile range.

Mann Whitney test

†p = 0.86

°p = 1.00

¶p = 0.20

Table 19 Gallbladder emptying characteristics in patients treated by cholecystectomy.

	CHOLECYSTECTOMY		NO CHOLECYSTECTOMY	
	CURED	NOT IMPROVED		
n	14	2	30	
EF(%)	65.5 (29-90)	66.5 (-)	68.5 (45-86)	NS†
$T_{1/2}$ (minutes)	19 (4-46)	19.2 (-)	13 (6-21)	NS°
TTP (minutes)	55 (45-80)	52.5 (-)	50 (40-70)	NS¶

Results are median and inter quartile range.

†Kruskal Wallis. Chi squared 0.18, 2df.

°Kruskal Wallis. Chi squared 3.59, 2df.

¶Kruskal Wallis. Chi squared 1.15, 2df.

There was no difference in gallbladder contraction between males and females when patients and volunteers were examined separately or together (Table 20).

Table 20 Gallbladder emptying characteristics in all males and females.

	ALL MALES	ALL FEMALES	
n	7	55	
EF(%)	65 (48-80)	66 (45-86)	NS†
$T_{1/2}$ (minutes)	20 (12-36)	13 (6.4-30)	NS°
TTP (minutes)	50 (40-65)	50 (40-70)	NS¶

Results are median and inter quartile range

Mann Whitney test

†p = 0.99

°p = 0.28

¶p = 0.59

DISCUSSION

By labelling a conventional contrast medium with ^{131}I, Englert and Chiu [211] were able to monitor the activity from the gallbladder when it was located by conventional X-rays. They were able to detect a decrease in gallbladder activity in response to a fatty meal but the instrumentation available did not allow them to image the gallbladder directly. Developments in radioisotope technology have allowed anatomical imaging and physiological measurements of in vivo gallbladder motility [31,123,124,210]. ^{99m}Tc DISIDA is labelled with a pure gamma emitter which has a short half life of 6 hours. It is completely cleared from the body by about 18 hours after administration. The total dose involved in a single gallbladder examination has been estimated at about 3 milli Sieverts and repeat examinations can be performed safely in individual subjects [212]. In this study ^{99m}Tc DISIDA has been used to image the gallbladders of patients with a diagnosis of acalculous biliary pain and of healthy volunteers. A standard stimulus to gallbladder emptying was used and the response in both groups was compared.

There is no agreed method of analysing the pattern of gallbladder filling and emptying determined using

this technique. There is acknowledgment that the time to fill the gallbladder after injection of the radiopharmaceutical may be important and that a non filling gallbladder suggests obstruction of the cystic duct. Two principal methods have been used to induce gallbladder emptying. A test or standard meal may be given and this has been either solid [180] or liquid [29,180] in published reports. Other workers have used the various preparations of CCK to induce gallbladder contraction but preparation, dose and rate of administration have all varied and no standard has been determined. Both techniques have disadvantages. Ingestion of foodstuffs may be more 'physiological' but makes separation of gallbladder function from gastric function difficult. Further a standard meal makes no allowance for individual body weight and rate of ingestion. Exogenous CCK overcomes these problems by eliminating the gastric emptying component and it is usually given as a dose per kilogram. The variations in method of administration however makes comparison of these studies difficult. Hopman and his colleagues [73] have demonstrated recently that low dose infusion over a period of 20-40 minutes is more effective in causing gallbladder contraction than the same dose given as a bolus. In this study an infusion was used and a dose

of 0.05 CHRU/kg.minute selected. Over 20 minutes this gave a total dose of 1 CHRU/kg which has been used by several workers [5,25,67,111]. Spellman and Shaffer in 1979 [123] demonstrated that 0.04 CHRU/kg.minute induced effective contraction in 90% of their patients with minimum associated symptoms. A dose of 0.05 CHRU/kg.min was used for the CCK provocation tests and the DISIDA scans. In the present study gallbladder response to this infusion was similiar in the majority of repeat examinations.

The lack of agreement in interpretation of gallbladder emptying is not complete. Most workers will calculate some form of ejection fraction (EF) as in the present study or residual activity as a measure of the quantity of gallbladder content emptied during stimulation. The EF is the difference between the activity at the beginning of the emptying stimulus and at the end. This may be expressed as a percentage of the initial value as in this study. Where food is used as a stimulus there are two components recognised in gallbladder emptying [29]. There is a lag time while food is processed within the stomach prior to presentation to the duodenum. This is followed by gallbladder emptying which is initially rapid but slows in an exponential manner

causing some workers to express the rate of emptying as two exponential functions [96]. With cholecystokinin the lag time is short and consists of the circulation time and the gradual onset of CCK action. Total gallbladder emptying could be ideally described by 2 exponential curves but a single exponential function fitted to the initial decay gives a useful assesment of the rapid emptying phase. The decay of this exponential provides a measure of the rate of emptying of the gallbladder ($T_{1/2}$) during CCK stimulation. The variability observed in $T_{1/2}$ in the repeat studies results from this method of derivation. Minor changes in slope which are of little clinical significance may result in relatively large changes in $T_{1/2}$ which is an inverse function of the decay constant. In this study three measurements of gallbladder motility have been derived for each patient. The time to maximum activity in the gallbladder (TTP), the ejection fraction as a percentage of peak activity (EF) and the half life of decay of gallbladder activity under the influence of CCK. The relationship between EF and $T_{1/2}$ observed in this study might have been predicted. It is not unreasonable to expect a gallbladder which contracts rapidly to eject a greater volume but this need not always be the case.

There was a wide spread of results in both the patient group and the volunteers. A number of our patients and two asymptomatic volunteers had low EF and long $T_{1/2}$. Six volunteers had EF < 50% but repeat studies in 2 volunteers leaves room to doubt the validity of these results. Repeated studies in patients would however suggest that reduced values are reproducible and initial problems experienced with the infusion pump may account for the different volunteer results. Previous studies have suggested that diminished EF (ie <30-50%) was abnormal and have recommended cholecystectomy on these grounds [29,31,37]. Nathan et al [5] in a report on volunteer CCK cholecystography suggested that failure to empty the gallbladder was not abnormal and of 200 studies he observed this in 10 asymptomatic subjects. This finding in addition to the present results in normal volunteers suggests that low EF and prolonged $T_{1/2}$ do not necessarily indicate abnormal gallbladder motility. It is debatable whether such findings alone should be sufficient indication for surgery although some workers report good response rates in patients with these values [6,31]. It is not impossible that the volunteers with low values have occult disease but their relative youth makes this unlikely and each remains entirely asymptomatic. Other investigations

have shown no evidence of cholelithiasis. The volunteers were significantly younger than the patients but there was no relationship between gallbladder emptying and age. This confirms the findings of others [100] and may not be a clinically important confounder in our study. Impaired contraction has been suggested to occur in association with gallstones but this was not the case in the single patient with a gallstone. This patient had a non filling gallbladder on 2 occasions due to obstruction of the cystic duct. This was confirmed at laparotomy and demonstrated the potential diagnostic value of DISIDA scanning in these patients.

Two patients developed pain during the CCK infusion at the time of imaging. This was in contrast to 10 patients during the blind provocation test (Chapter 6). There was no clear explanation for this finding but the CCK provocation test has not been reported to be reproducible and may be very dependent on psychological factors. Comparison of the emptying characteristics of all males and all females did not confirm the sex difference observed by other workers [29]. The increased contraction reported in females may have been related to the use of foodstuffs to induce gallbladder emptying and may

reflect differences in gastric function. This difference would not be expected with CCK infusion.

Only 2 of the patients treated by cholecystectomy have failed to obtain symptomatic improvement (Chapter 6). Although the numbers are small there was no difference in gallbladder behaviour between patients who improved, those who did not improve and those who have not had a cholecystectomy. Of the 46 patient scans obtained, 13(28%) have EF<50%. It remains to be proven that impaired gallbladder contraction represents a pathological state although the symptoms in just over a quarter of our patients could be explained in this way. In the 12(26%) patients with high EF(>85%) and short $T_{1/2}$ the gallbladder empties quickly. It is possible that rapid shifts of bile into the common bile duct or duodenum could result in symptoms which would be alleviated by cholecystectomy. This is conjecture and 2 normal volunteers also had high EF and short $T_{1/2}$. A number of symptomatic patients have values which lie at the extremes of the range and in isolation these might be considered abnormal. Taken with similiar findings in asymptomatic volunteers this study suggests that gallbladder contraction is not different from 'normal' in patients with acalculous

biliary pain. The numbers in the control group are small and the potential for a type II error exists in the statistical analyses with the wide range of values in both groups masking a real difference.

CONCLUSIONS

In this study dynamic radionuclide imaging has failed to detect a consistent motility abnormality in patients with acalculous biliary pain. These patients have gallbladder function which cannot be distinguished from that of normal subjects. Some alternative explanation for their pain must be considered.

CHAPTER 8

PATHOLOGICAL ASSESSMENT AND IN VITRO BEHAVIOUR OF GALLBLADDERS FROM PATIENTS WITH ACALCULOUS BILIARY PAIN

INTRODUCTION

Abnormalities of gallbladder contraction have been detected by dynamic gallbladder imaging [7,37,67]. The significance of these abnormalities is open to question and the administration of CCK which is commonly used to induce gallbladder contraction may itself produce some of the abnormalities seen. In patients with gallstones different clinical studies have suggested both increased [46,47] and impaired [29,37] contraction of the gallbladder. The relationship of gallstone development and gallbladder motility remains undecided.

Gallbladder motility disorders have been associated with acalculous biliary pain and have been implicated as a cause of this condition. In particular impaired contraction has been related to the presence of a pathologically narrow cystic duct in some cases and in others to the presence of cholesterol crystals in bile [7,30,31,37]. The sensitivity of the gallbladder to histamine has been shown to be increased when gallstones are present and it has been suggested that sensitivity to CCK is also increased [47,48]. The aim of this study was to examine the physical

characteristics and invitro behaviour of gallbladders removed for acalculous biliary pain. These have been compared to the characteristics and behaviour of gallbladders from patients with gallstones and with a group of controls. The control group consisted of patients without gallstones who had cholecystectomy performed in the course of hepatic artery cannulation.

METHODS

CLINICAL SPECIMENS

Eighty six gallbladders were examined in the operating theatre immediately on removal. Twenty five of the 64 patients with acalculous biliary pain had cholecystectomy performed by 15 different surgeons. Forty six gallbladders were obtained at laparotomy from patients in whom preoperative investigations had confirmed the presence of gallstones. During hepatic artery cannulation for intra-arterial chemotherapy cholecystectomy is routinely performed to avoid a subsequent chemical cholecystitis [213]. Fifteen gallbladders removed from patients having this procedure served as a 'control' group. Surgeons were asked to preserve the cystic artery for as long as possible and ischaemic time was less than 10 minutes in all cases. At laparotomy a note was made of any adhesions, kinking or compression of the cystic duct. Operative cholangiography was performed in all cases using an umbilical cannula in the cystic duct. The resected gallbladder was placed immediately in Kreb's solution at 4°C and opened at the fundus. Any stones were removed and counted and the presence or absence of gross cholesterolosis noted. Four longitudinal strips of gallbladder wall approximately 5 x 20 mm

were removed and placed in ice cold oxygenated Kreb's solution. A conical plastic pipette tip (Jencons Laboratory Supplies) minimum diameter 1 millimetre; maximum diameter 10 millimetre; length 8 centimetre, was used to assess cystic duct diameter. This was passed gently through the cut end of the cystic duct and divided at the maximum diameter of the duct. The cut end of the pipette tip was measured using a graduated rule to the nearest 0.5 millimetre. The remainder of the gallbladder was fixed in buffered formalin solution.

IN-VITRO ANALYSIS

A modified Kreb's solution was used throughout the study. This incorporated sodium pyruvate, sodium glutamate and disodium fumarate (Sigma Pharmaceuticals) in addition to the standard electrolytes (Table 21) [179]. This solution gave the most reproducible results during preliminary studies. The full thickness strips of gallbladder wall were placed in 10 ml organ baths containing Kreb's solution saturated with 95% oxygen and 5% carbon dioxide (British Oxygen Company) at 4°C. They were rewarmed over 10 minutes to 37°C. The baths were maintained at 37 $\pm$ 1°C by constant circulation

Table 21 Composition of modified Kreb's solution used in in vitro experiments.

Compound	Concentration (mmol/l)
Sodium chloride	103
Potassium chloride	4.7
Calcium chloride	2.56
Magnesium chloride	1.13
Sodium bicarbonate	25
Sodium dihydromonophosphate	1.5
D-Glucose	2.8
Sodium pyruvate	4.9
Sodium fumarate	2.7
Sodium glutamate	4.9

of warm water through a surrounding water jacket. Each strip was transfixed at both ends with a black silk suture. One end was mounted on a hook and the other tied to an isometric strain gauge transducer (Palmer Laboratory Supplies). The transducers were of the Wheatstone bridge type with an output of 50 microvolts / gramme when connected to a Devices DC2C preamplifier (Figure 20). The output from the preamplifiers was connected to a Devices M4 pen recorder to give an overall maximum sensitivity of 200 mg/cm. A resting tension of 0.75g was established as length tension curves have shown this to give good responses with minimal fatigue. Following a 30 minute period of stabilisation when a stable baseline was achieved, cumulative dose response curves were obtained to fresh solutions of histamine free base (10^{-7}-10^{-2} molar), acetylcholine chloride (10^{-7}-10^{-2} molar) and cholecystokinin octapeptide ($4.5x10^{-11}$-$1.35x10^{-6}$ molar) (Sigma Pharmaceuticals). Fresh dilutions of each agonist were made up on the day of the experiment and discarded thereafter. Dose response curves were performed consecutively on each strip, copiously washing with warm Kreb's solution over 20 minutes between agonists. Preliminary studies have shown this preparation to remain viable and responsive for between 2 and 4 hours. Specimens with

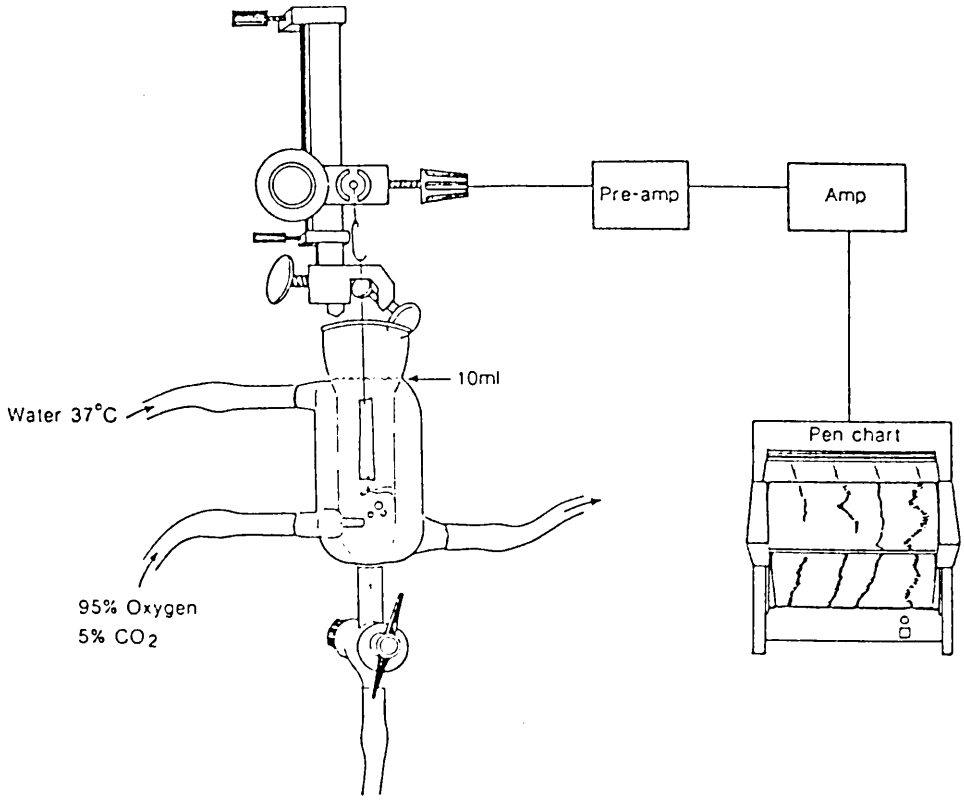


Figure 20 Schematic representation of experimental set up for in vitro analysis. Each bath is surrounded by a water jacket perfused using a roller type pump (Travenol). This maintains the bath temperature at 37°C. The transducer can be racked up or down to determine initial baseline tension. Draining and refilling operations can be performed in less than 20 seconds.

a declining baseline were considered non viable and were discarded. In some experiments after an initially stable period the baseline tension fell and it was not possible to perform dose response curves for all three agonists. The response at each dose was expressed as a percentage of the maximum for that agonist and plotted against the logarithm of the concentration which produced that contraction. From the linear part of these curves the dose required to produce 50% of maximum contraction was estimated. This value was termed the expected dose for 50% contraction or ED_{50} and was derived for each agonist (Figure 21). The ED_{50} was taken as a measure of the sensitivity of each strip for that agonist. The maximum contraction in grammes obtained with cholecystokinin octapeptide was also noted for each strip.

MUSCLE VOLUME AND CONTRACTILITY

In view of the difficulty of making each gallbladder strip exactly the same size, the size of each individual strip was measured. At the end of each experiment the strips were blotted dry and their surface areas were traced. Planimetry was performed on the traced areas using a Digitizer graphics tablet

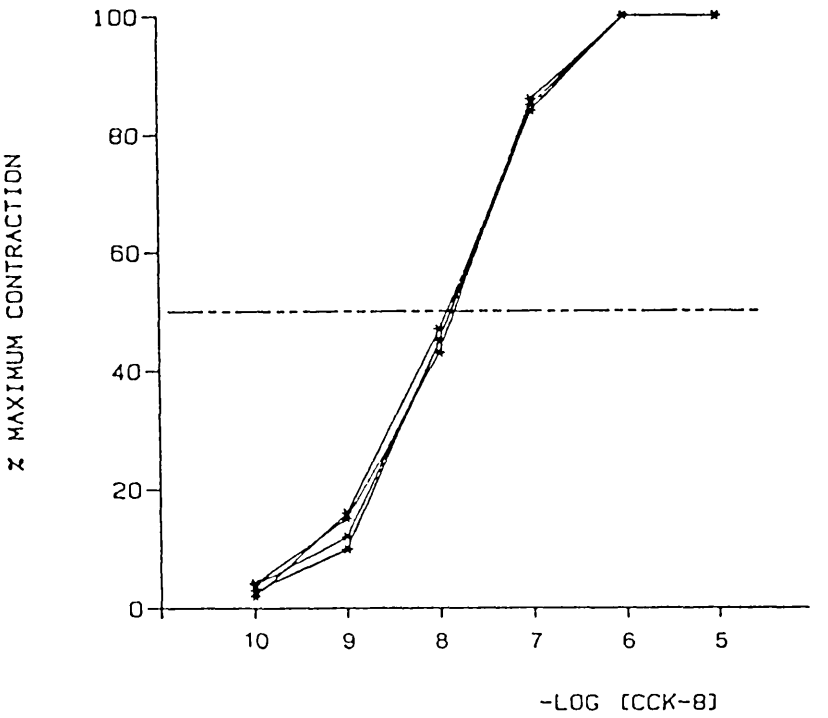


Figure 21 Plot of percentage contraction achieved at differing doses of CCK-8 in one control experiment. Each line represents the response of an individual gallbladder strip. The dotted line represents 50% of maximum contraction. The ED_{50} value is derived by projection from the dose response curve on to the X-axis.

connected to a Cromenco 16 computer. This technique has been evaluated in gallbladder strips of varying size in unpublished work in this laboratory. The measurements are accurate to 1 mm^2 and the measured area correlates closely with the weight of the strip ($r = 0.99$) for any individual gallbladder (Figure 22). The mean of 4 measurements on each tracing was taken to represent the surface area of the gallbladder strip in square centimetres. The value for the surface area combined with the histological measurement of muscle thickness provides a measure of the muscle volume within each gallbladder strip (cubic centimetres). When the maximum contraction of each strip was divided by its muscle volume the value in g/cm^3 represented the unit muscular activity or contractility of each strip.

HISTOLOGY

Representative areas were taken from the body and cystic duct/neck region of the gallbladder for processing. After drying and mounting in paraffin blocks, sections 5 micrometres in thickness were cut from the blocks and stained with haematoxalin and eosin. Slides from each gallbladder were examined 'blind' by an experienced pathologist (CGS) and each

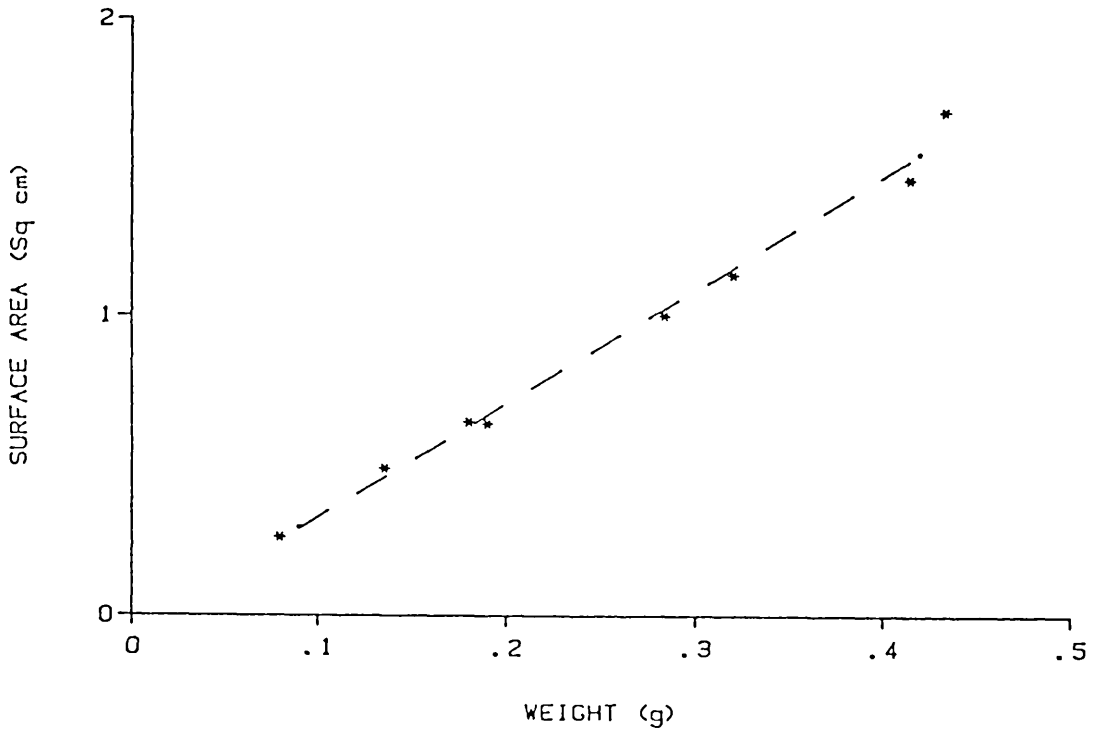


Figure 22 Plot of measured area of gallbladder strip against weight of strip. To validate the planimetry technique a number of specimens were removed from a single gallbladder. Each was blotted and traced as in the experimental protocol. The specimens were also weighed independently and the results are shown here. The results of weighing correlate closely ($r = 0.99$) and this is an accurate measure of the surface area of each gallbladder strip.

specimen was given a score using a system described previously by Lennon and his colleagues [48]. This scoring method quantifies the degree of inflammatory reaction present within each of the mucosal, muscle and serosal layers. Each layer is scored separately with each feature, for example, lymphocyte infiltration scoring 2 if extensive or only 1 if present. The score for each layer is summed and a total derived for all 3 layers. If all features were present and extensive that gallbladder would have the theoretical maximum score of 46 (Figure 23). In addition to the histology score the transverse muscle thickness in the gallbladder wall was determined at histological examination. Using a micrometer eyepiece calibrated on the x10 objective lens of a Leitz SM Lux microscope, the mean muscle thickness in the wall of each gallbladder was measured. The system was calibrated to read 8.4 units / millimetre and values were expressed in centimetres $\pm$ 0.01 (Figure 24).

STATISTICAL ANALYSIS

Four strips were examined from each gallbladder where possible and the measured and derived values were expressed as the median and interquartile range for that subject. Median values were used for comparison

HISTOLOGICAL SCREENING GALL BLADDER STUDY

PATIENT No. ..... DATE.....

SCORE 0 ABSENT 1 PRESENT 2 PRESENT AND EXTENSIVE

LAYER/FINDING		SCORE	NOTES
MUCOSA (Include lamina propria)			
Cholesterosis			
Infiltrate:	Lymphocytic		
	Neutrophilic		
	Eosinophilic		
	Plasma cell		
RBC's	(Extravasation)		
Oedema			
R/A sinus			
MUSCLE			
Hypertrophy			
Infiltrate:	Lymphocytic		
	Neutrophilic		
	Eosinophilic		
	Plasma cell		
RBC's	(Extravasation)		
Fibrosis			
Oedema			
SEROSA			
Infiltrate:	Lymphocytic		
	Neutrophilic		
	Eosinophilic		
	Plasma cell		
RBC's	(Extravasation)		
Fibrosis			
Oedema			

TOTAL SCORE

MUSCLE THICKNESS

Figure 23 Proforma used for the histological scoring system. The total score was used to represent the status of each gallbladder. Muscle thickness was measured at the same time (Figure 24).

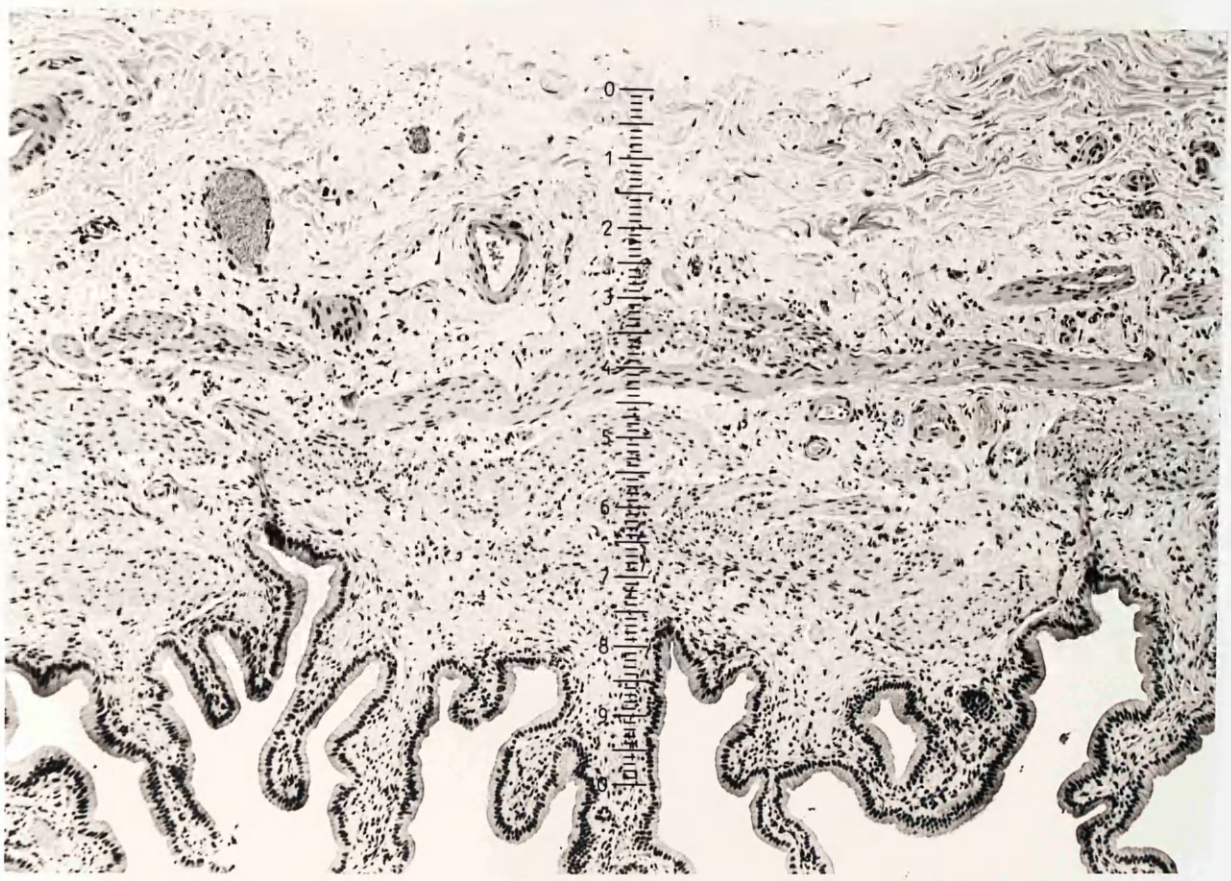


Figure 24 Photomicrograph of a histological specimen from a gallbladder in the calculous group. Superimposed is the grid from the measuring eyepiece. Measured muscle thickness in this specimen was 3.5 units. By conversion this became 3.5/8.4 mm. The value was then 0.042 cm.

between groups. ED_{50} values were converted to logarithmic values for ease of handling. The parameters measured in the three groups were initially compared using the Kruskal Wallis test. When this suggested some difference between the groups further analysis was performed using the Mann Whitney test to compare one group with another. Differences between groups were accepted as statistically significant when the possibility that such a difference arose by chance was less than 1 in 20 ($p < 0.05$).

RESULTS

The patient groups examined are shown in Table 22. There was no evidence of any adhesions, kinking or compression of the cystic duct in any of the patients with acalculous biliary disease. Four of these patients had an obvious explanation for their symptoms at laparotomy (Table 23). The patient with a gallstone was transferred to the calculous group but the others were excluded from further analysis. No patient in the acalculous or control groups had common bile duct calculi. Three patients in the calculous group had common bile duct exploration in addition to cholecystectomy because abnormalities were found on the cholangiogram films. The distribution of cystic duct diameter was similiar in each group (Table 24). More patients in the acalculous group had gross cholesterolosis on inspection but this was not statistically significant (Table 24). Histology scores (Figure 25) and histological muscle thickness (Table 25) were similiar in the control and acalculous groups. The calculous group had a significantly greater degree of inflammatory change and muscle thickening. There was no significant difference in maximal contraction achieved to CCK-8 between the three groups

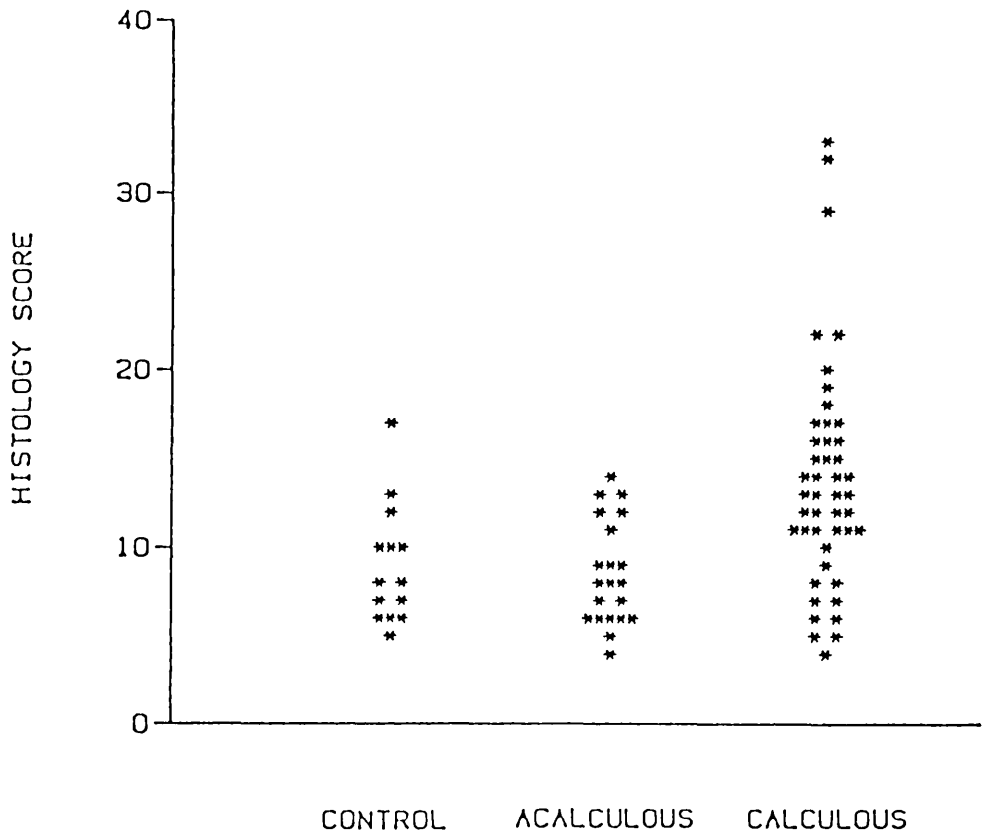


Figure 25 Histology scores for all gallbladders examined. The Kruskal Wallis test suggested a significant difference between the three groups (Chi squared = 16.35, 2df, $p < 0.001$). There was no significant difference between Control and Acalculous scores. Mann Whitney analysis reveals significant differences between the Control and Calculous gallbladders ($p = 0.009$) and between the Acalculous and Calculous gallbladders ($p = 0.003$).

Table 22 Age and sex distribution of patients at cholecystectomy.

	CONTROL	ACALCULOUS	CALCULOUS	
n	15	25	46	
AGE	56 (48-65)	43 (28-56)	56 (44-68)	*
MALE	9	3	9	
FEMALE	6	22	38	**

* Median and interquartile range.
Kruskal Wallis. Chi squared = 8.74, 2df, $p < 0.05$.

** Chi squared = 13.18, 2df, $p < 0.01$.

Table 23 Findings at laparotomy in acalculous patients excluded from study.

SEX	AGE	OPERATIVE FINDINGS
Female	35	Gallstone impacted in Hartmann's pouch
Male	60	Pancreatitis and gallbladder grit
Female	48	Prepyloric peptic ulcer
Female	56	Crohns disease of terminal ileum

Table 24 Cystic duct diameter and cholesterolosis noted on immediate inspection.

	CONTROL	ACALCULOUS	CALCULOUS	
Cystic duct diameter (mm)	4 (3.8-6.0)	5 (3.5-6.0)	4.5 (3.0-6.0)	NS†
Cholesterolosis				
Present	3	7	9	
Absent	12	14	38	NS°

† Median and interquartile range.
Kruskal Wallis. Chi squared = 0.014, 2df

° Chi squared = 1.74, 2df

(Table 25). The median and inter quartile range of derived ED_{50} values are shown in Table 26 for each agonist. There appeared to be slightly increased resistance to acetylcholine in the acalculous group but this did not achieve statistical significance. Acalculous gallbladders were significantly more resistant to histamine compared to both control ($p = 0.02$, Mann Whitney) and calculous ($p < 0.001$, Mann Whitney) patients. There was no significant difference in sensitivity to CCK-8. Taking all gallbladder specimens together there was a significant correlation between the sensitivity as expressed by the ED_{50} and the histology score for acetylcholine (Figure 26) and histamine (Figure 27). This effect was not found in response to CCK-8 (Figure 28). Calculous gallbladders were significantly weaker when median contractility values were compared with the acalculous group (Kruskal Wallis Chi squared = 11.56, 2df, $p < 0.01$: Mann Whitney $p = 0.014$) (Figure 29). There was no significant difference between the acalculous and control groups. Within the acalculous group of patients there was no significant difference in sensitivity to CCK-8 or contractility between gallbladders from patients positive to the CCK test and those who were negative (Table 27).

Table 25 Measured muscle thickness and maximum contraction achieved in vitro to CCK-8.

	CONTROL	ACALCULOUS	CALCULOUS
Muscle thickness (cm)	0.047 (0.033-0.059)	0.035 (0.032-0.042)	0.059 (0.045-0.074) *
Maximum contraction (g)	1.78 (1.35-2.58)	1.75 (1.31-2.34)	1.75 (1.19-2.88) NS°

Results are expressed as Median and interquartile range.

* Kruskal Wallis. Chi squared = 17.63, 2df, $p<0.001$.

Mann Whitney:

Control vs Acalculous $p = 0.13$

Control vs Calculous $p = 0.032$

Acalculous vs Calculous $p < 0.001$

° Kruskal Wallis. Chi squared = 0.066, 2df

Table 26 ED_{50} values obtained for each group of gallbladders.

	CONTROL	ACALCULOUS	CALCULOUS	
Cholecystokinin octapeptide (nM)	40.7 (34.6-50)	44.6 (17.3-91.2)	40.7 (10-72.4)	NS†
Acetylcholine (μM)	10 (3.8-70.7)	54.9 (29.1-91.2)	15.1 (6.3-64.5)	NS°
Histamine (μM)	137.4 (59-933)	1000.0 (537-8128)	69.1 (24.5-196)	*

Results expressed as median and interquartile range.

Kruskal Wallis †-Chi squared = 0.09, 2df

°-Chi squared = 5.54, 2df

*-Chi squared = 16.6, 2df, $p < 0.001$.

Mann Whitney:

Control vs Acalculous · $p = 0.02$

Control vs Calculous $p = 0.08$

Acalculous vs Calculous $p < 0.001$

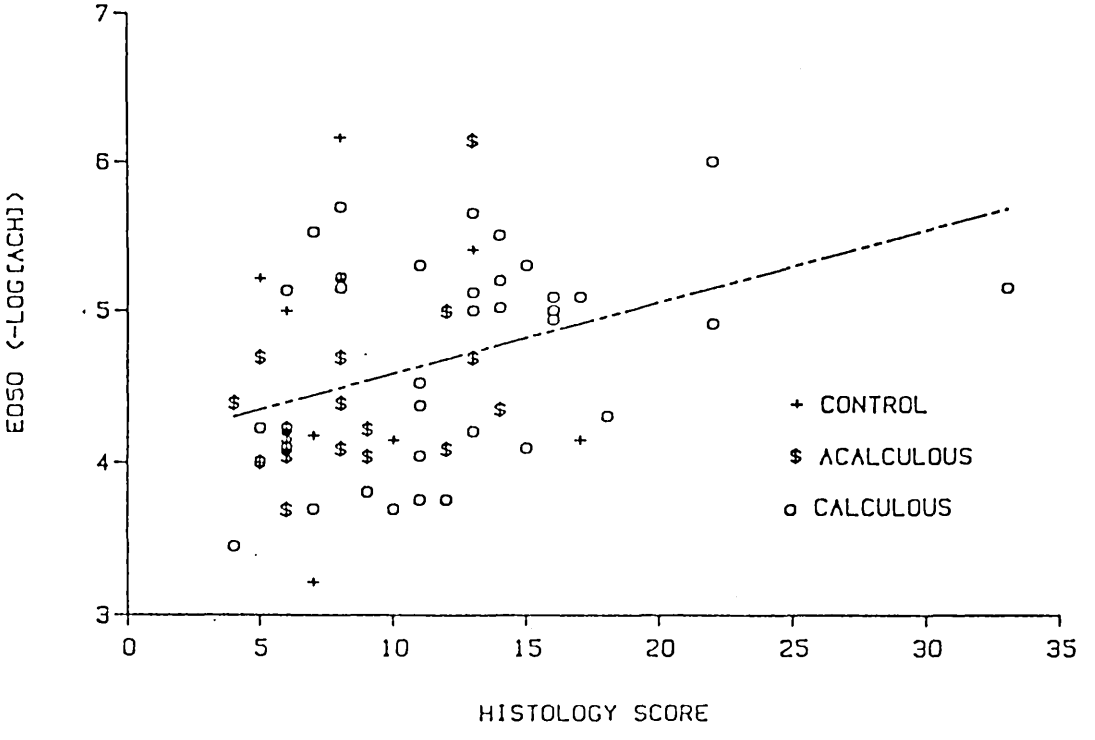


Figure 26 Correlation of median ED_{50} for acetylcholine with histology score for each individual gallbladder. There is a significant correlation ($r = 0.36$, 73df, $p < 0.01$) between the two parameters.

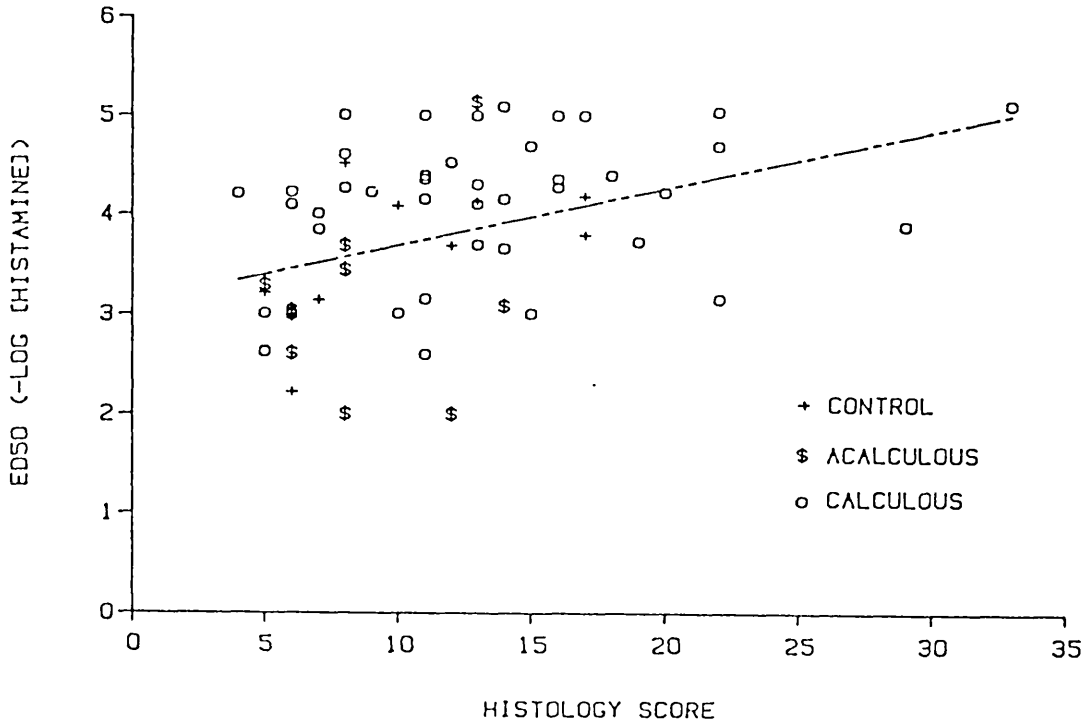


Figure 27 Correlation of median ED_{50} for histamine with histology score for each individual gallbladder. There is a significant correlation ($r = 0.39$, 73df, $p < 0.01$) between the two parameters.

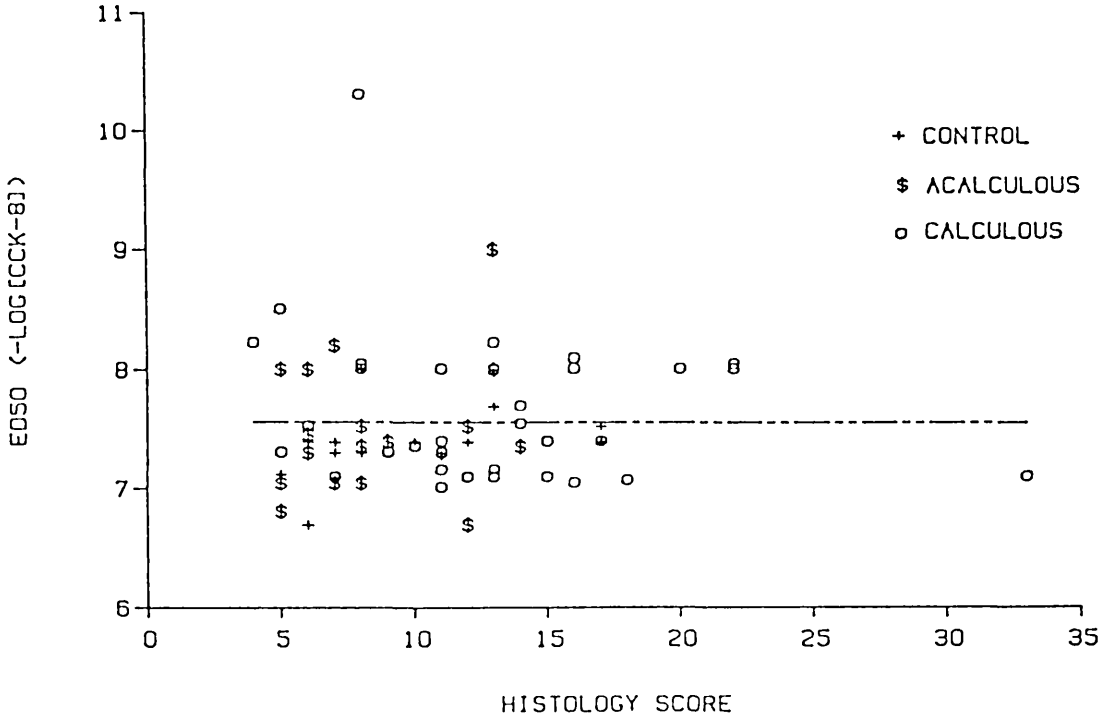


Figure 28 Correlation of median ED_{50} for CCK-8 with histology score for each individual gallbladder. There is no correlation between the two parameters (r = 0.001, 70df.)

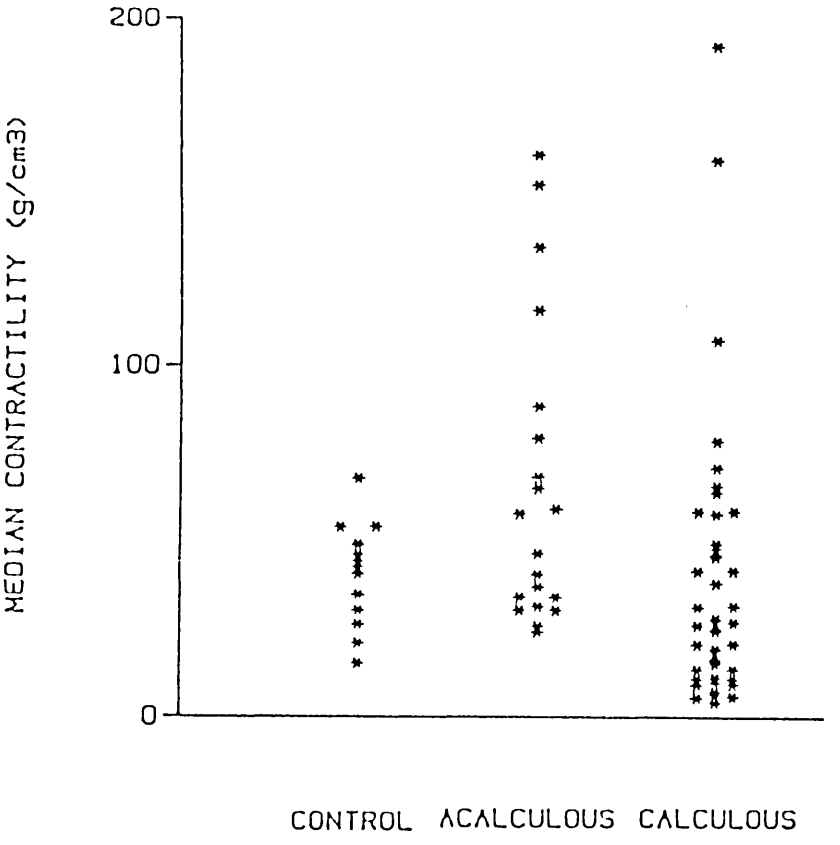


Figure 29 Median contractility values for all gallbladders. There was a wide scatter of values in both the acalculous and the calculous groups. The Kruskal Wallis test suggested a significant difference between the three groups (Chi squared = 11.56, 2df, $p<0.01$). Mann Whitney analysis revealed a significant difference between the acalculous and the calculous patients ($p=0.014$). The difference between the control and the calculous patients did not reach statistical significance ($p=0.06$).

Table 27 Comparison of sensitivity to CCK-8 and contractility in patients who had pain with CCK and those who did not.

	POSITIVE CCK TEST	NEGATIVE CCK TEST	
n	4	17	
ED_{50} CCK-8 (nM)	32.3 (30.1-91)	31.6 (10-45.7)	NS†
CONTRACTILITY (g/cm^3)	44.8 (25.6-115.3)	57.5 (33.8-88.5)	NS°

Values are median and inter quartile range

Mann Whitney test

†p=0.46

°p=0.48

DISCUSSION

The cause of acalculous biliary pain is not known. The gallbladder is commonly implicated but the assumption is generally made that it harbours occult stones or cholesterol crystals [19,37,65]. As a result the motility disorders seen in gallstone disease are expected in clinical examination of acalculous disease [29-31]. There is some evidence to support this view but it remains possible that some other abnormality is common to acalculous biliary disease. Abnormal narrowing of the cystic duct has been proposed as one mechanism, and recent work has confirmed impaired emptying of the gallbladder in these patients [30]. In the present study the gross characteristics, histological features and in vitro characteristics of gallbladders removed from patients with a diagnosis of acalculous biliary disease have been examined. These have been compared with the findings in gallbladders from patients with gallstones and a group of control patients. The control specimens were taken from a group of patients with hepatic metastases having hepatic artery cannulation for intra-arterial chemotherapy. These patients had at no time been shown to have gallstones and had no complaints referrable to the biliary

tract. None of these patients had tumour adjacent to the gallbladder and although hepatic metastases may have some inflammatory element such changes are unlikely to affect the gallbladder proper. Appropriately for their condition the control group were significantly older than the acalculous patients but were of a similar age range to the gallstone patients. The difference in age between the groups is a potential confounder in the analysis of these data. Keane et al [95] have shown in vitro that gallbladder sensitivity to acetylcholine increases with age in men but decreases in premenopausal women. Histological changes within the wall of the gallbladder are likely to occur with age [11] and this could also confound the results. A further potential source of error is the significant difference in the sex ratio between the acalculous patients and the control group. In vivo work has suggested that women empty their gallbladders more completely and more rapidly than men [29] although this has not been our experience (Chapter 7). In vitro work has demonstrated a depressant effect on gallbladder strip contraction from progestogens [95] and other workers have suggested poorer contraction in women of child bearing age [96-98]. Most of the patients in the control and calculous groups were post menopausal and

any hormone effect should have been minimal. A number of the acalculous group were of child bearing age and two were taking an oral contraceptive preparation. This was discontinued as standard practice one month prior to their surgery being performed.

SURGICAL PROCEDURE

The findings at laparotomy have been considered important by some authors [13,16,23]. There was no evidence of external compression or kinking of any cystic duct or gallbladder in this series. There were no adhesion bands or evidence of previous inflammation around the gallbladder in the patients with acalculous disease. Alternative pathology was found at operation in some patients including in one case a gallstone impacted in Hartmann's pouch. This confirms the findings of other workers that 'biliary' symptoms can be present in other conditions and that standard investigations are fallible. It also confirms a role for laparotomy in the management of undiagnosed abdominal pain.

CYSTIC DUCT DIAMETER

In this study the cystic duct was patent in all the gallbladders. Using a 'bougie' technique is the best

way to assess the 'real' diameter of the cystic duct. Alternative techniques such as using water flow [214] or histological fixation [215] were either impractical in this situation or are liable to considerable error. Small diameter cystic ducts were present in all the patient groups and there was no difference in distribution of cystic duct diameters between the groups. On this evidence the cystic duct syndrome is not a common cause for acalculous biliary pain.

HISTOLOGICAL EXAMINATION

Gross cholesterolosis was present in 30% of patients with acalculous biliary pain in contrast to only about 20% in each of the other groups. Cholesterolosis coexisting with gallstones is not unusual and has been reported in up to 29% of surgical specimens [40] but a 20% incidence in our control group is higher than might be expected [19,205]. Despite the trend for cholesterolosis to be more common in the acalculous patients these differences failed to achieve statistical significance. Cholesterolosis alone is unlikely to be the cause of acalculous pain although it was a common finding in these patients.

Scoring of the histological changes in the gallbladder wall has been reported previously. The scoring system described by Lennon et al in 1984 [48] was used in this study. The score was based on points awarded for the presence and severity of the specific changes associated with cholecystitis such as fibrosis, Rokitansky-Aschoff sinuses, erythrocyte and leucocyte infiltration. The total score from all layers of the gallbladder represented the degree of inflammatory change in an individual organ. The points classification used by these workers was not found to be of value i.e. 0-5 mild chronic cholecystitis; 6-10 advanced chronic cholecystitis; >11 acute cholecystitis. By this classification the majority of acalculous patients would have had advanced chronic cholecystitis and a few acute cholecystitis which was not the case. The scoring system was a useful method for comparison of histological changes between groups and the greater scores obtained in the gallstone group would be consistent with this. The presence of histological changes in the gallbladder wall of 'normal' patients has been recorded by other workers. In 1924 Carmen, and his colleagues [11] observed that the changes of cholecystitis were ubiquitous and Moynihan in 1909 [2] had declared the histological diagnosis of chronic

cholecystitis to be of little clinical relevance. McKibben and coworkers [208] have also noted that the presence of polymorphonuclear leucocytes alone is not an indication of inflammation in the gallbladder. One group of workers has suggested that inflammatory changes do not occur in otherwise normal gallbladders [12] but the evidence available suggests these changes occur in most individuals. Using a 'blinded' scoring technique the calculous patients were found to have a significantly greater degree of histological change than either of the other groups. It was not possible to distinguish acalculous patients from control patients using histological criteria. This finding suggests that acalculous patients have had no more chronic inflammation in their gallbladders than patients without biliary symptoms. This confirms the suspicion of others that histology changes cannot be relied upon as an end point in acalculous biliary pain. It may imply that autoimmune or micro-organism induced inflammation was unlikely to be the cause of acalculous biliary disease and indirectly strengthens the case for a motility disorder. Some patients with gallstones have low histology scores and this emphasises the limited value of histological assesment.

Muscle layer thickness in the wall of the gallbladders was measured in this study. One of the earliest changes in response to gallstones is thickening in this layer. If this were solely muscle hypertrophy the gallbladder may contract more forcefully or rapidly as has been suggested by some workers [26,47]. Light microscopy was unable to determine the precise nature of this thickening and electron microscopy studies which were not part of this study may be useful in this regard. In early disease the muscle appears hypertrophic but fibrosis becomes apparent with loss of muscle cells in late stage disease. It is possible that acalculous patients would have had some abnormality in this layer of the gallbladder wall. The results parallel those of the histological changes, with calculous patients having significantly greater muscle layer thickness. There was no detectable difference between the acalculous and control patients in respect of muscle layer thickness.

CONTRACTILITY

Previous work has examined the maximum contraction achieved by full thickness gallbladder strips in vitro and used this as a measure of the ability of

the intact gallbladder to contract [28,48,179,216]. Workers who employ this technique have endeavoured to maintain the size of different gallbladder strips using strips of the order of 4 x 15mm. It is impossible to consistently produce strips of gallbladder wall exactly the same size. This technique also fails to take into account the thickening of the gallbladder wall including the hypertrophy of the muscle layer present in chronic cholecystitis. Measurements of maximum contraction of full thickness strips revealed no difference between the three groups of patients in the study. Dividing the maximum contraction by an estimate of muscle layer volume gave a value for contractility. This showed a clear and significant reduction in the ability of strips from the calculous patients to generate tension. This would be consistent with the in vivo findings of authors who have found impaired or normal contraction in the presence of gallstones [27,37]. Acalculous patients had greater contractility values with a number of patients in this group generating high levels of tension. High contractility values were also observed in a small number of calculous patients. The difference in contractility between the control and calculous patients failed to reach significant values. One

implication of these findings is that acalculous patients have gallbladders which can generate more tension for a given volume of muscle layer or are stronger than the other groups. This has been suggested in the past but has not been shown previously in experimental work [26]. The histological appearances of the muscle layer in early chronic cholecystitis are believed to represent muscle hypertrophy predominantly. There is likely to be a variable degree of infiltration with oedema fluid and fibrosis which will reduce the contractile component of the muscle layer. Such muscle 'dilution' could generate the decreased contractility values seen in our gallstone patients but would not account for the increased values in acalculous patients. The reduced contractility is in keeping with current views on gallstone pathophysiology. If this muscle dilution effect were significant we might infer that the contractile component of the gallbladder overall was unaffected by the presence of gallstones. Further extrapolation of this hypothesis suggests that gallstones are not associated with any intrinsic muscle abnormality and the decreased contraction seen in vivo is due to inflammatory changes consequent on the presence of gallstones. Further studies are required to clarify this point.

The 'strong' gallbladders which were present among the acalculous patients and also in the gallstone patients are difficult to account for. They may represent the extreme of normal and were not representative of a particular age or sex. Such an increased contractility may be a marker of disease and represent early changes in the gallbladder consistent with muscle hypertrophy. In the acalculous patients there was no correlation between the response to CCK in vivo and the contractility values obtained. The numbers in the present study were too small to determine a meaningful subdivision of these patients.

AGONIST SENSITIVITY

This study has confirmed the finding of Lennon et al [48] that sensitivity of gallbladder strips to histamine tends to increase as the degree of inflammatory change increases. This effect also occurs with acetylcholine but was not observed with CCK-8. Both acetylcholine and histamine rely on depolarisation of the muscle cell membrane for their agonist effect. It is recognised that injury to cells leads to limited depolarisation and this may reduce the threshold potential of muscle cells. The

inflammatory changes present in cholecystitis will undoubtedly cause some muscle injury and Lennon and his colleagues showed that gallbladder muscle was most sensitive in acute cholecystitis. This mechanism may account for the increase in sensitivity to these agonists. CCK-8 does not require depolarisation of the surface membrane to induce contraction [137-139]. The mechanism of contraction of CCK-8 is a direct one causing a decrease in cAMP within the cytoplasm and contraction of the muscle [139]. It has been shown to be effective in K^+ depolarised muscle cells [138] and changes in membrane potential are unlikely to affect the response of gallbladder muscle to this agonist. Other workers have reported previously that there is no alteration in sensitivity to CCK-8 with inflammatory change although regional differences have been observed between the gallbladder body and neck [28].

The range of ED_{50} values obtained for CCK-8 and acetylcholine in this study are consistent with the published data on these preparations in man [28,48,179]. Values obtained for histamine appear to be higher than those published by Lennon et al in 1984 [48]. They observed values of 28-37μM in patients with mild chronic disease and 31-135 μM in their

control group. The gallstone patients and control patients examined in the present study have values of this order but the acalculous patients are a factor of 10 less sensitive to histamine than the others. In this study histamine free base was used in distinction to the histamine diphosphate salt which has been used by others. This might account for minor differences between the studies but not for the substantial difference found in the acalculous group. It might be expected that methodological problems would have displayed any major difference across all three groups and the systematic selection of one group seems unlikely considering the random basis of presentation. This resistance of acalculous patients to histamine is not what might be expected. The histological changes present in the acalculous patients are no less than the control patients. Although the relationship between histology and sensitivity holds when all the gallbladders are examined, acalculous patients appear to have been more resistant than expected. Examination of the ED_{50} values to acetylcholine reveals that these also were greater in the acalculous patients although not significantly so. The relative resistance of acalculous patients to these agonists may represent no more than an expression of the normality of these

tissues. This finding casts some doubt on the status of the control group of patients but might be explained by the age difference between the groups. If histological changes increase with age as has been discussed the presence of such changes in the acalculous patients equivalent to those in patients 10-15 years older may be a significant observation. The combination of resistance to agonists and the presence of histological changes may weaken the argument for a muscle disorder unique to acalculous patients. This study has been complicated by the inclusion of an elderly control group and comparison of the acalculous patients with these controls may not be entirely appropriate. What was clear from this work were the differences between gallstone and acalculous patients. Conjecture that acalculous biliary pain may be a pregallstone condition is not supported by these differences. These data have suggested that strips of gallbladder wall removed from patients diagnosed as acalculous biliary disease, differed markedly from gallstone patients. There were similarities in their contractile behaviour to strips from apparently normal individuals although there were important differences in sensitivity to histamine.

CONCLUSIONS

This study has shown that the histological changes present in the gallbladders of patients with acalculous biliary pain are less than those associated with gallstones but of the same order as those in asymptomatic patients 10-15 years older. Gallbladder strips from patients with acalculous biliary pain are able to develop significantly more tension/unit volume than gallbladder strips from gallstone patients but not more than control patients.

Sensitivity to CCK-8 was the same in all three groups of patients. Acalculous patients were significantly more resistant to histamine stimulation than either control or gallstone patients.

CHAPTER 9

SPHINCTER OF ODDI ACTIVITY

IN PATIENTS WITH

ACALCULOUS BILIARY PAIN

INTRODUCTION

Recent development of manometry techniques has allowed accurate and reproducible recording of pressure from the sphincter of Oddi, common bile duct and pancreatic duct [126,192,217]. Such recordings have improved our knowledge of biliary physiology and proved of value in the investigation of clinical disorders [189].

Abnormalities of the sphincter of Oddi have been implicated in the development of post cholecystectomy symptoms [163,188,218-220]. Endoscopic or surgical sphincterotomy has been shown to provide symptomatic relief in those patients where sphincter pressure characteristics are abnormal [220] although not all workers have been convinced of its value [221]. Patients who have cholecystectomy for acalculous biliary pain have the highest incidence of post cholecystectomy symptoms [16,17,163]. There may be many reasons for this but one possibility is that sphincter of Oddi abnormalities exist prior to cholecystectomy and predispose to these symptoms.

Sphincter of Oddi pressure has not been examined in patients with acalculous biliary pain prior to cholecystectomy. It is generally believed that the

gallbladder is the source of the patient's symptoms in this condition and this accounts for the frequent use of cholecystectomy as the treatment of choice.

In this study ERCP manometry has been performed in patients with a diagnosis of acalculous biliary pain prior to cholecystectomy. We sought to determine the existence or otherwise of sphincter of Oddi abnormalities in these patients before surgery.

METHODS

PATIENTS

Manometric measurements were attempted in 143 patients over a 2 year period. Patients were undergoing ERCP for a number of differing conditions and these are detailed in Table 28. Of the 64 patients referred with acalculous biliary pain, 40 have had ERCP performed as part of the diagnostic sequence (Chapter 4). Patients for ERCP were admitted the day before the procedure. Each gave written informed consent. All patients were fasted from midnight and intravenous saline was administered throughout this time to avoid dehydration. ERCP was carried out in the X-ray Department with imaging provided by a single plane antero-posterior screening system (Phillips). Immediately prior to intubation the oropharynx was sprayed with Xylocaine (Astra). Diazepam (Diazemuls, Kabivitrum) was given intravenously in a titrated dose between 10 and 40mg and was the only sedation used. Respiration and temporal pulse were monitored continuously throughout the procedure by a trained nurse. All ERCP examinations were performed by the same surgeon (CGM). With the patient in the left lateral

Table 28 Details of patients having ERCP manometry attempted. Diagnoses may be those after ERCP if this provided further information.

DIAGNOSIS	n	MALE:FEMALE	MEDIAN AGE	RANGE
ACALCULOUS BILIARY PAIN	40	3:37	38.5	24-70
COMMON BILE DUCT STONES (Gallbladder present)	33	7:26	65	50-87
PANCREATITIS (All types)	24	12:12	39	22-78
COMMON BILE DUCT STONES (Gallbladder absent)	20	6:14	70	37-83
POST CHOLECYSTECTOMY PAIN	17	0:17	45	35-68
OTHERS*	9	3:6	60	30-75

* Includes 3 patients with a bile duct stricture and 3 with extra-biliary pathology.

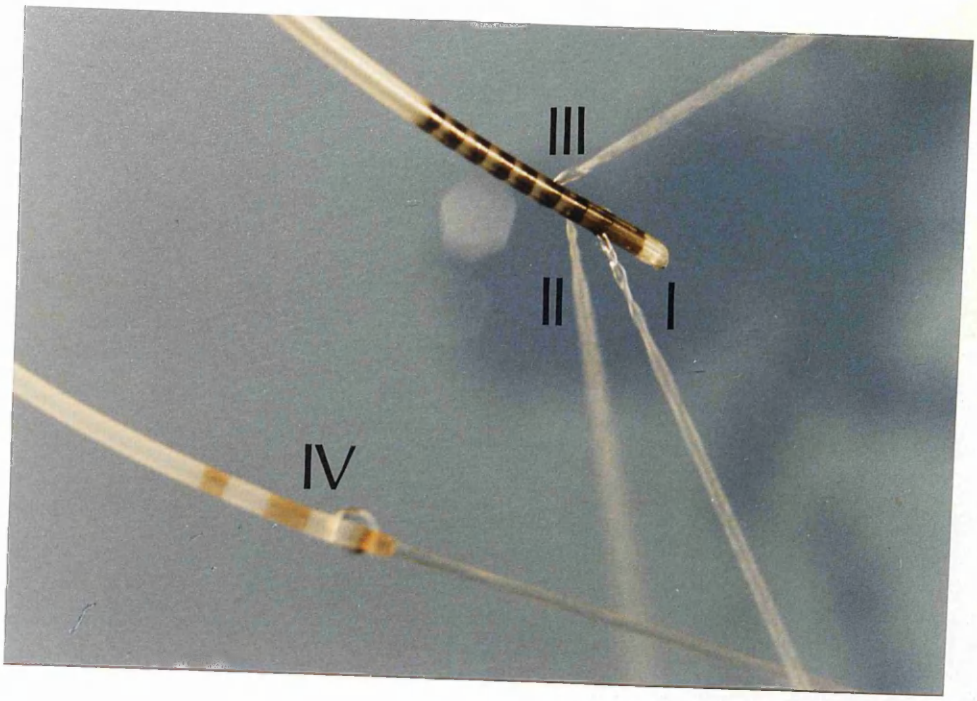
position an Olympus JF 1T side viewing duodenoscope (Keymed) was introduced into the second part of the duodenum. The papilla of Vater was identified and cannulated with a triple lumen ERCP catheter (Arndorfer Medical Supplies, Wisconsin). This teflon catheter had an outside diameter of 1.7 millimetres (mm) and contained 3 channels each of 0.5 mm inside diameter. Each lumen terminated in a side hole with the most distal orifice 4 mm from the catheter tip and the others at 120°, 2 and 4 mm more proximal (Figure 30a). The distal 2 centimetres (cm) of the catheter was marked in 2 mm divisions. A second standard ERCP catheter was attached to the endoscope using transpore tape (3M) with its tip 5 mm proximal to the exit of the catheter channel (Figure 30b).

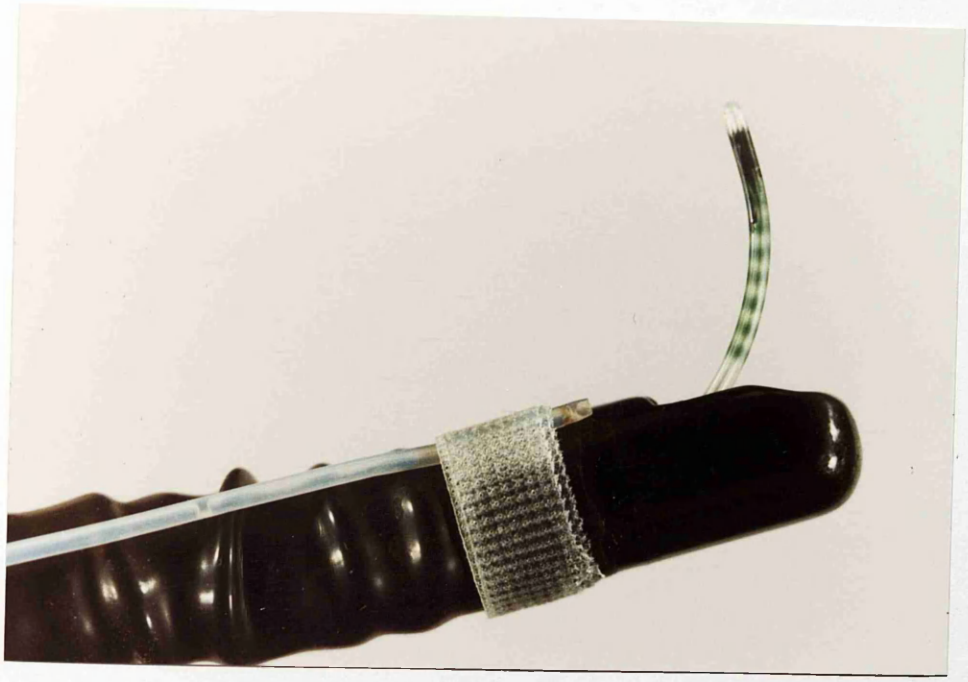
MANOMETRY APPARATUS

A hydraulic capillary infusion apparatus was constructed following the model described by Arndorfer and his colleagues [216] (Figure 31). This system forced water to flow along a catheter with pressure monitoring in a side limb. Obstruction to flow at the catheter tip caused an increase in pressure in the side limb and this was directly proportional to the pressure exerted on the orifice

Figure 30a Manometry catheter with all three channels perfused at high pressure for demonstration. A standard ERCP catheter used for duodenal reference is shown for comparison. I-IV correspond to channel numbers on recordings.

Figure 30b Manometry catheter passed through biopsy channel of endoscope. Reference catheter fixed 3-4mm proximal to biopsy channel.


III
II
I
IV



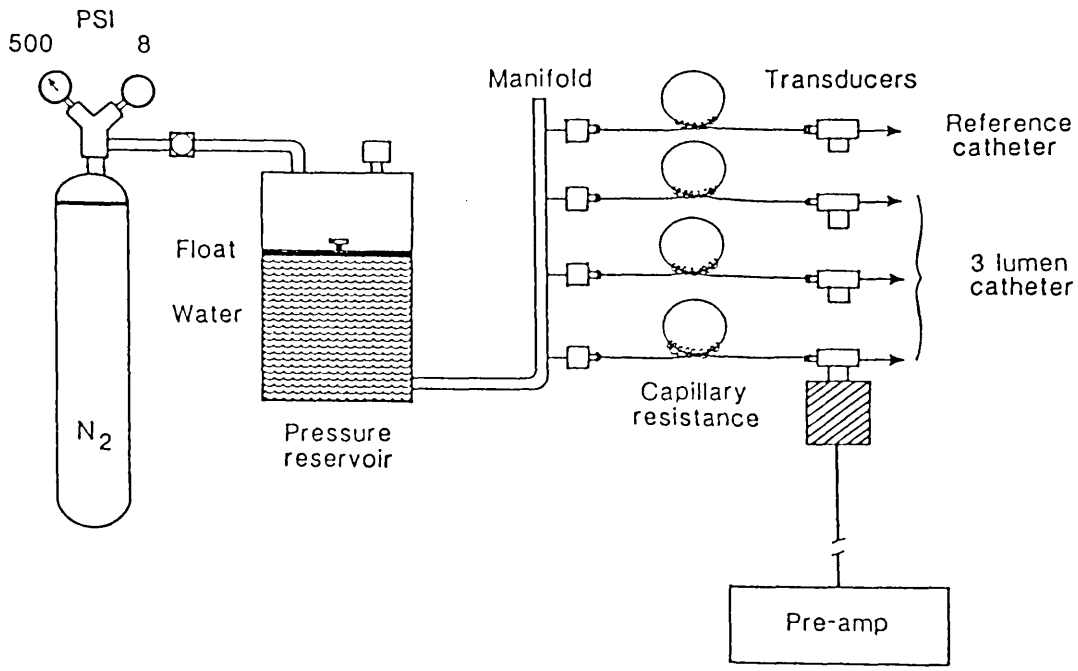


Figure 31 Schematic representation of hydraulic capillary infusion apparatus. The float in the reservoir is optional but prevents bubbles forming in the system when pressurised for long periods. Note that each channel is monitored by a separate pressure transducer.

of the catheter. A 500 millilitre (ml) reservoir was pressurised via a reduction valve from a 450 litre cylinder of nitrogen. The reservoir was maintained at a pressure of 380 mmHg. Degassed water within the reservoir was forced out to a manifold which distributed the flow equally to all 4 channels. Water was then conducted through four 60 cm coiled stainless steel capillary tubes of internal diameter 0.1 mm to smooth the flow and thereafter to four 3-way junctions. The catheters were attached at this point via 100 cm extension tubes and pressure was measured in the side arm of the 3-way junction. The distance from transducer to catheter tip was 2.1m. This system maintained a flow rate of 0.25 ml / min / channel. Pressure changes were monitored by 4 Gould 24 AD transducers (Electromed). These transducers were of the Wheatstone bridge type and provided an output directly proportional to pressure when an excitation voltage was applied. A 5 volt excitation voltage was supplied from a series of 4 Gould transducer preamplifiers and the output amplified and displayed on a Gould 4-channel thermal writing recorder (Electromed). All patient recordings were made at a chart speed of 2.5 mm / second. With the system pressurised and continuous flow established the transducers were balanced and a zero

level set corresponding to the mid point of the patient in the left lateral position. The system was calibrated by placing both catheters in a chamber which could be pressurised to between 0 and 250 mmHg using a mercury column sphygmomanometer. Preliminary experiments with this system have shown in practice an error of no more than 2% over the range of pressures expected in vivo (Figure 32). The minimum post occlusion rise time was 200 mmHg / second. These figures were well within the range necessary to record without attenuation likely changes in sphincter pressure which rarely exceed 120 mmHg / second [221].

MANOMETRIC MEASUREMENTS

Prior to the administration of contrast medium the papilla was deeply cannulated with all three openings in the catheter through the sphincter and within the duct. The most distal channel was aspirated using a 10 ml syringe. The endoscopist was able to report the appearance of bile within the catheter from the change in colour and this meant the catheter was in the common bile duct. If there was no bile then the catheter was likely to be in the pancreatic duct. This technique has been reported previously [221-223]

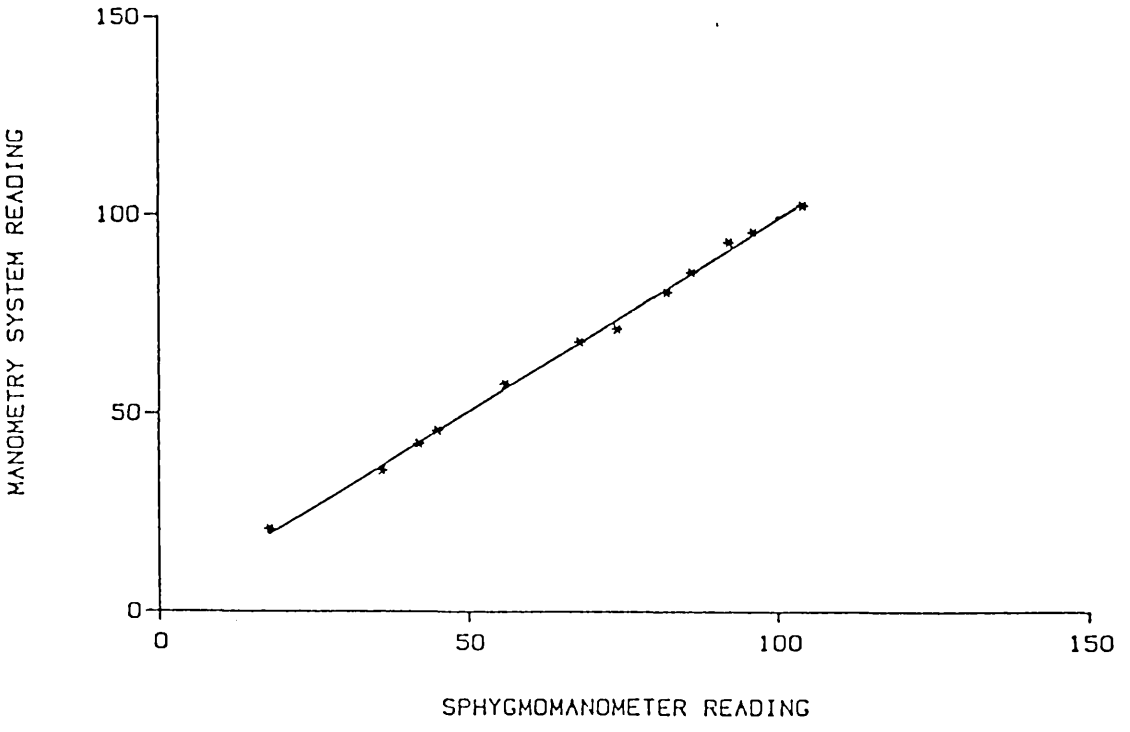


Figure 32 Readings obtained on bench testing of manometry system. Pressure within the test chamber was set by a colleague using a mercury sphygmomanometer and readings taken blind. There is a clear linear relation between the two measurements ($r = 0.998$) which falls on the line of identity.

and we have found it to be accurate in early studies when contrast was introduced during X-ray screening to confirm the position of the catheter. The catheter was then withdrawn under direct vision until the most proximal marker strips are seen or activity was recorded in the most proximal channel (III). Withdrawal was continued until all 3 channels were recording sphincter activity (Figure 33). This position was maintained for as long as possible and spontaneous sphincter activity recorded. The aim was to achieve 5 minutes of continuous recording in each case but this was not always practical. At least 2 minutes of activity was recorded in all cases before a study was acceptable. Following this recording the catheter was inserted fully into the duct and a semi-rapid pull through of the sphincter performed. The endoscopist began a steady pull on the catheter and the chart was marked as the first ring was seen appearing through the papilla. The catheter was then pulled through at 1 mark (2 mm)/second, until it lay free in the duodenum.

ADMINISTRATION OF CCK

CCK (Pancreozymin, Boots) was administered during ERCP examinations in an intravenous bolus dose of

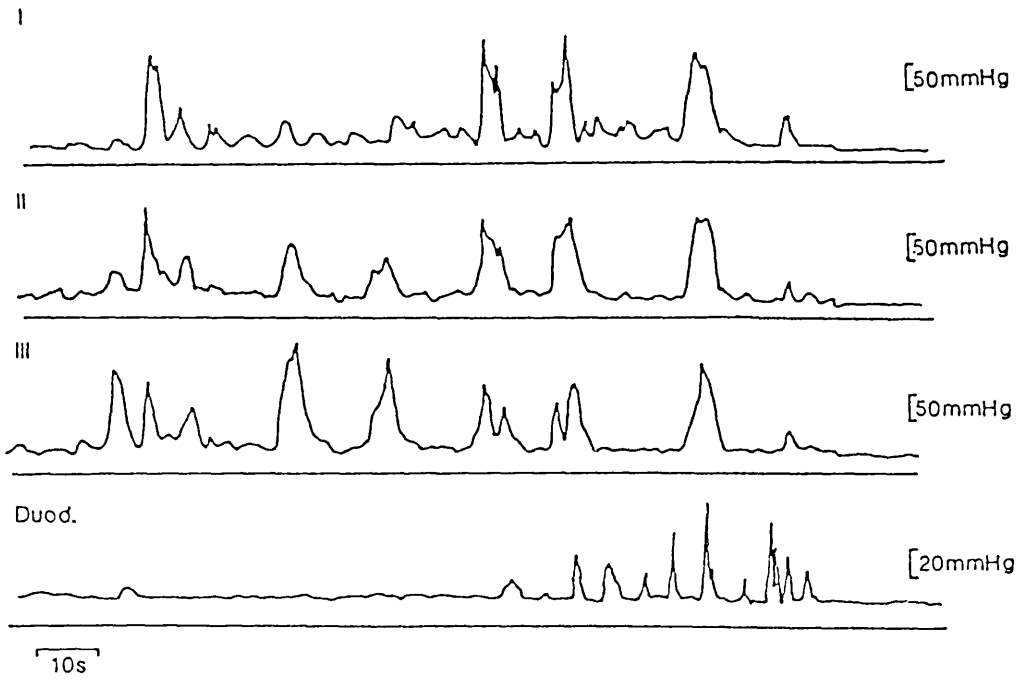


Figure 33 Spontaneous activity recorded over 2 minutes from patient No. 141. Phasic activity occured in all three catheter channels (I-III) and was absent in the duodenum (Duod). Latterly there was duodenal activity which was not reflected in sphincter pressure changes. Note change of scale between doudenum and sphincter pressure.

1 Crick Harper Raper (CHR) unit/Kg over 30 seconds. This was given immediately following the initial period of recording. The papilla was recannulated and a further recording of sphincter activity made at 3 minutes after injection of CCK. Patients then had formal imaging of biliary and pancreatic ducts using a standard ERCP catheter and Urograffin 90 contrast medium (Schering Pharmaceuticals).

ANALYSIS OF RECORDINGS

The methods used in this study for analysis of pressure recordings have been described previously [126] and are now generally accepted by workers in this field [222]. The principal values derived are the duct pressure (DP), the basal sphincter pressure (SOP), the peak pressure (PP) and the frequency (F) of the phasic contractions. In addition the direction of propagation of the phasic contractions along the length of the sphincter was determined. Propagation may be either antegrade, towards the duodenum (I->III), or retrograde, towards the duct proper (III->I). Simultaneous contractions occurring in all channels are also described [126,127,192]. Figure 34 shows the method by which these variables were derived. The duct pressure

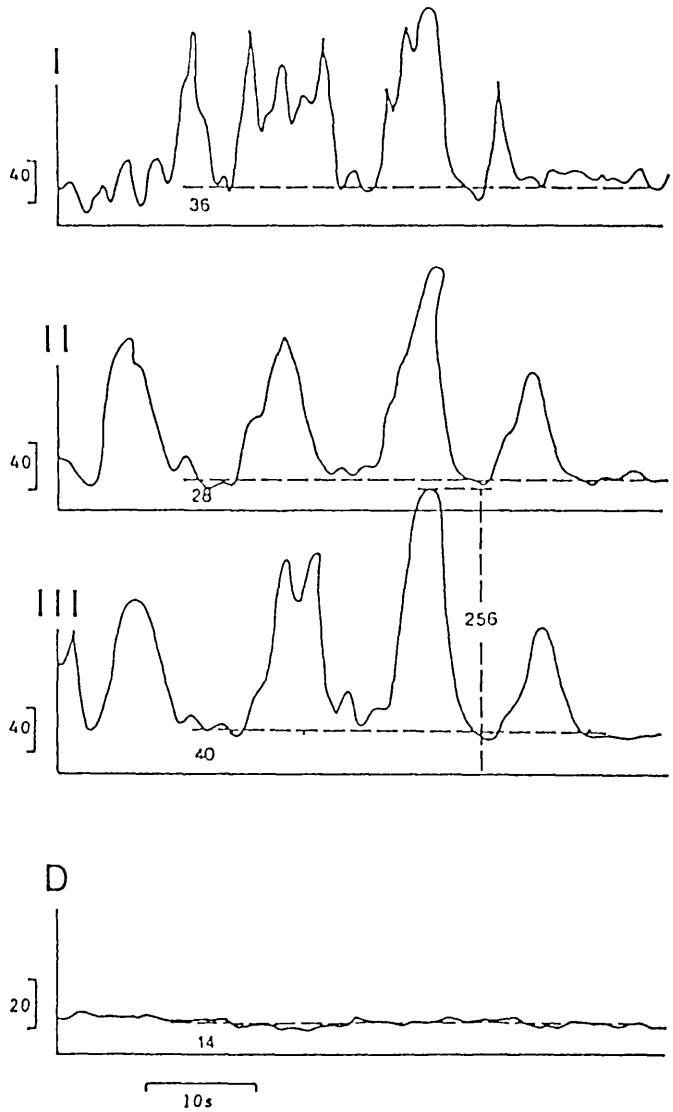


Figure 34 Annotated recording of sphincter activity showing derivation of values. A more sensitive scale was used to measure duodenal pressure. Values derived were Basal pressure = 21mmHg; Peak pressure = 235mmHg; Duodenal pressure = 14mmHg; Frequency = 5/minute.

was taken as the mean of all three channels minus the duodenal pressure following initial full cannulation. The basal pressure was the mean trough pressure recorded in all 3 channels minus the duodenal pressure when the catheter orifices lay within the sphincter zone. The mean basal pressure was calculated over as long a period as possible and always over a period greater than 1 minute. The peak pressure was the greatest pressure obtained during a phasic contraction minus the basal pressure. The frequency of phasic contractions was the number of positive deflections in excess of 20 mmHg over 1 minute occurring in all 3 channels. Figure 35 shows examples of the types of phasic contractions. Antegrade contractions began at the distal catheter orifice at least 0.4 seconds before the middle catheter orifice (I) and similarly retrograde contractions should begin at the proximal catheter orifice (III) 0.4 seconds before any change in the middle channel. In addition to the above measurements the staged pull through procedure provided a sphincter profile from which was derived a peak pull through pressure and the sphincter length. The peak pull through pressure was taken as the maximum deflection minus the previous basal pressure. Sphincter length was derived by assuming the pull

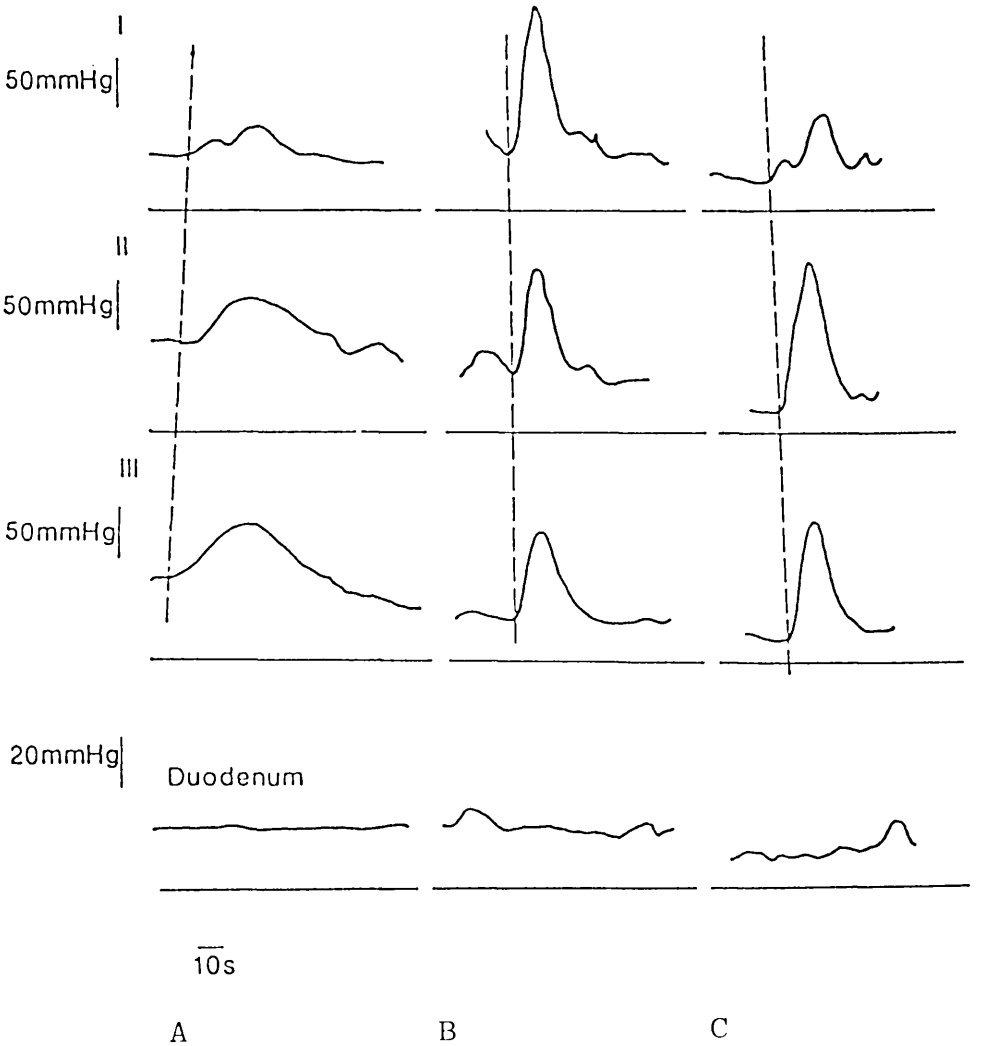


Figure 35 Examples of the three types of phasic waves described. A and B were taken from the same individual and C obtained from another patient.

through rate to be a steady 2 mm/second. From the trace the mean duration of pressure change over all 3 channels was measured and from this the length of the sphincter zone was calculated.

When CCK was given the second recording period was analysed in the above manner and the values obtained compared with those pre CCK. A normal response consistent with observed behaviour in animals and man is a reduction or abolition of phasic contractions and reduction of basal pressure [218]. Several "paradoxical" responses have been described both experimentally and in clinical practice [142,183,184,189]. In this paradoxical situation there may be no change or a rise in the basal pressure noted following CCK.

REPRODUCIBILITY

It was possible to repeat pressure studies in only very few patients who had not undergone some change such as sphincterotomy between the studies. Laboratory testing demonstrated good reproducibility within 1% on successive readings in vitro (Figure 32) and readings were stable during any single examination (Figure 33). The values obtained in those patients examined twice are shown in Table 29.

Table 29 Reproducibility of sphincter of Oddi parameters in 4 patients. Measurements were taken at least one month apart.

	BASAL PRESSURE (mmHg)		PEAK PRESSURE (mmHg)		FREQUENCY (n/minute)	
	1	2	1	2	1	2
PATIENT						
AN	10	14	134	186	4	6
RZ	12	16	88	96	38	6
MF	32	34	230	240	6	5
CM	90	60	280	250	-	6

Although the values obtained were not always numerically the same pressures which were elevated above the normal range in one recording were never normal in repeat recordings. It was possible to perform measurements in 5 patients with common bile duct stones before and after sphincterotomy. The basal pressure changes following sphincterotomy are shown in Figure 36. This clearly demonstrates the efficacy of endoscopic sphincterotomy in abolishing sphincter pressure.

NORMAL VALUES

We have not had access to normal individuals to develop a normal range for ERCP manometry. Several authors have published values observed in normal individuals [127,190,224,225] and these are shown in Table 30. The values obtained for ERCP manometry have been comparable between the groups working in this field [222] and we have accepted the values in Table 30 as our normal range.

STATISTICAL METHODS

Pressure values for each patient were expressed as means over all three channels referenced to duodenal pressure as zero with the exception of peak pressure

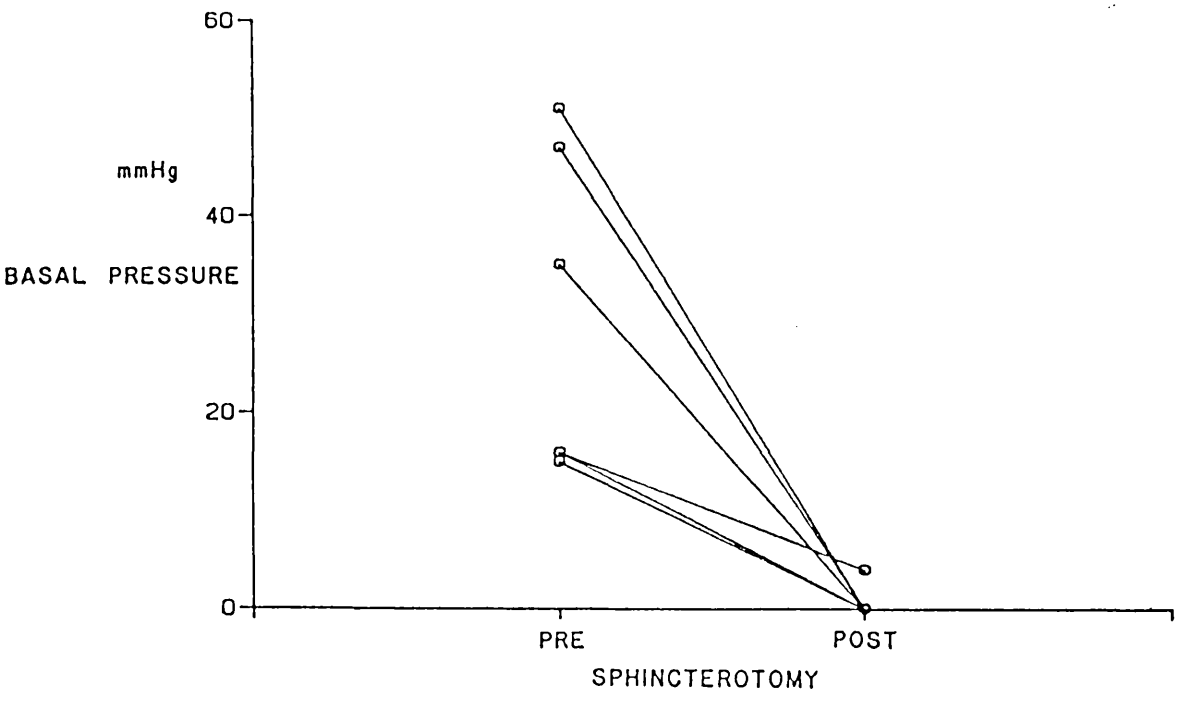


Figure 36 Basal sphincter pressure recorded before and after endoscopic sphincterotomy in 5 patients with common bile duct stones. In 3 of the 5 patients examined no sphincter activity was detectable on the second occasion.

Table 30 Range of sphincter parameters for patients without biliary disease extracted from the literature .

PARAMETER	RANGE OF NORMAL VALUES*
Basal sphincter pressure	13-17 mmHg
Peak phasic contraction	50-188 mmHg
Frequency of phasic contractions	4-6 /minute

*These values are taken from the quoted mean values for 'normal' patients. Patients have been examined in United States of America [126], England [127], Brazil [190] and Australia [226].

which was the single greatest value. The direction of propagation was expressed as a percentage of the total number of phasic contractions during the recording. Within patient values were compared using paired rank correlation tests and between patient groups the Mann Whitney test. Statistical significance was accepted when the likelihood of a difference arising by chance was less than 1 in 20 ($p < 0.05$).

RESULTS

Sphincter of Oddi manometric measurements were possible in 34 (85%) of the 40 patients with acalculous biliary pain who had ERCP. In comparison measurements were also possible in 28 (85%) of the 33 patients with common bile duct stones and a gallbladder in situ. The patients with common bile duct stones although similiar in sex distribution were significantly older (median age 38.5 vs 65, p=0.04, Mann Whitney). In the patients with acalculous pain the common bile duct was cannulated on 18 occasions (median pressure 5mmHg, IQ range 2-10) and the pancreatic duct on 16 occasions (median pressure 9mmHg, IQ range 8-12)(p=0.04, Mann Whitney). In the patients with common bile duct stones the common bile duct was cannulated on 18 occasions (median pressure 6mmHg, IQ range 3-8) and the pancreatic duct on 10 occasions (median pressure 12mmHg, IQ range 10-30)(p=0.03, Mann Whitney). Table 31 shows the manometric profile of the patients with acalculous pain and for illustration the profile of the patients with common bile duct stones and a gallbladder in situ. Where the total number of phasic waves in a record was less than 10 it was not practical to derive percentage values for the

Table 31 Sphincter of Oddi manometric profile of 34 patients with acalculous biliary pain. The profile of 28 patients with common bile duct stones and a gallbladder in situ is included for illustration.

	ACALCULOUS BILIARY PAIN MEDIAN (IQ RANGE)	COMMON BILE DUCT STONES MEDIAN (IQ RANGE)
Duodenal pressure (mmHg)	10 (5-20)	12 (10-15)
Basal pressure (mmHg)	20 (13-35)	15 (6.5-23)
Peak pressure (mmHg)	195 (170-280)	199 (108-285)
Frequency (n/minute)	5 (4-7)	5 (4-6)
Contraction sequences (%)†		
Antegrade	32 (12-26)	26 (12-40)
Simultaneous	31 (25-46)	41 (33-52)
Retrograde	21 (16-28)	13 (6-38)
Sphincter length (mm)	10 (7-11)	9.3 (8-12)

† 20 patients with acalculous pain.
18 patients with common bile duct stones.

directions of propagation. In addition 4 patients with acalculous disease and 3 patients with common bile duct stones exhibited no phasic wave activity in their sphincters. Directions of phasic wave activity were only derived in 20 patients with acalculous pain and 18 patients with common bile duct stones.

Mean basal pressure was in excess of 30mmHg in 10 patients with acalculous biliary pain and in 5 patients with common bile duct stones (Figure 37). Peak phasic pressure was $\geq$ 300mmHg in 6 patients with acalculous pain and in 5 patients with common bile duct stones (Figure 38). Frequency of phasic contractions was 8 or more per minute in 6 acalculous patients and in 2 patients with common duct stones (Figure 39). No patients with acalculous biliary pain had more than 50% retrograde contractions although this was observed in 2 patients with common bile duct stones (50% and 53%).

Response to CCK was determined in 16 patients with acalculous biliary pain. An increase in basal pressure or 'paradoxical' response was shown in 7 of the patients examined (Figure 40). When response to CCK was included only 12 (35%) of the patients in the group of patients with acalculous biliary pain showed no abnormality of sphincter manometry. One or more

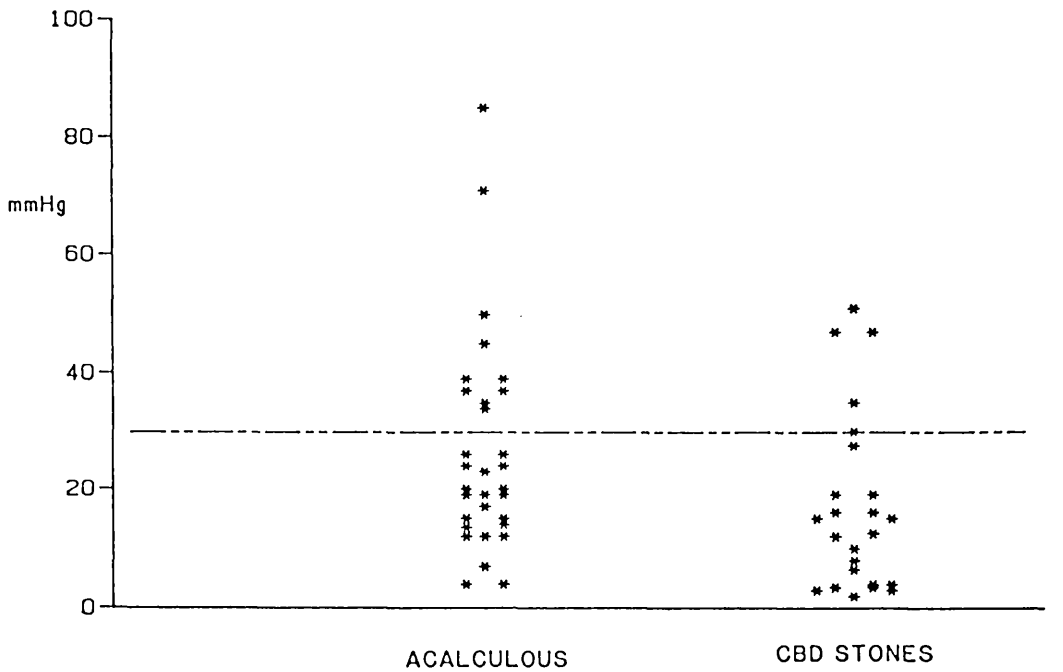


Figure 37 Mean basal pressure measurements in 34 patients with acalculous biliary pain and 28 patients with common bile duct stones. The broken line represents 30mmHg, the upper limit of normal. 10 patients with acalculous pain and 5 patients with common bile duct stones have basal pressure in excess of 30mmHg.

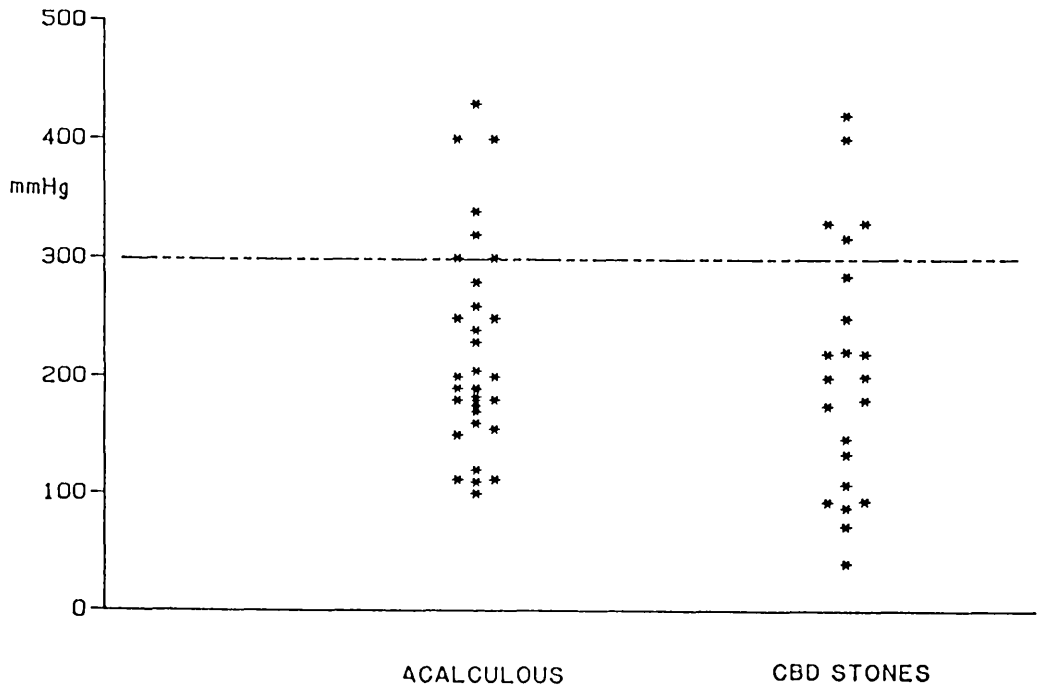


Figure 38 Peak pressure measurements in 34 patients with acalculous biliary pain and 28 patients with common bile duct stones. The broken line represents 300mmHg, the upper limit of normal. 6 patients with acalculous pain and 5 patients with common bile duct stones have peak pressure in excess of 300mmHg.

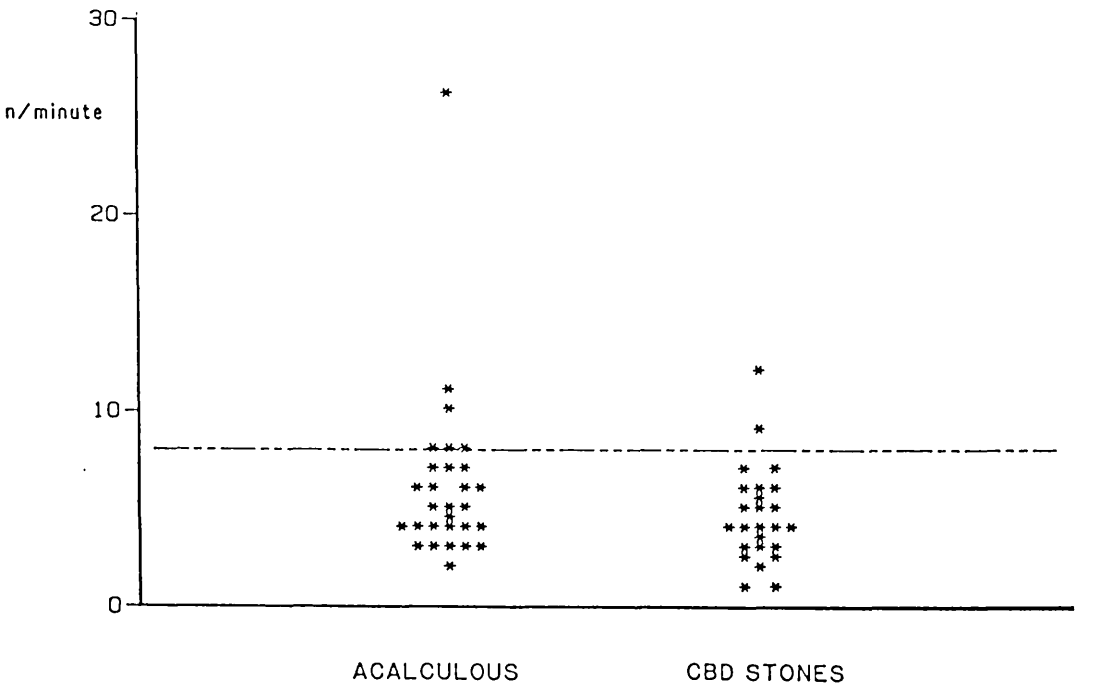


Figure 39 Frequency of phasic contractions in 30 patients with acalculous biliary pain and 25 patients with common bile duct stones. The broken line represents 8 contractions/minute the upper limit of normal. 6 patients with acalculous pain and 2 patients with common bile duct stones have peak pressure in excess of 8 contractions/minute.

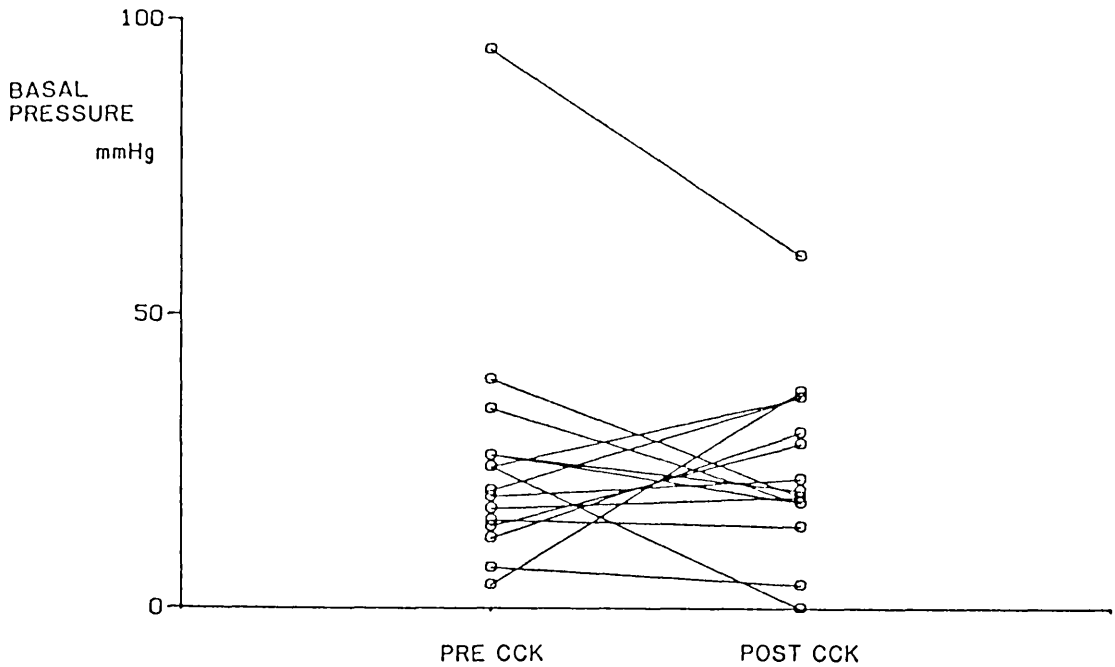


Figure 40 Response of basal pressure to CCK in 16 patients. The first value is that measured before CCK was given. The second value is the same patient measured 3 minutes later. A normal response is for pressure to fall. 7 patients with initially normal basal pressure demonstrate a 'paradoxical' rise after CCK.

variables was considered abnormal in 22 (65%) of the 34 patients with acalculous biliary pain and these abnormalities are summarised in Figure 41.

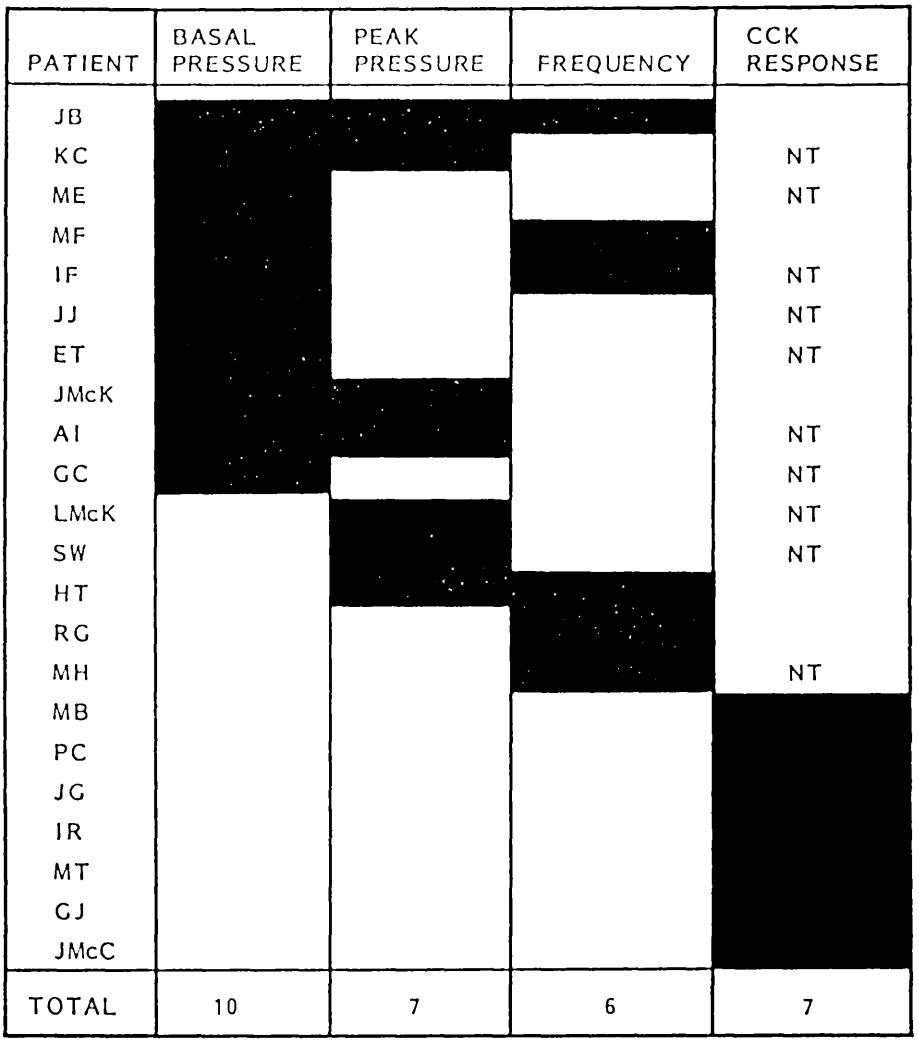


Figure 41 Summary of abnormalities in 22 of 34 patients with acalculous biliary pain. The black rectangles represent abnormal values and thw white are considered normal. Ten of these patients did not receive CCK and these are shown in the last column by the symbol 'NT". Note that the patients who had a paradoxical response to CCK had otherwise normal manometry.

DISCUSSION

PRESSURE MEASUREMENT IN THE BILIARY TREE

Recording of biliary pressure has been possible since the early part of this century [77,164]. Using a T-tube placed in the common bile duct at operation and simple manometer systems estimates have been made of common duct pressure and the secretory pressure of bile [52,186]. Distension of the common bile duct was also possible with these methods and has been shown to cause pain in some patients [53,77]. The sphincter of Oddi was recognised as a relative resistance to outflow from the bile duct at low pressures. Attempts have been made to quantify this resistance by means of a 'breakthrough' technique where pressure was steadily increased in the bile duct until flow rapidly increased [77,227]. The sensitivity of these studies to subtle changes in sphincter behaviour is doubtful and in addition insertion of a T-tube implies a surgical insult on an abnormal patient. This technique can only be performed in patients after cholecystectomy.

In dogs cholecystectomy has been noted to have marked effects on sphincter of Oddi function [163]. In particular total paresis of the sphincter may occur

leading to continuous bile drainage. There is some evidence based on T-tube studies which has suggested that sphincter function is unchanged in man after cholecystectomy but the effects of cholecystectomy on sphincter function are not known [77,226]. The aim of this study was to examine sphincter characteristics prior to cholecystectomy and therefore T-tube techniques were not applicable. Indirect measurement of sphincter of Oddi activity can be made by using an indwelling catheter placed in the common bile duct at ERCP as described by Tanaka et al [55,218]. This provides information on sphincter behaviour as it is reflected in common bile duct pressure changes and is a valuable technique in monitoring pressure patterns in the bile duct over prolonged periods and in response to repeated stimulation. It has the disadvantage that duodenal activity cannot be measured simultaneously and rapid changes in sphincter pressure will not be recorded without attenuation.

Continuous perfusion methods of pressure measurement are accurate at high flow rates and syringe driver systems have been widely used in oesophageal manometry. The flow rates required for fidelity of recording (>1ml/minute) meant that this system was of

limited use in the biliary tree [224]. Introduction of the low flow hydraulic capillary infusion apparatus initially for oesophageal manometry [217] and later for ERCP manometry [126,222] allowed for the first time practical direct measurement of sphincter activity. Using a fine catheter, pressure could be recorded from the bile duct, the pancreatic duct and the lumen of the sphincter proper, taking into account simultaneous recording of duodenal activity. The acute recording of sphincter activity over a short period, in the fasting state and with an endoscope in the duodenum has been criticised as less than physiological [228]. Torsoli and colleagues [228] have performed prolonged manometry using a triple lumen catheter passed via a T-tube and have shown that over a protracted period pressure and frequency of phasic contractions may rise beyond the normal range at times. This evidence may itself be criticised on a number of points. The patients were clearly studied after cholecystectomy and the authors themselves observed that the 'abnormalities' were not observed when the patients were fasting. All other studies including the present study has been performed in fasting patients. Consistent values have been obtained in normal and abnormal people from centres throughout the world and success has been reported

recently with treatment based on sphincter pressure abnormalities [220]. The apparatus is accurate and although invasive has not been associated with any major ill effects [223]. The procedure is performed under diazepam sedation only. Absence of buscopan or glucagon which would affect sphincter function makes cannulation of the papilla technically difficult and may account for the failure to obtain manometric readings in 15% of our patients.

SPHINCTER MOTILITY ABNORMALITIES

In this study a number of sphincter parameters have been measured in each patient. The principal abnormalities recognised are elevation of basal pressure, elevation of peak pressure and high frequency of phasic contractions [192,226]. In addition the direction of phasic wave propagation and the response to cholecystokinin may be important. Apart from the response to CCK one or more of the principal abnormalities were found in 44% of the patients with acalculous biliary pain examined using ERCP manometry. The absence of a normal range makes analysis of these findings difficult and to some extent arbitrary. By comparison experience of 28 patients with common bile duct stones and a

gallbladder in situ showed 10 (36%) with abnormal sphincter measurements. It is recognised that sphincter abnormalities occur in patients with common bile duct stones but the majority of patients studied have been examined post cholecystectomy [220,224,228]. There were no significant differences between the group of patients with acalculous pain and the patients with common bile duct stones in terms of sphincter manometry. This suggests that the abnormalities seen are a real phenomenon. The common duct stone patients were significantly older although the effect of age on sphincter function is unknown. The levels determined for abnormality i.e. $\geq$30mmHg for basal pressure, $\geq$300mmHg for peak pressure and $\geq$8/minute for frequency are not universally held and some authors might chose higher or lower values for each measurement. These values have been useful in practice and patients who have been found to have another diagnosis have had measurements within this normal range. The direction of wave propagation has not been valuable in the assessment of patients. In only about half of the patients examined could a useful statement be made about the direction of propagation. In particular retrograde activity in

excess of 50% was not observed in any of the patients with acalculous biliary pain in this study.

RESPONSE TO CCK

Cholecystokinin was not administered to patients with common bile duct stones. A rise in basal pressure or 'paradoxical' response to CCK was seen in 7 (44%) of the 16 patients with acalculous biliary pain examined. This was a high percentage and was more than might have been expected. One explanation may be that sphincter abnormalities were the source of pain in these acalculous patients and the administration of CCK reproduced this. No patients complained of pain during this particular study and this would not support this hypothesis although diazemuls sedation was used in each case. Alternatively the method of CCK administration may have induced this very abnormality. The constraints of an acute ERCP examination demanded that CCK was given rapidly as a bolus dose. It is known from work in primates that a bolus injection may lead to an increased sphincter pressure and this may occur in man [184]. Only a longer term study using bolus and infusion of CCK with prolonged manometry could resolve this question.

This study has shown that sphincter of Oddi motility abnormalities can be detected prior to cholecystectomy in patients with acalculous biliary pain. The significance of these sphincter abnormalities is open to question. Of the 34 patients in whom manometry was performed two thirds demonstrated at least one abnormality of sphincter motility. In 7 of these patients 'paradoxical' response to CCK was the only abnormality observed. It remains possible that this was iatrogenic although with the same method 9 of the 16 patients tested had a normal response to CCK. Fifteen patients had other abnormalities with elevation of basal pressure the most common. This abnormality is thought to be due to a relative denervation of the sphincter [142,190] and has been demonstrated to occur in patients with Chagas disease which is a general depletion of post ganglionic neurones [190]. Such a mechanism is the most likely cause of sphincter abnormalities. If these observed abnormalities mean that there is sphincter of Oddi dysfunction then this might provide two possible mechanisms for the patients' pain. Contraction of the gallbladder against the relatively increased resistance of the sphincter could cause distension and pain from the common bile duct [52]. Secondly 'spasm' in the sphincter itself is thought

to cause pain and this may be more likely in patients with pre-existing abnormalities. The sphincter controls the flow of bile in the biliary tree and has a large role to play in determining gallbladder volume [183,194,229]. It is of note that in those patients with diminished gallbladder ejection (<50%, Chapter 6) manometry was abnormal in 5 of the 6 patients examined with both techniques. The presence of these disorders may also account for the reported high incidence of post cholecystectomy symptoms in patients with acalculous biliary pain. It is recognised that the post cholecystectomy syndrome may be associated with sphincter of Oddi abnormalities [218,221]. By implication this would suggest that patients with evidence of sphincter dysfunction prior to cholecystectomy would be more likely to have recurrence of symptoms and cholecystectomy should be avoided. A further therapeutic implication is the possibility that endoscopic sphincterotomy, a much lesser procedure than cholecystectomy, may afford symptom relief in a number of patients with acalculous biliary pain [218,220].

CONCLUSIONS

This study has demonstrated the presence of sphincter of Oddi abnormalities in 15 (44%) of the 34 patients with acalculous biliary pain examined prior to cholecystectomy. The proportion of patients with abnormalities was similiar to that found in a non comparable group of patients with common bile duct stones before cholecystectomy. A further 7 patients with otherwise normal sphincter manometry demonstrated a 'paradoxical' response to CCK as their only abnormality.

CHAPTER 10

GENERAL DISCUSSION

DISCUSSION

Surgeons continue to be faced with patients who complain of abdominal pain in the face of negative investigations. The group of patients who complain of pain referrable to the biliary tract present a particular problem. Gallbladder surgery is common and can be performed with relatively low short and long term risk in fit patients. Historically patients with acalculous pain have not had a good outcome from cholecystectomy and in this situation operation is viewed with disfavour by the majority of gastroenterologists. Attempts have been made to clarify the indications for surgery in these patients. Some techniques have appeared to show promise but have failed to stand up to critical examination. In the absence of positive findings the diagnosis of this condition rests on the history presented and this has been examined in the present series. These studies have suggested that patients were considered to have pain of biliary origin when they had right sided abdominal pain and especially when this pain radiated to the right shoulder. It was clear that although the pain distribution described by these patients was consistent with biliary disease the pattern of pain occurence was different. Further,

patients with acalculous pain had other symptoms which were significantly less common in patients with gallstones. These were symptoms which might occur in the irritable bowel syndrome and it has been proposed that this condition can cause the symptoms reported in acalculous billiary pain [85]. This theory does not explain why patients should improve following cholecystectomy as has been reported by some workers [20,25]. Two thirds of the patients in this study did not give a convincing history of biliary disease at the extended interview conducted following referral. Duodenal ulceration and the irritable bowel syndrome were felt to be the most likely diagnoses in 29 of these 42 patients. Duodenal ulceration had been excluded however by endoscopy prior to referral and many patients had already had a trial of anti-spasmodic therapy. Using the computer classification few patients fulfilled all the criteria neccessary for these diagnoses to be reached as first choice. This may be explained by methodological problems in the calculation of diagnostic probabilities from this group of patients (Chapter 5, Appendix). It may also have been artificial to consider these patients as a single group since a number had alternative diagnoses confirmed later. Nonetheless at the time of referral

each patient was a candidate for cholecystectomy and all were believed to have the same condition based on the first clinical history. Analysis of the presenting history has confirmed that a diagnosis of biliary disease is very observer dependent. Some of the features of gallstone disease were present and this has undoubtedly suggested the diagnosis. Other features could be elicited which did not support a diagnosis of gallbladder disease. It would appear that the diagnosis of 'a biliary history' was unreliable in this study. This group of patients does not differ in any significant way from other reported series and it is clear that a potential confounder in the analysis of such studies is the heterogeneity of the subjects involved. This observation may account for previously reported poor results and suggests that some further evidence of disease should be required before surgery is offered for this condition.

It has been reported that CCK provocation will reliably identify gallbladder pathology from this group of patients [24,25,205]. The present study has shown that patients had the same outcome following cholecystectomy irrespective of the result of a CCK provocation test. This is in keeping with the

findings of other workers who have operated on both positive and negative patients [23,67,160]. The numbers and follow up in the present study are insufficient for meaningful statistical analysis between the groups. There is no doubt however that in the time period common to most reported series CCK negative patients have had a good outcome from cholecystectomy. Similiar good results have been reported in apparently unselected patients [20,21]. Others have suggested that the placebo effect plays an important role in early improvement and that long term results will deteriorate [159]. Only prolonged follow up can reveal the contribution of any placebo effect to the present results.

Early studies of gallbladder emptying using oral cholecystography, identified a number of disorders which were proposed as a mechanism for biliary pain [65,68]. More recent work has suggested that impaired gallbladder contraction indicates gallbladder disease [27,30,37]. The use of dynamic radionuclide imaging was not useful in the assesment of the present group of patients with acalculous biliary pain. This technique allowed gallbladder emptying to be quantified but the variability within the volunteer population rendered comparison of

limited value. On the data from this study there is no motility disorder specifically associated with acalculous biliary pain which is not found within normal volunteers. From this study there is no evidence to support the belief that impaired gallbladder emptying is associated with disease. The volunteer group was relatively small and the possibility of a type II error remains. The broad spread of results obtained make it unlikely that increasing the numbers of subjects will reveal a specific value which could be considered abnormal. Further work on the nature of normal gallbladder behaviour is required to clarify this point.

It has been common practice to regard the finding of chronic cholecystitis in the resected specimen as proof of gallbladder disease [7-10]. Histological examination of the gallbladders removed from the patients in the present study confirmed that the changes associated with chronic cholecystitis were present in all specimens. The finding of equivalent changes in the control group supports the view that histological changes cannot be used as evidence of current or previous disease [2,12,19]. Cholesterolosis was common in acalculous patients but not so common that it could be regarded as the sole problem in this

condition [40,205]. Cystic duct stenosis has been proposed as a possible aetiology for acalculous biliary pain [7,30]. There was no evidence that cystic duct diameter was unduly narrowed in patients with this complaint. The in vitro behaviour of gallbladder strips from acalculous patients was not the same as that of strips from gallstone patients. This finding suggested that acalculous biliary pain was not a precursor of gallstone disease [27,29]. Follow up studies to answer this question are unlikely to be performed and the natural history of acalculous pain remains unknown. Gallbladder behaviour was broadly similiar to that of strips obtained from older patients without gallstones. Whether this means that acalculous patients behaved as normal or behaved as gallbladders from older patients cannot be determined from the present study [95]. A small number of acalculous and gallstone patients appeared to have 'stronger' gallbladder muscle than the control patients but the significance of this observation is not clear with respect to acalculous disease.

The available literature has concentrated on the gallbladder as the source of pathology in patients with acalculous biliary pain. The impression which arises from the preoperative and in vitro studies is

of relatively normal gallbladder behaviour in a group of patients believed to have biliary pain. In this situation the sphincter of Oddi, as the only other contractile part of the biliary tree, must be considered as a possible source of the patients' symptoms. Studies in approximately half of the total patient group have demonstrated abnormalities in two thirds of the patients examined. Although these patients represent a highly selected group this is a higher incidence than might have been expected. Patients with apparently impaired gallbladder emptying were noted to have abnormal sphincter function although a number with 'normal' gallbladder activity also had sphincter abnormalities. The significance of these sphincter abnormalities is open to debate but they may represent biliary disease. Given the appreciable incidence of irritable bowel symptoms it remains possible that sphincter abnormalities are a manifestation of a whole gut disease process. The data available do not allow firm conlusions to be drawn about the significance of these abnormalities.

In this series of studies, examination of patients believed by consultant surgeons to have acalculous biliary disease has shown that although these

patients share many features with gallstone patients they have a number of symptoms which might arise from other disorders. The CCK provocation test has not proven of value in predicting accurately those patients who will respond to cholecystectomy. In vivo and in vitro studies of gallbladder motility have not shown any evidence of a motility disorder unique to acalculous biliary pain. Sphincter of Oddi motility abnormalities were detected in a high percentage of those patients who were examined at ERCP. These sphincter abnormalities raise the possibility of alternative diagnostic and management options in patients who present with acalculous bilairy pain.

CHAPTER 11

CONCLUSIONS

AND

FUTURE WORK

CONCLUSIONS

From a series of studies performed to evaluate patients referred to the University Department of Surgery with a diagnosis of acalculous biliary pain the following conclusions have been drawn:

1 The diagnosis of acalculous biliary disease rests on the history. In many patients the features presented are not solely those of biliary disease.

2 The distribution of pain in the majority of patients suggests biliary disease but the pattern of the pain does not.

3 The Cholecystokinin provocation test does not predict the outcome from cholecystectomy.

4 Impaired gallbladder contraction occurs in patients with acalculous biliary pain but can also be demonstrated in normal individuals and may not indicate gallbladder pathology.

5 A narrowed cystic duct lumen was not observed in the present series and is not likely to be a common cause of acalculous biliary pain.

6 Cholesterolosis was more commonly observed in patients with acalculous biliary pain but not significantly so.

7 In general gallbladder muscle from acalculous patients behaves in vitro like gallbladder muscle from older patients who do not have gallstones. Its behaviour differs from that of gallbladder muscle from patients with gallstones.

8 Sphincter of Oddi motility abnormalities were present in 65% of patients with acalculous biliary pain examined before cholecystectomy.

These studies have raised a number of questions to which the answers are not known. Further work is required to address the question of selection of patients for surgery and the nature of this condition. In particular studies on the natural history of acalculous disease would be valuable. High rates of spontaneous improvement have been reported but this was not observed in the present study. It has also been proposed that acalculous pain may lead to the development of gallstones but this remains conjecture.

The present studies have shown no motility disorder in the acalculous patients which did not occur in

normal volunteers assessed by radionuclide imaging. The accepted view that impaired emptying signifies disease is challenged by this finding and further work is required to investigate the motility of the normal gallbladder.

The presence of sphincter of Oddi motility disorders in patients prior to cholecystectomy is a significant finding. If cholecystectomy remains the treatment of choice in this condition careful follow up will reveal if those patients with sphincter abnormalities develop post cholecystectomy pain more often than those with normal sphincter function. Randomised studies are also required to determine if treatment directed at modifying sphincter function is a feasible alternative to cholecystectomy. Further development of this method raises the possibility of investigating the effect of pharmaceutical preparations or endoscopic sphincterotomy as an alternative to cholecystectomy in patients with acalculous biliary pain.

CHAPTER 12

INVESTIGATION

AND

MANAGEMENT OF

ACALCULOUS BILIARY PAIN

FUTURE MANAGEMENT OF ACALCULOUS BILIARY PAIN.

The present studies have suggested that a heterogeneous group of patients will be considered to have acalculous biliary pain. In the short term at least a number will be found to have other conditions and cholecystectomy will prove beneficial in approximately 80% of the remainder. Selection of patients for surgery remains a problem but certain aspects of the present work allow a management plan to be formulated for these patients. There is a lack of unequivocal evidence to support the prognostic ability of CCK. The withdrawal of inexpensive preparations coupled with the lack of evidence for its value leaves no place for its use as a blind provocation test in the management of patients thought to have acalculous biliary pain. Figure 42 shows a suggested flow chart which may be of value in the investigation of patients with acalculous pain. Having established from the patients' history that their pain is consistent with a biliary origin it is important to exclude positively any alternative upper gastrointestinal pathology. This is usually achieved by barium meal or endoscopy. Careful questioning regarding the symptoms associated with irritable bowel syndrome should be carried out. If a sufficient

Figure 42 Decision tree showing suggested management plan for patients presenting with acalculous biliary pain. A full explanation is given in the text.

Abbreviations used:-

US - ultrasound

OC - oral cholecystogram

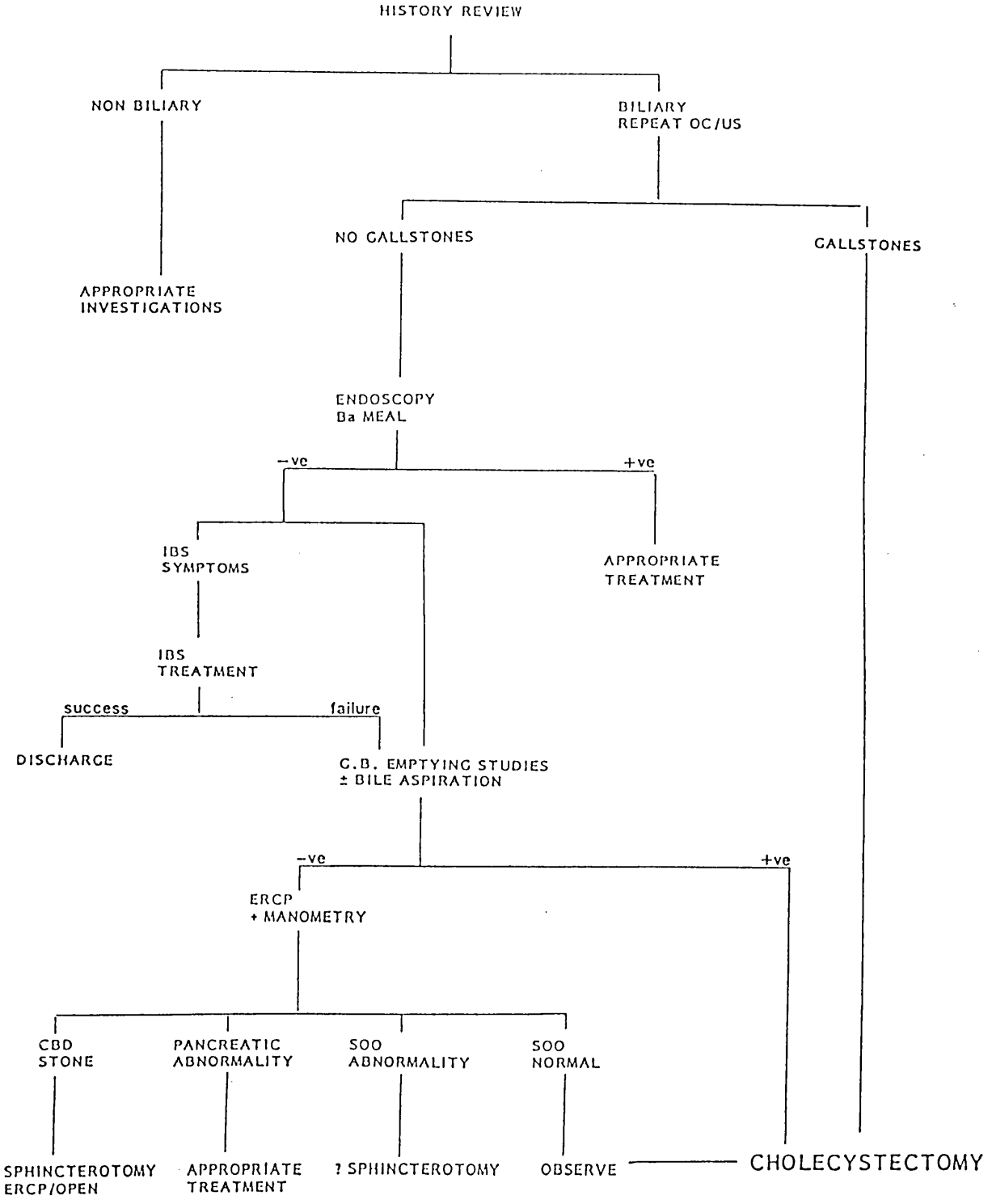
IBS - irritable bowel syndrome

GB - gallbladder

CBD - common bile duct

SOO - sphincter of Oddi

PATIENTS WITH 'BILIARY HISTORY'
NEGATIVE US/OC



number of symptoms are present a trial of appropriate diet and antispasmodics may clarify the situation and can lead to symptomatic improvement.

Only dynamic tests of gallbladder function can demonstrate the existence of gallbladder motility disorders and these relatively non invasive procedures (ultrasound or DISIDA scanning during gallbladder contraction) should be performed next. If CCK is used to contract the gallbladder it must be given by low dose infusion or intramuscular injection. Rapid bolus injections can undoubtedly cause spasm and abnormal contraction even in normal gallbladders and could result in falsely positive results. In the present series radionuclide imaging was of little value in differentiating patients with acalculous biliary pain but persistently poor gallbladder function in the presence of appropriate symptoms may still be a relative indication for cholecystectomy. Abnormalities found on examination of bile aspirated from the duodenum following gallbladder contraction may be useful although we have no practical experience of such techniques. The absence of such abnormalities however cannot exclude a biliary disorder.

There is evidence that sphincter of Oddi motility disorders can lead to biliary pain and these abnormalities have been identified previously in post cholecystectomy patients. The present studies have shown for the first time their existence in some patients with acalculous biliary pain prior to cholecystectomy. When gallbladder contraction is shown to be normal the patient must be considered for ERCP to exclude common bile duct and pancreatic pathology and to assess sphincter of Oddi function. The presence of a sphincter motility disturbance must be excluded prior to cholecystectomy as loss of the biliary reservoir may only exacerbate the situation.

A small number of patients may remain undiagnosed following these investigations. Laparotomy remains the final court of appeal in this situation. We know that laparotomy is a blunt diagnostic instrument for detecting occult disease and surgery should not be undertaken lightly. Having gone to surgery few surgeons will not perform cholecystectomy and few pathologists will not support a diagnosis of mild chronic cholecystitis. The placebo effect of cholecystectomy must not be underestimated in examining reports of this condition. It is likely that favourable short term results will deteriorate

with longer follow up. Acalculous biliary pain remains a real clinical problem with many potential causes. The precise nature of this condition remains unknown although it is clear that cholecystectomy is not always the best treatment. Careful planned investigation will allow the various disorders which can present under this banner diagnosis to be identified. Intervention should in general only be considered in the presence of some positive indication.

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APPENDIX

PREDICTION OF DIAGNOSIS

FROM FEATURES PRESENT

IN THE HISTORY

GLASGOW DYSPEPSIA PREDICTIVE ANALYSIS

It is recognised that certain conditions are associated more or less commonly with specific symptoms or features in a patient's history. For example radiation of right hypochondrial pain to the shoulder is common in patients with gallbladder disease but is usually absent in other gastrointestinal diseases. Consequently when a patient presents such a symptom the diagnosis of gallbladder disease becomes more likely as other diagnoses become less likely. When several specific symptoms combine together, one diagnosis may be considerably more likely than those which are not associated with this symptom complex. Most clinicians reach a diagnosis in this or a similiar manner. It is possible to assign a predictive value for the presence of each symptom or feature towards a particular diagnosis. In the same way it is possible to use the absence of a symptom against a particular diagnosis. Where a symptom is not associated with a particular condition its presence can also count against that diagnosis. The predictive value assigned to a symptom is known as the weight of evidence. The weight of evidence for any symptom is related to the frequency with which it occurs in association with a

particular diagnosis. This frequency can only be calculated from examination of the history in a group of patients who have that diagnosis. This work was carried out on patients attending the Southern General Hospital, Glasgow and has been reported previously [196]. Clinical interviews were carried out in 1200 patients and about 150 symptoms were sought during each interview. Patients were carefully followed up and were assigned to disease groups as 'certain', 'probable' and 'possible' depending on the results of investigations. Allowing for patient exclusions there were 57 patients who had gallstones diagnosed radiologically and confirmed at surgery and 1119 patients with other disorders who did not have gallstones radiologically. Examination of all the symptoms and features elicited showed that a number of variables discriminated between the two states and these have been discussed in detail in Chapter 5 (Table 5). The weight of evidence can be expressed as a ratio of two well known terms namely sensitivity (the proportion of diseased patients with a positive feature) and specificity (the proportion of non diseased patients without the feature).

Attacks of pain were common in the patients with gallstones and were defined as having a clear onset

and offset and lasting between 15 minutes and several hours. Attacks of pain occured in:-

49/57	gallstone patients
101/1119	non gallstone patients

This gives a **Sensitivity** = 0.86

Specificity = 0.91

Weight of evidence = 100ln (Sensitivity/1-Specificity)

= 100ln (0.86/0.09)

= +225

Therefore if a patient had attacks of pain the weight of evidence adds 225 towards a diagnosis of gallstones. The weight of evidence may also have a negative value. For example age is important in the development of gallstones and patients are more likely to be more than 25 years old. For a patient less than 25 years old the weight of evidence for that feature towards a diagnosis of gallstones is -151. The weight of evidence forms the basis for a score for each symptom in relation to a particular diagnosis. The scores can be summed to give a total and this can be converted to a probability that a particular disease is present based on the formula

$$p(D) = [1 + \exp(-T/100)]^{-1}$$

where p(D) is the probability of disease and T the total score. The final total score is greatly dependent on the specificity and sensitivity of each feature examined but also depends on the prevalence of the disease within the community from which the patient comes. The calculations therefore include a starting score which takes this into account. In the case of gallstones this was about 5% of the total giving a prior probability of p=0.05 which approximates to a starting score of -300. The starting score will vary for each disease studied and will be unique to the population from which the patient comes. The GLADYS computer program extracts the features from the patients and calculates the weight of evidence and a total score for each of its recognised diagnoses. This allows a list of diagnoses to be printed with their respective predicted probabilities (Chapter 4, Figure 9). A full and detailed explanation of the theory behind the prediction of diagnoses can be found in the report of Spiegelhalter and Knill-Jones to the Royal Statistical Society in 1984 [201].