THE NATURAL HISTORY AND MANAGEMENT OF PATIENTS WITH PANCREATIC PSEUDOCYSTS AS A COMPLICATION OF ACUTE PANCREATITIS.

THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF MEDICINE.

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PREFACE

PREFACE

The research detailed in this thesis was undertaken during the time I worked as research and clinical registrar for Mr. C.W. Imrie at Glasgow Royal Infirmary.

The writing, illustration and typing of this thesis has been entirely my own work.

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Finally, without the support and constant encouragement from my wife I would not have been able to complete this work.

SUMMARY

In this thesis I have studied the natural course, outcome and management of patients who developed a pancreatic pseudocyst following an episode of acute pancreatitis. The clinical information for this work originated in 2 studies involving a total of 129 patients with a pseudocyst. This represents one of the largest reports of such patients in medical literature.

One study was of 100 patients with a pseudocyst presenting to Glasgow Royal Infirmary, over a period of 23 years (1962 - 1984) (Chapter 3)(Imrie et al 1988. Appendix 1). The second study was of 29 similar patients (Chapter 4) documented during a prospective trial of therapeutic peritoneal lavage in patients with severe acute pancreatitis recorded in Leeds, Bristol and Glasgow (1982 - 1984) (Corfield et al 1985, Mayer et al 1985. Appendix 1).

Using the information derived from these studies, I have formulated an assessment system for predicting the likelihood of spontaneous resolution of a pseudocyst (Chapter 8). With the addition of results obtained from an analysis of percutaneous needle aspiration (Chapter 6) and analysis of acute phase reactant proteins within pseudocyst fluid (Chapter 7) I propose a new plan of management for patients with acute pancreatic pseudocysts.

The important findings of this thesis are summarised as follows:-

1. **The "waiting time" for conservative management of a pancreatic pseudocyst could safely be extended to 12 weeks.**

Bradley et al (1979) have suggested that a period of 6 weeks from the time of pseudocyst formation should be regarded as both the maximum time to wait for spontaneous resolution of a pseudocyst and the optimum time to consider some form of drainage procedure. A pseudocyst was drained surgically in 78 (%) of the 100 patients from Glasgow Royal Infirmary and resolved spontaneously in the other 22 (%). The median time from diagnosis to drainage by cystogastrostomy was 12 weeks (range 2 - 69 weeks). The median time to complete spontaneous resolution was also 12 weeks (range 2 - 104 weeks). Of the 29 patients from Leeds, Bristol and Glasgow surgical drainage was performed in 11 (38%) at a median time of 7 weeks (range 3 - 38 weeks) and spontaneous resolution occurred in 15 (52%) at a median time of 7 weeks (range 2 - 20 weeks).

Bradley et al (1979) also found an increasing proportion of patients developed complications the greater the time a pseudocyst was left untreated. Only 6 (5%) of all 129 patients studied suffered complications as a result of an undrained pseudocyst.

Based on the above results I suggest that 6 weeks is too short a period and 12 weeks is a more appropriate time to wait for spontaneous resolution to occur provided the patient is repeatedly assessed by clinical examination and ultrasound scanning to confirm that the diameter of the pseudocyst is not increasing and that the clinical state of the patient is not deteriorating.

2. No single factor causing acute pancreatitis predisposes to pseudocyst formation.

Of the 100 patients from Glasgow Royal Infirmary alcohol was the cause of acute pancreatitis in 59%, gallstones in 27% and the aetiology was idiopathic in 9%. In contrast, of the 29 patients from Leeds, Bristol and Glasgow alcohol was the aetiological factor in 23%, gallstones in 48% and it was idiopathic in 23%. This distribution was very similar to that of a total of 418 patients with acute pancreatitis studied in the three cities (Chapter 4)(gallstones 54%: alcohol 20%: idiopathic 21%). This suggests that no single aetiological factor of acute pancreatitis is more likely to cause pseudocyst formation.

3. The aetiology of the preceding acute pancreatitis is an important factor in determining the outcome of patients with a pseudocyst.

The mortality amongst patients from Glasgow Royal Infirmary with gallstone induced pancreatitis and pseudocyst formation was 22%, significantly greater than that of patients with alcohol induced disease (5% mortality). The majority of patients who died as a result of gallstone induced disease did so because of sepsis and/or haemorrhage. The implication from this is that, if possible, in order to decrease the possibility of infection, the biliary tract should be cleared of stones at the time of definitive pseudocyst surgery.

4. Spontaneous resolution of a pseudocyst can be predicted using a multi-factor assessment system.

A pseudocyst resolved spontaneously in 22 (%) of the 100 Glasgow Royal Infirmary patients and 15 (52%) of those from Leeds, Bristol and Glasgow. Differences in clinical, laboratory and radiological findings in these patients were compared with those of patients whose pseudocyst needed drainage. The proportion of patients with a palpable abdominal mass was significantly greater in those who required surgery in both groups of patients. The results for the patients from Leeds, Bristol and Glasgow also showed a significantly higher proportion with abdominal distension and a leukocytosis ($>10 \times 10^9$ cells/l) amongst those who underwent surgery.

A pseudocyst diameter of 6cm was found to provide a valuable discriminating level between those pseudocysts resolving spontaneously and those requiring drainage. Only 1 of 7 (14%) pseudocysts (Leeds, Bristol, Glasgow patients) with a diameter greater than 6cm resolved spontaneously compared to 9 of 11 (82%) with a size of 6cm or less.

The features noted above have been incorporated into a 5 factor scoring system for predicting the outcome of a pancreatic pseudocyst. The 5 criteria are:-

1) a maximum pseudocyst diameter of greater than 6cm
2) a serum amylase at the time of pseudocyst diagnosis of 450 IU/l or greater
3) a leukocytosis of 12×10^9 cells/l or greater
4) the presence of an abdominal mass
5) the presence of abdominal distension.

If 3 or more of these criteria are positive then spontaneous resolution is unlikely. When this scoring system is applied to the results from Leeds, Bristol and Glasgow, 12 of the 15 patients whose pseudocyst resolved had less than 3 criteria positive (80% sensitivity) and 10 of 11 patients whose pseudocyst was drained had 3 or more positive (92% specificity).

It had been hoped that analysis of acute phase proteins within pseudocyst fluid (Chapter 7) would have provided a useful marker in addition to the criteria noted above but this was not the case.

5. A new plan of management for patients with a pancreatic pseudocyst is proposed.

Having developed a method for assessing outcome I considered the place of percutaneous needle aspiration and catheter drainage in the management of patients with a pseudocyst.

Percutaneous needle aspiration was successful in only 6 (29%) of 21 patients studied. The use of percutaneously placed long term catheters is more successful (Chapter 6) and there is a limited place for this type of treatment in selected patients.

I propose that the management for patients who form a pseudocyst because of acute pancreatitis (Chapter 8) should now include:-

1) assessment of outcome by multifactor scoring system.

2) repeated assessment of the patient with clinical examination, ultrasonic scanning and estimation of C reactive protein for at least 12 weeks from the time of pseudocyst diagnosis providing that the general condition of the patient is not deteriorating and the size of the collection is not increasing.

3) consideration of percutaneous catheter drainage if the diameter of the pseudocyst is not decreasing. This may help to prevent late complications e.g. rupture and haemorrhage.

CHAPTER 1

INTRODUCTION

The principle aims of this thesis are directed towards:-

1) establishing the natural history of patients developing pseudocysts as a complication of pancreatitis. In particular, it considers whether the maxims of "6 weeks" and "6 centimetres" relating to the critical "age" and size of a pseudocyst are valid parameters for determining the necessity and timing of some form of intervention to drain a pseudocyst.

2) determining important and significant differences in the clinical course of patients in whom a pseudocyst resolved spontaneously as compared with those in whom a pseudocyst required surgical drainage. The information from this part of the thesis was used to formulate a set of criteria into a system for predicting the outcome in patients who develop a pseudocyst after an episode of acute pancreatitis.

3) assessing the place of percutaneous aspiration in the management and treatment of pancreatic pseudocysts.

4) evaluating analysis of acute phase reactants in pseudocyst fluid with a view to finding a factor for predicting outcome.

DEFINITION OF PANCREATITIS

Since 1963 there have been three meetings of international experts with a particular interest in the pancreas specifically convened to establish a practical, international classification of acute and chronic pancreatitis. The meetings took place Marseilles in 1963 (Sarles 1965) and 1984 (Singer et al 1985), and in Cambridge in 1983 (Sarner and Cotton 1984). The definition finally produced from the most recent Marseilles meeting is as follows:- "Clinically, acute pancreatitis is characterised by acute abdominal pain accompanied by increased pancreatic enzymes in blood or urine, or both. Though it usually runs a benign course, severe attacks may lead to shock with renal and pulmonary insufficiency that may prove fatal. Acute pancreatitis may be a single episode or it may recur.

Morphologically, there is a gradation of lesions seen in acute pancreatitis. In the mild form, peripancreatic fat necrosis and interstitial oedema can be recognised, but as a rule pancreatic necrosis is absent. The mild form may develop into a severe form with extensive peripancreatic and intrapancreatic fat necrosis, parenchymal necrosis and haemorrhage. The lesions may be either localised or diffuse. Occasionally, there may be little correlation between the severity of the clinical features and the morphologic findings." (Singer et al 1985)

This definition has been quoted in full because it was an attempt to encompass both clinical and pathological aspects of the disease. However, it made no mention of specific complications relating to acute or chronic pancreatitis. There was no specific definition for pseudocysts, pancreatic abscess or infected pancreatic necrosis and unfortunately, the repeated defining of a condition often only serves to add to the confusion particularly when discussing patients with these complications.

There is, as yet, no reliable method of determining which patients will develop pseudocysts and, in consequence, no effective prophylactic therapy.

There have been very few prospective studies concentrating on patients who develop a pseudocyst following an episode of acute pancreatitis. The present work is an attempt to remedy this situation.

HISTORICAL BACKGROUND

Introduction

Morgagni (1761) is quoted by Judd et al (1931) as being the first observer to describe a cystic lesion of the pancreas in a cadaver. Claessen (1842) reviewed several reports of pseudocysts from the existing literature and Friedrich (1875) wrote the first major review on the subject. By that time, the pathology of the disease had been described in detail, and the term pseudocyst was employed because of the fibrous wall and lack of an epithelial lining around the cavity.

Between 1888 and 1910 numerous individual reports of patients with a pseudocyst were published and further reviews of the condition were written by Korte (1898), Lazarus (1904) and Oser (1903).

Most of the literature addressed the problems of the anatomical and pathological detail of pseudocysts. The association between such collections and acute pancreatitis was recognised by these early authors.

Opie (1903) suggested that pseudocysts formed as a result of rupture of a small branch of the pancreatic duct system allowing leakage of the exocrine secretions into the surrounding tissue and subsequent activation of pancreatic enzymes. He postulated that this produced necrosis and inflammation within the lesser peritoneal sac and around the pancreas. This hypothesis, suggesting a direct communication between duct and pseudocyst, was not readily accepted because of failure to confirm a fistula in many of the early specimens.

PANCREATIC PSEUDOCYSTS AS A CONSEQUENCE OF PANCREATITIS

Definition of a pseudocyst

A pancreatic pseudocyst is defined as:-

> a localised fluid collection of pancreatic origin in, or around the pancreas confined by a fibrous lining devoid of an epithelium. As a result of the inflammatory reaction of pancreatitis, especially following acute pancreatitis, there is frequently rupture of a pancreatic duct leading to a persistent communication between the duct system and the collection. The fluid is therefore rich in pancreatic enzymes.

On histological examination a pseudocyst has a wall of fibrous granulation tissue with fibroblasts and chronic inflammatory cells surrounding a fluid filled cavity (Figure 1). In order to confirm completely that a fluid collection forming around the pancreas following acute pancreatitis is a true pseudocyst it would be necessary to analyse the fluid, demonstrate a fistula between a pancreatic duct and the collection, and biopsy the wall to demonstrate the fibrous tissue. Such complete analysis can occasionally be achieved, particularly in patients who ultimately undergo surgery but is inappropriate in patients in whom a collection resolves spontaneously.

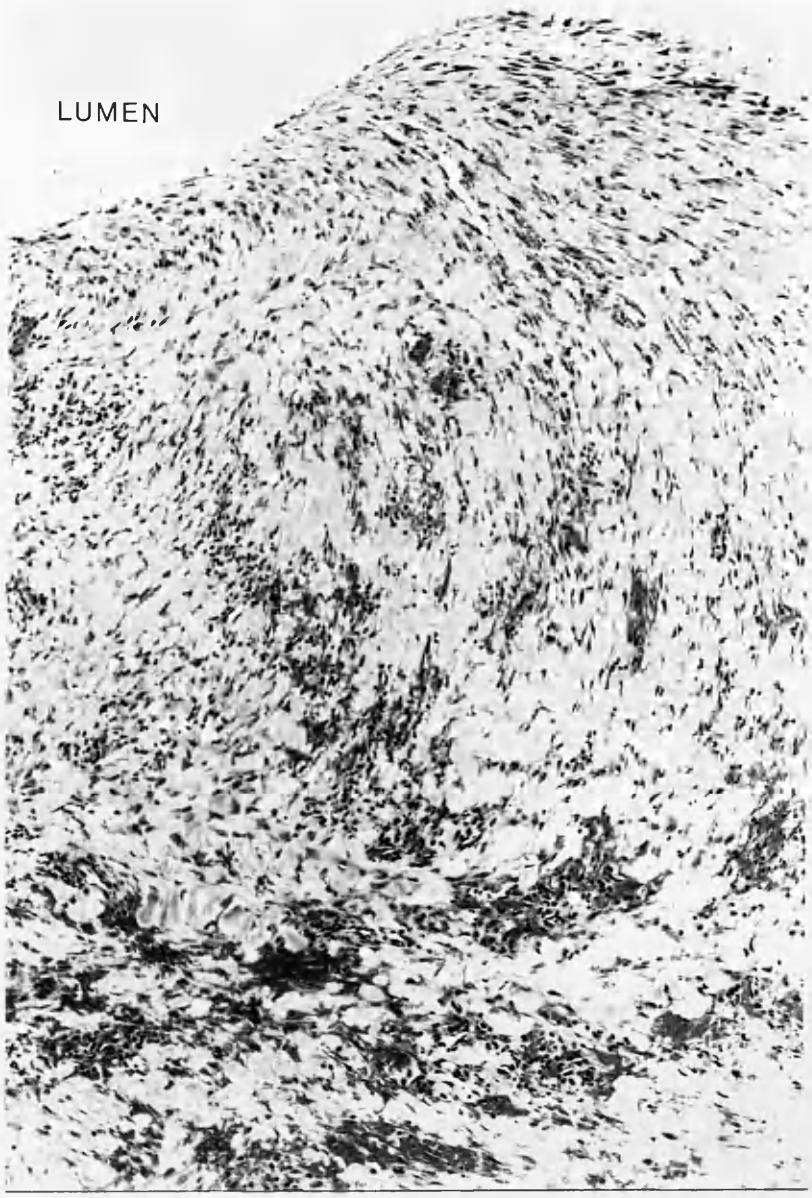


FIGURE 1 Histology of pseudocyst wall showing dense fibrous tissue devoid of an epithelial lining.

Lumen marked. The tissue bordering the pseudocyst consists of fibrosing granulation tissue.

Haemotoxylin and eosin x100

With the development of contrast radiography and techniques of performing pancreatograms during surgery, a communication between the duct system and a pseudocyst cavity has been reported in 70% of patients with pseudocysts (Kaiser et al 1964). Following the introduction of pancreatograms performed via an endoscope, these findings have been confirmed (Silvis et al 1974) and it is clear that Opie's (1903) hypothesis has been substantiated (Frey et al 1988).

Experimental Studies

There are only 7 reports of experimental attempts at producing pancreatic pseudocysts. The most frequently quoted has been the work of Warren et al (1957). Using dogs, these authors inserted a sponge filled plastic bag into the lesser peritoneal sac in order to create a cavity lined with fibrous, granulation tissue. Four to 6 weeks later a second operation was performed to transpose the transected end of the pancreatic duct into the cavity in order to fill it with pancreatic juice. When the second stage of this experiment was performed the majority (66%) of the animals had died. In the remaining dogs the authors noted that the pseudocyst wall was lined with granulation and fibrous tissue similar to the histological changes found in the human. There was no record of sequential studies of the development of the wall but based on histological appearances at 4-6 weeks it was regarded that the fibrous tissue was mature.

Following this work and based on clinical experience, it was deduced that a period of 6 weeks was sufficient time to allow mature pseudocyst wall fibrosis to occur in humans (Bradley et al 1976; Cerilli and Faris 1967; Ephgrave 1986).

Prior to 1957 only three attempts at creating pseudocysts had been documented and none was particularly successful (Lazarus 1903: Senn 1886; Thiroloix 1903). Subsequently there have been three other experimental studies. Karlan et al (1958) implanted the distal transected pancreas into an omental sac but this caused atrophy of the pancreas and only small pseudocysts formed. Rosello and Novoa (1978) used a similar first stage to Warren and then, like Karlan, implanted the distal pancreas into this cavity. Again the distal portion degenerated and failed to produce pancreatic secretion.

More recently Salinas et al (1985), has further modified the Warren technique. The cavity was created as formerly and 6 weeks later the pancreatic duct was transected and both ends implanted into the cavity. These authors subsequently administered secretin intravenously in order to stimulate enzyme production from the pancreas. In three animals they also partially ligated the pancreatic duct. A cavity developed in all animals but only those with the ligated ducts produced a fluid filled pseudocyst.

These authors suggested that an obstructive element may be critical in the development of a pseudocyst in humans. These aforementioned, complex experimental studies are not strictly analogous to the human clinical situation (Kane and Krejs 1984) and no experimental model developed to date has been able to demonstrate sequential formation of a pancreatic pseudocyst

After consideration and discussion with several authorities viz: my supervisor, Mr C W Imrie, Dr A Foulis, Pathologist with a special interest in the pancreas; Professor E Bradley, Atlanta, U.S.A., Professor D Carter, Glasgow, it was decided that none of the previously described experimental models of pancreatic pseudocyst adequately reflected the situation in humans and no new model could be envisaged. Therefore, considering the advice given, no attempt was made to create such a model.

Pathogenesis

The factors involved in the pathogenesis of pseudocysts have been deduced from consideration of the available evidence. The pathological features necessary for the production of a pseudocyst are (Figure 2):

1) pancreatic duct rupture, either as a result of pancreatitis or trauma (Erb and Grime 1960; Kane and Krejs 1984; Opie 1903)

2) continued secretory function of at least part of the gland (Elliot 1975; Winship et al 1977).

3) obstruction, partial or complete, of normal pancreatic duct drainage (Bradley 1982; Doubilet and Mulholland 1953)

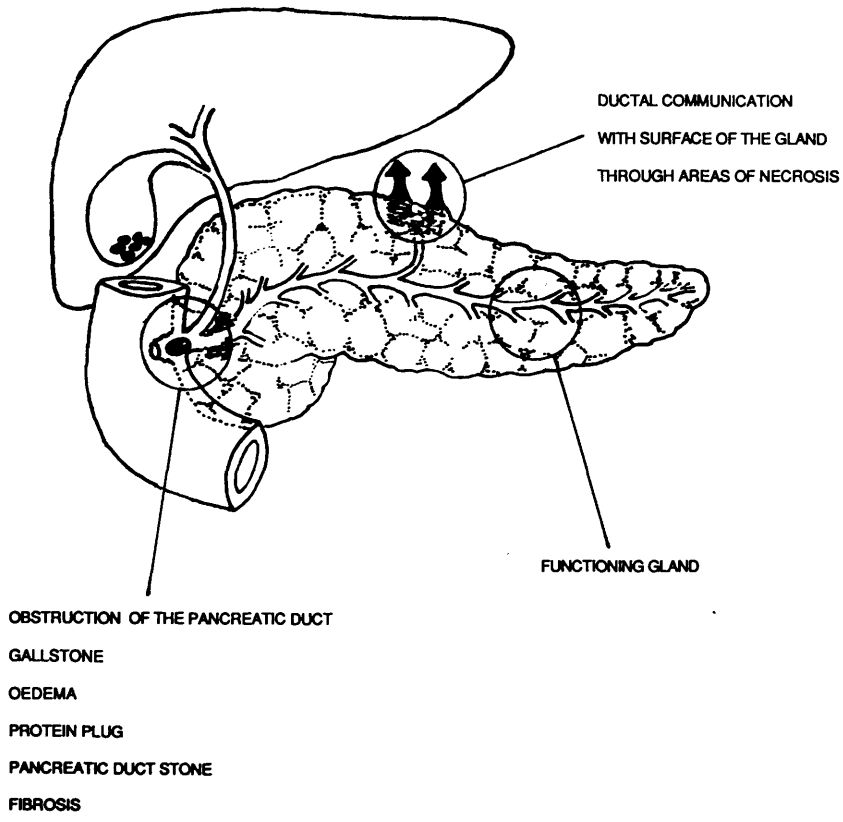


FIGURE 2 Illustration of factors necessary for the formation of a pancreatic pseudocyst.

The duct obstruction occurring in a pseudocyst which develops as a result of chronic pancreatitis may be caused by protein plugs, pancreatic stones or fibrosis (Sarles et al 1965), whereas the obstruction in those forming after acute pancreatitis most likely results from oedema around the proximal pancreatic duct or the presence of a gallstone impacted just proximal to the ampulla of Vater (Acosta and Ledesma 1974). Other less common causes of duct obstruction, for example carcinoma, can also cause pancreatitis.

The most common site for a pancreatic pseudocyst is within the lesser peritoneal sac, and for a collection to be contained within this space the entrance to the sac (the foramen of Winslow) has to be temporarily occluded (Bradley and Klein 1956).

The size to which a pseudocyst will develop is, in part, determined by the duration of obstruction to normal duct drainage. It has been postulated that a pseudocyst will increase in size until the pressure exerted by the surrounding tissues exceeds that of the secretory pressure within the pancreatic duct (White and Bourde 1970).

The fluid within a pseudocyst has a high protein content and, once localised, further tissue fluid is attracted into the cyst by osmosis (Elliot 1975), resulting in further expansion of the collection. Once released, the activated pancreatic juice stimulates a considerable tissue reaction leading to the formation of fibrous, granulation tissue.

Diagnosis

The diagnosis of a pseudocyst must be based on a combination of clinical, biochemical and imaging information but early studies relied solely on clinical evidence with the presence of an abdominal mass being paramount. Judd et al (1931) reported the Mayo clinic experience of 44 patients with pseudocysts. The authors noted a high incidence of abdominal pain, a palpable mass and persistent nausea and vomiting following an episode of acute pancreatitis as being the most important clinical features. The majority of the pseudocysts which these authors reported were of considerable size. At the time of their review, serum amylase estimation was not generally available despite being introduced as a diagnostic test for pancreatitis in 1927 (Elman and McCaugham 1927). Pinkham (1945) noted that a sustained elevation of serum amylase following acute pancreatitis was suggestive of a pseudocyst. An elevated level of the enzyme is a useful indicator and is still the mainstay of biochemical diagnosis.

In a review of 12 studies, the incidence of a raised serum amylase in patients with proven pseudocysts varies from 11-100% (Median value 70%). (Becker et al 1968; Brilhart and Priestley 1951; Caravati et al 1966; Folk and Freeark 1970; Frey 1978; Gonzalez et al 1976; Grace and Jordan 1976; Kaiser et al 1964; Sankaran and Walt 1975; Scharplatz and White 1972; Thomford and Jesseph 1969; Tucker and Webster 1972). At present there are no other specific biochemical markers for pseudocysts.

Perhaps the most significant advance in establishing a positive diagnosis of a pancreatic pseudocyst in the past 20 years has been the use of ultrasonic scanning of the pancreas (Filly and Freimanis 1970). Prior to this, a barium meal with lateral erect views to demonstrate displacement of the stomach or duodenum by the pseudocyst, was the most sensitive radiological investigation (Figure 3). A diagnosis was only possible in those collections which were of sufficient size to distort the stomach or duodenum and it was not until ultrasonic scanning was introduced, that pseudocysts were more readily identified and their natural course revealed.

Filly and Freimanis (1970) reported the ultrasonic characteristics of various pancreatic diseases, but the first important study specifically related to cystic collections was performed by Bradley and Clements (1974). They provided a detailed analysis of the ultrasonic appearances and characteristics of pseudocysts. Since this report, technical improvements in ultrasonic equipment have resulted in improved definition and it has become possible to characterise the natural history of pseudocysts particularly when these are associated with acute pancreatitis (Bradley 1982).

Bradley et al (1976) established that fluid collections in the vicinity of the pancreas following acute pancreatitis were more common than had been previously imagined.

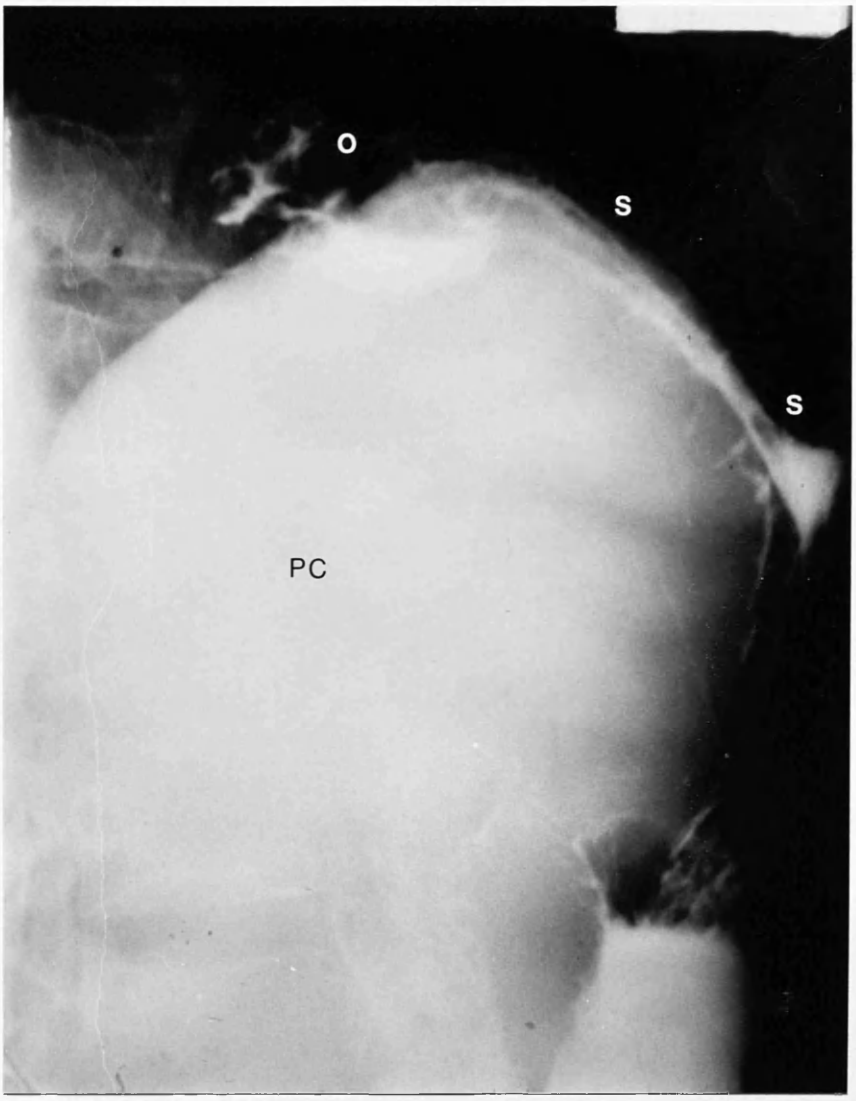


FIGURE 3

Radiograph of a lateral erect view of a barium meal in a patient with a large pseudocyst.

The stomach and oesophago-gastric junction are displaced anteriorly by the pseudocyst.

PC = pseudocyst
O = oesophagus
S = stomach

Some of these collections represented local loculi of peritoneal exudate released from the damaged gland but such collections frequently resolved spontaneously within 2 to 3 weeks of the episode of acute pancreatitis. These authors also demonstrated that a proportion of the collections which they assessed as true pseudocysts resolved spontaneously. This observation resulted in a considered reappraisal of pseudocyst management and led to a policy of continued conservative observation being advocated (Czaja et al 1975; Duncan et al 1976; Pollak et al 1978). The ability to repeatedly monitor the size of collections is of paramount importance in adopting such a management policy and clearly, would not have been possible without the advent of ultrasonic techniques.

Technical improvements in ultrasonic machines have led to improved definition of the images such that a pseudocyst and the surrounding tissues can be clearly identified (Figure 4).

In more recent years computerised tomography (CT scanning) has also been used to delineate pancreatic morphology and is now being used with increasing frequency in patients with pancreatitis (Hill et al 1982; Siegelman et al 1980). High resolution scanners and contrast enhanced dynamic scanning have increased the diagnostic capabilities of these techniques (Figure 5). Both ultrasound and CT scanners are now capable of defining the thickness of the wall of a pseudocyst and, with the appropriate appearances of a fluid collection surround by a thick wall, are frequently regarded as sufficient to substantiate the diagnosis.

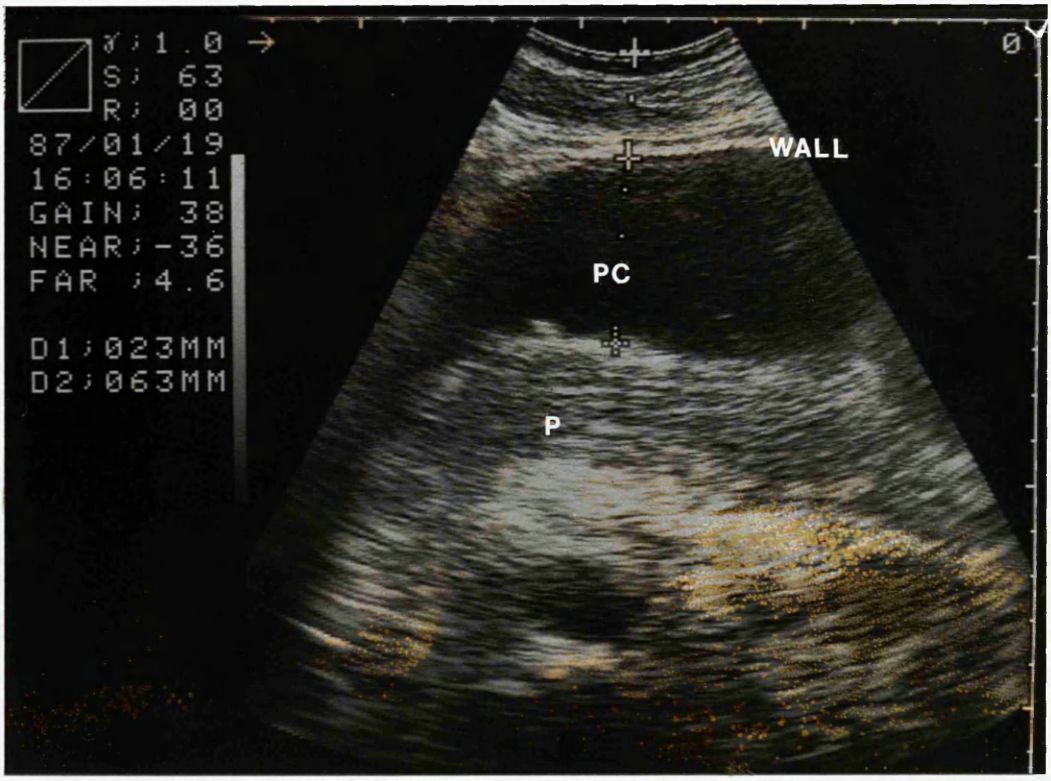


FIGURE 4 Ultrasound scan of a large pseudocyst showing a large fluid filled cavity overlying the pancreas.

PC = echolucent fluid filled cavity
WALL = echo dense wall of pseudocyst
P = pancreas

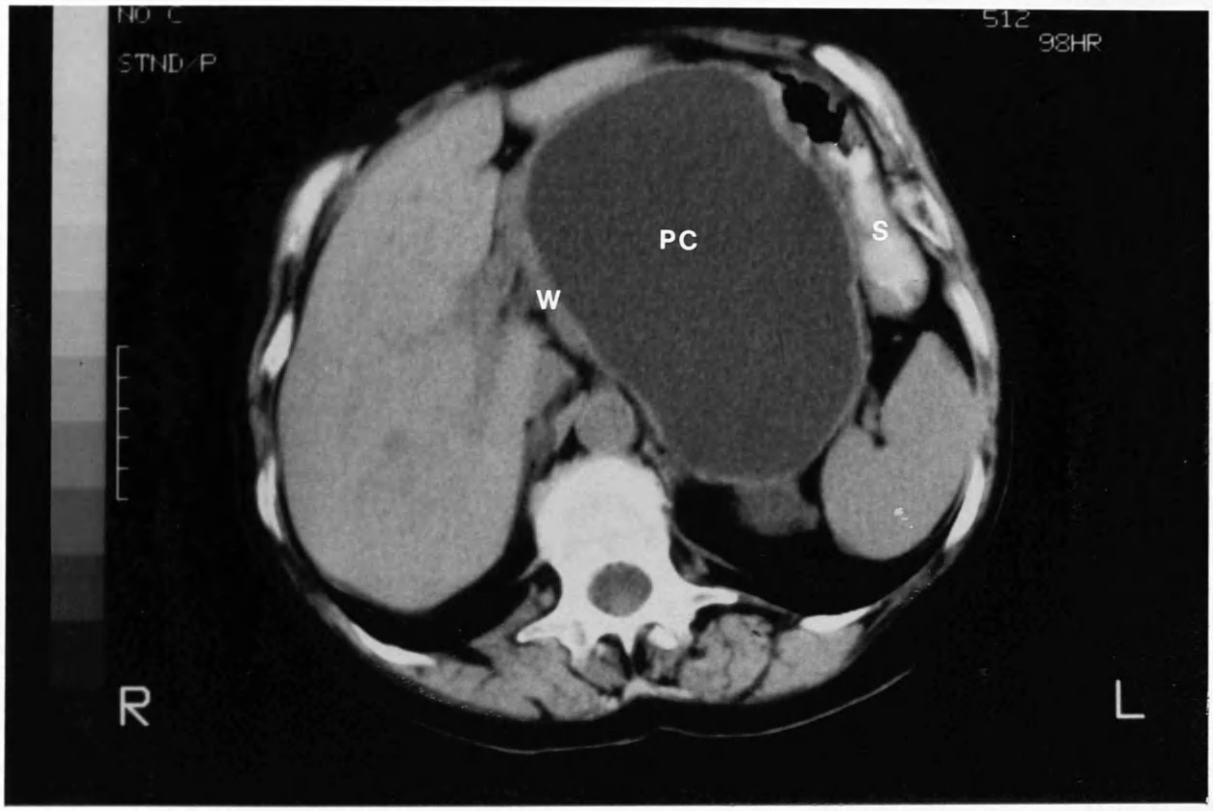


FIGURE 5 Computerised tomographic scan of large pseudocyst.

The uniform density of the fluid within the pseudocyst and the thick surrounding wall are both clearly demonstrated.

PC = pseudocyst
WALL = thick fibrous wall
S = stomach compressed by pseudocyst

The other important diagnostic technique which has been employed is endoscopic retrograde pancreatography. This permits assessment of the pancreatic ducts and can confirm the presence of a fistula from the ducts into the collection (Figure 6). This technique is clearly more invasive than ultrasound or CT scanning and can introduce infection into a previously sterile collection.

Aetiology

A pseudocyst can develop in any patient suffering from acute or chronic pancreatitis irrespective of the aetiology of the acute pancreatitis. The majority of studies relating to pseudocysts have comprised patients with alcohol induced pancreatitis. A review of retrospective reports of pseudocysts covering the period from 1921 until 1982 encompasses 1124 patients of whom 66% had alcohol induced pancreatitis; 13% gallstone associated disease; 11% developed pseudocysts following trauma ; in 7% the aetiology remained unknown and the remaining 3% had miscellaneous causes for their disease. (Anderson 1972; Aranha et al 1983; Becker et al 1968; Bradley et al 1976; Caravati et al 1966; Crass and Way 1981; Erb and Grimes 1960; Folk and Freeark 1970; Frey 1978; Gonzalez et al 1976; Grace and Jordan 1976; Hastings et al 1975; Judd et al 1931; Kaiser et al 1964; McConnell et al 1982; Sankaran and Walt 1975; Scharplatz and White 1972; Thomford and Jesseph 1969; Tucker and Webster 1972). Many of these studies emanated from areas where alcohol was the predominant cause of pancreatitis and the results were undoubtedly biased towards this aetiology.

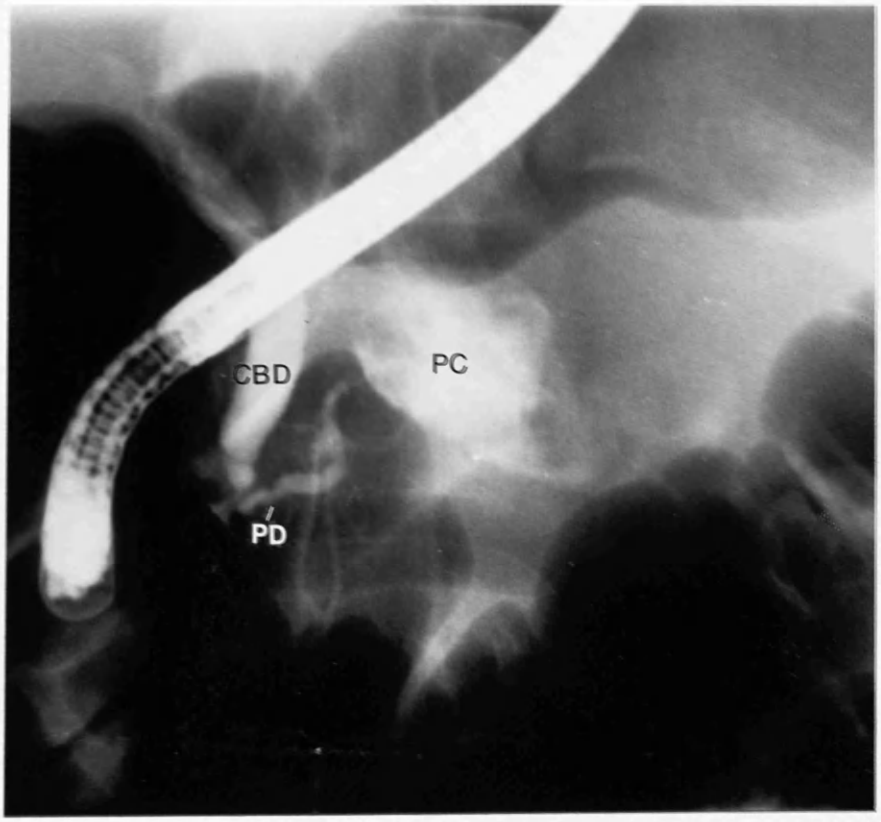


FIGURE 6 Radiograph taken during an ERCP. Contrast is seen leaking from the pancreatic duct into a large cavity.

CBD = common bile duct
PD = pancreatic duct
PC = pseudocyst with leak of contrast

As a result, pseudocysts have become associated with alcohol induced pancreatitis but many of the reports failed to differentiate between collections forming after acute pancreatitis and those which were associated with chronic pancreatitis.

Outcome

Because detection of a pseudocyst was based on clinical examination and relatively insensitive radiological techniques, prior to the introduction of ultrasonic scanning, most pseudocysts were treated by some form of surgical drainage (Warren et al 1958). Spontaneous resolution was regarded as rare and possibly related to rupture into a hollow viscus or peritoneal cavity (Becker et al 1968; Hanna 1960; Kaiser et al 1964). The ability to repeat a scan of a collection has confirmed spontaneous resolution in as many as one third of pseudocysts.

Spontaneous resolution of pancreatic pseudocysts

The advent of ultrasonic scanning has greatly enhanced the understanding of the natural history of pseudocyst formation and there is no doubt that pseudocysts associated with acute or chronic pancreatitis can resolve spontaneously. The seminal literature on this subject has come from Atlanta, Georgia, U.S.A. (Bradley and Clements 1974; Bradley and Clements 1975; Gonzalez et al 1976; Bradley et al 1976; Bradley et al 1979). In this series of papers, the authors described in detail the use and application of ultrasound scanning in assessing and following the natural history of pancreatic pseudocysts.

The authors observed that fluid collections around the pancreas in response to acute pancreatitis were more frequent than had been previously thought, and they demonstrated that between 25 and 50% of these collections would resolve spontaneously within 6 weeks of onset.

In their study of 93 patients with a pseudocyst (Bradley et al 1976), 11 were subjected to emergency surgical drainage of their collections, 28 others had what was referred to as "elective" operative drainage and the remaining 54 patients were managed with repeated clinical and ultrasound examination. Spontaneous resolution occurred in 11 (20%) of these 54 patients, 10 within 6 weeks of formation. The authors also found an increasing incidence of complications in the other patients with pseudocysts older than 6 weeks. The mean time from the development of a pseudocyst until a complication supervened was 13.5 +/- 6 weeks. Seven (13%) of the 54 patients died. In contrast, there were no deaths amongst the 28 patients who underwent elective surgery.

On the basis of these results Bradley et al (1979) concluded that if a pseudocyst had not resolved within 6 weeks from formation elective drainage surgery should be performed.

A number of authors (Table 1) have also referred to a period of six weeks in relation to the "age" of a pseudocyst and the likelihood of spontaneous resolution.

AUTHOR	PSEUDOCYSTS NUMBER	SPONTANEOUS NUMBER	%	RESOLUTION <6 WEEKS
Agha (1984)	20	5	25%	5
Aranha et al (1983)	105	29	28%	19
Bradley et al (1979)	54	11	20%	10
Crass et al (1981)	22	3	14%	3
Warshaw et al (1985)	42	3	7%	3
Total	243	51	21%	40

TABLE 1 Reports in relevant literature in which a period of 6 weeks is mentioned in relation to the time to complete spontaneous resolution of pancreatic pseudocysts.

Only 11 of 51 pseudocysts did not resolve within 6 weeks and 10 of these were reported by Arahna et al (1983).

Not all authors regard it as a critical time and, in particular, the high incidence of complications in untreated pseudocysts after this time, noted by Bradley et al 1979, has not been consistently supported by others (Agha 1984; Aranha et al 1983; Beebe et al 1984; Lasson et al 1988; O'Malley et al 1985; Wade 1985).

In addition, this time of 6 weeks has been discussed with reference to the timing of surgical drainage but without supporting data to confirm it as the optimal period at which to instigate surgical intervention (Beebe et al 1984; Cerilli and Faris 1967; Wade 1985).

A second feature of importance in the assessment of pseudocysts is the maximum size of the collection. Until 1985 (the time of the end of the patient data collection in the current study) there were only 4 reports (Table 2) detailing pseudocyst diameter (on ultrasound examination) in pseudocyst resolved spontaneously and those in whom surgical drainage was performed. Aranha et al (1983) noted that only 4 (15%) of 26 pseudocysts greater than 6cm in diameter resolved spontaneously. The relevance of this size as a useful gauge as to whether a pseudocyst will resolve or not is discussed in Chapter 5.

AUTHOR	PSEUDOCYSTS NUMBER	SPONTANEOUS RESOLUTION NUMBER	%	COMMENT ON SIZE
Agha (1984)	20	5	25%	MEAN SIZE OF RESOLVED 5cm MEAN SIZE OF OTHERS 9.7cm
Aranha et al (1983)	82	29	35%	MEAN SIZE OF RESOLVED 4.2cm MEAN SIZE OF OTHERS 8.7cm ONLY 4 OF 26 >6cm RESOLVED
Beebe et al (1984)	55	10	18%	9 OF 10 <4cm
O'Malley et al (1985)	69	11	16%	ALL 11 <4cm

TABLE 2 Reports in literature in which reference is made to the size of pancreatic pseudocysts in relation to spontaneous resolution or the need for surgical drainage.

The majority of pseudocysts that resolved were less than 6cm in diameter.

The incidence of spontaneous resolution of pseudocysts recorded in the literature varies from 8 - 84% (Table 3. Agha et al 1984; Aranha et al 1983; Beebe et al 1984; Bradley and Clements 1975; Bradley et al 1976, Bradley et al 1979; Crass and Way 1975; Czaja 1975; Gonzalez et al 1976; McConnell et al 1982; O'Malley et al 1985; Pollak et al 1978; Sandy et al 1981; Sankaran and Walt 1975; Vajcner and Nicoloff 1969; Wade 1985; Warshaw and Rattner 1985).

Many of the above reports were retrospective reviews of patients, the majority of whom had alcohol induced pancreatitis. Few of the studies documented the number of pseudocysts occurring after acute pancreatitis as opposed to those associated with chronic disease. With a high incidence of alcohol induced pancreatitis, even those patients who had a specific event of pain and hyperamylaseamia prior to pseudocyst development may have had chronic changes within the pancreas (Sarner et al 1984).

Differentiating between "acute" and "chronic" pseudocysts is of considerable importance because the behaviour of cystic collections in each circumstance is different (Crass and Way 1981; Lasson et al 1988; Mullins et al 1988). The frequency of spontaneous resolution and complications of pseudocysts forming after an episode of acute pancreatitis is greater than that for collections forming in association with chronic pancreatitis.

AUTHOR	RESOLUTION (%)
Vajcner et al (1969)	21
Bradley et al (1975)	13
Czaja et al (1975)	84
Sankaran et al (1975)	8
Gonzalez et al (1976)	20
Bradley et al (1976)	26
Bradley et al (1978)	19
Pollack et al (1978)	30
Bradley et al (1979)	26
Crass et al (1981)	14
Sandy et al (1981)	22
McConnell et al (1982)	20
Aranha et al (1983)	28
Beebe et al (1984)	18
Agha (1984)	25
O'Malley et al (1985)	16
Wade et al (1985)	12
Warshaw et al (1985)	14
mean	23
median	20

TABLE 3 Reports in literature (1969 - 1985) quoting an incidence for spontaneous resolution of pancreatic pseudocysts.

The features of pseudocyst age and size must not be considered in isolation when assessing the likelihood of spontaneous resolution. Equally important is the clinical condition of the patient. If there are no signs or symptoms of continued inflammation, pyrexia, pain, leukocytosis, or hyperamylaseamia, then a pseudocyst is more likely to resolve than if these features are present (Bradley et al 1979)

Opie's (1903) original suggestion that a pseudocyst forms because of a communication between the pancreatic ductal system and the surface of the gland remains true and, with the advent of sophisticated interventional radiological techniques capable of demonstrating a fistula between a pseudocyst and the pancreatic duct, Opie's hypothesis has become accepted (Frey et al 1988). The presence of such a fistula is obviously important when considering the possibility of spontaneous resolution. If there is a continuous leak of pancreatic fluid into a cavity then resolution is less likely than if a fistula has sealed.

There are few studies comparing the clinical course of patients in whom a pseudocyst resolves spontaneously with those ultimately requiring surgery. This problem is specifically addressed in Chapter 5.

Surgery for pancreatic pseudocysts

The majority of patients forming a pseudocyst still require to have them drained surgically and much of the literature relating to pseudocysts concerns surgical management. Le Dentu (1862) punctured and drained a pseudocyst via a percutaneously introduced needle. He had thought he was draining a liver cyst and the patient ultimately died. Four years later Lucke and Klebs (1867) drained a pseudocyst externally but again the patient died.

The first successful surgery is attributed to Bozeman (1881) who removed a large pseudocyst from a 41 year old female patient. He reported, that at laparotomy, a large cystic lesion was discovered arising from the tail of the pancreas and contained 1.5 gallons of fluid. This was successfully removed and the patient made an excellent recovery.

The following year Gussenbauer (1883) successfully drained a pseudocyst by a marsupialisation procedure. This remained the accepted method of surgical management for many years. Ombredanne (1911) performed a cystoduodenostomy using a lateral side to side anastomosis between a pseudocyst within the head of the pancreas and the duodenum.

As a variation of this technique, transduodenal cystoduodenostomy was described by Kerschner (1929) and this approach proved more successful. In 1923 Jedlicka described drainage of a pseudocyst into the stomach. He excised a portion of the cyst wall and anastomosed the remainder to the posterior wall of the stomach.

A modification of this was recorded by Jurasz (1931) and his technique is similar to that used today. Successful drainage into a loop of jejunum was performed by Henle and Hahn (1927) and a method employing a Roux en Y technique was described by Koning (1946). Some surgeons still favour this method as the internal drainage technique of choice.

There are also reports of pseudocysts drained into the gallbladder (Neuffer 1932; Walzel 1926) and common bile duct (Carter and Slattery 1947).

In 1958 Warren et al published a review of surgical operations for pseudocysts. External drainage or marsupialisation were the most frequent procedures (47% of all operations), and all methods of internal drainage together accounted for 42%. In 11% of patients the pseudocysts were excised. The mortality associated with external drainage was 3%, and 24% of patients required further surgery.

Internal drainage via a cystogastrostomy carried a similar mortality but only 5% needed further operations. Other methods of internal drainage into the duodenum or a loop of jejunum had a high incidence (>20%) of second operations.

A decade later Becker et al (1968) published a similar review and found the proportion of patients undergoing each type of operation to be almost the same as that noted by Warren et al (1958) and that all methods of internal drainage had a low incidence of re-operation while this remained greater than 20% for those patients whose pseudocyst was drained externally.

Over the years, the proportion of patients treated by internal drainage gradually increased as highlighted by Hastings et al (1975) who compared the relative incidences of each operation before and after 1962 (Table 4). In subsequent studies of pseudocysts (post 1976), 61% of patients have been treated by internal drainage compared to 32% externally (Table 5). Internal drainage methods are associated with a lower mortality and morbidity than external drainage but there are times when the former may be inappropriate .

A critical factor in determining the choice of operation and outcome has been the timing of surgery in relation to the development of the pseudocyst. Cerilli and Faris (1967) demonstrated a significant difference in mortality between those treated within 6 weeks of pseudocyst formation(mortality 60%), compared to those in whom operation was deferred beyond this time (mortality 9%). These authors related the poor outcome of early drainage to the presence of pancreatic inflammation and the lack of a suitably fibrosed pseudocyst wall.

Most patients undergoing external drainage are treated within the first 6 week period and tend to be more acutely ill. Shatney and Lillehei (1981) however, considered patients in two groups; (1) those acutely ill whatever the apparent age of the pseudocyst; and (2) those stable at the time of pseudocyst diagnosis.

	PRE-1962	POST-1962	MORTALITY
EXTERNAL DRAINAGE	66%	27%	27%
CYSTOGASTROSTOMY	34%	73%	6%

TABLE 4 External v internal surgical drainage of pseudocysts: distribution of operations pre and post 1962 (Hastings et al 1975).

AUTHOR	EXTERNAL DRAINAGE	CYSTO GASTR OSTOMY	CYSTO DUODEN OSTOMY	CYSTO JEJUN OSTOMY	EXCISION
Grace et al (1976)	18	36	6	6	3
Owens et al (1977)	6	13	-	-	-
Pollack et al (1978)	12	8	-	6	6
Crass et al (1981)	21	3	6	19	2
Sandy et al (1981)	10	43	2	11	-
Schattenkerk et al (1982)	7	7	2	6	3
Boggs et al (1982)	11	5	1	10	3
Beebe et al (1984)	16	10	1	7	1
O'Malley et al (1985)	11	11	1	19	8
Warshaw et al (1985)	8	15	3	8	-
Ephgrave et al (1986)	28	25	2	34	7
TOTAL	169	175	21	126	32
%	32	<-------- 61% ------>			6%

TABLE 5 Detail of literature reporting experience of drainage operations for pseudocysts 1976 - 1986.

The table illustrates that methods of internal drainage accounted for 61% of operations and external drainage 32%.

These authors (Shatney and Lilehei 1981) found that mortality and morbidity became independent of the timing of operation. Acutely ill patients had a higher mortality than stable patients, but the incidence of complications was similar whether operation was performed before or after six weeks from the time of pseudocyst formation.

The external and internal drainage techniques already mentioned constitute the majority of operations for pseudocysts but other methods have been described. Doubilet and Mulholland (1953) have advocated drainage of the pancreatic duct via a transduodenal sphincteroplasty, believing that the proximal duct obstruction would be relieved and the collection would drain through the widened orifice. This technique has not proved successful.

Percutaneous drainage of pancreatic pseudocysts

The majority of patients require surgical drainage of their pseudocysts. Internal drainage, in particular, is a relatively safe procedure but there is still morbidity and mortality associated with surgical drainage. A method of drainage that avoids operation but achieves resolution with minimal morbidity has appeal. Percutaneous drainage procedures may be an answer to such a problem.

The first percutaneous aspiration of a pancreatic pseudocyst was reported by Le Dentu (1862). Five years later Lucke and Klebs (1867) recorded a similar method of drainage in one patient.

Success with percutaneous techniques depends on accurate localisation of the collection and lack of an appropriate imaging modality was the predominant reason why this type of drainage was not vigorously pursued until recently.

Wiechel et al (1971) described a small group of patients in whom fluoroscopic control was used to localise the pseudocyst and as a method of guiding the aspiration needle. The collections these authors drained were relatively large but with the introduction of ultrasonic scanning not only have smaller cysts become easier to localise but it was soon realised that this imaging technique was particularly useful as a method of guidance for percutaneous needle procedures (Holm et al 1972).

Bradley (1982) in his review of pancreatic pseudocysts quoted 4 authors (Andersen et al (1977), Barkin et al (1981), Hancke and Pedersen (1976), MacErlean et al (1980)) with a combined experience of percutaneous drainage in thirty patients. The pseudocyst refilled rapidly in 21 (70%) of these subjects.

Bradley (1982) concluded "it seems unlikely that this technique will find an important place in the treatment of uncomplicated patients with pancreatic pseudocysts." Advances in interventional radiological techniques in the last decade have proved this statement wrong. A review of the literature (Tables 6,7 & 8) reveals almost 600 patients who have undergone some form of percutaneous drainage of a pseudocyst.

AUTHOR	YEAR	NUMBER	ACUTE/ CHRONIC	RESOLVED	RECUR	SUCCESS (%)
Andersen et al	1977	8	ns	1	7	12.5%
Barkin et al	1981	8	chronic	2	6	25%
Gerzof et al	1979	2	acute	2	-	100%
Gronvall et al	1982	1	acute	1	-	100%
Hancke et al	1976	9	ns	2	7	22%
McDermott et al	1981	3	chronic	3	-	100%
MacErlean et al	1980	5	ns	4	1	80%
TOTAL PRE-1982 ASPIRATION ONLY		**36**		**15**	**21**	**mean 42%**

TABLE 6 Reports in literature of percutaneous aspiration **only** of pseudocysts **prior to 1982** detailing the number of pseudocysts drained, the type of the antecedent pancreatitis and the overall success of the technique.

[NUMBER = number of pseudocysts
ACUTE/CHRONIC = type of antecedent pancreatitis
ns = not specified]

AUTHOR	YEAR	NUMBER	ACUTE/ CHRONIC	RESOLVED	RECUR	SUCCESS (%)
Andersson et al	1989	13	both	10	3	77%
Andren-Sandberg et al	1983	9	ns	1	9	11%
Bianchi et al	1989	9	both	8	1	89%
Cadotte et al	1988	18	ns	17	1	94%
Colhoun et al	1984	10	both	9	1	90%
Fisher et al	1989	11	acute	5	6	44%
Gandini et al	1987	21	both	6	15	29%
Kuligowska et al	1985	4	ns	-	4	0%
Klem et al	1987	4	acute	2	2	50%
Laugier et al	1986	18	chronic	6	12	33%
Schulze et al	1988	14	both	6	8	43%
SHEARER		**21**	**both**	**6**	**15**	**29%**
Torres et al	1986	5	both	-	5	0%
van Sonnenberg et al	1985	10	both	3	7	30%
TOTAL FOR POST 1982 ASPIRATION ONLY		**168**		**79**	**89**	**47%**

TABLE 7 Reports in literature of percutaneous aspiration **only** of pseudocysts **after 1982** detailing the number of pseudocysts drained, the type of the antecedent pancreatitis and the overall success of the technique.

[NUMBER = Number of pseudocysts
ACUTE/CHRONIC = type of antecedent pancreatitis
ns = not specified
both = patients with acute or chronic pancreatitis not separated]

AUTHOR	YEAR	NUMBER	ACUTE/ CHRONIC	RESOLVED	RECUR	SUCCESS (%)	TYPE OF DRAINAGE
Andersson et al	1989	9	both	9	-	100%	external
Bernadino et al	1984	1	acute	1	-	100%	internal
D'Egidio et al	1989	4	acute	4	-	100%	external
Freeny et al	1988	38	both	36	2	95%	external
Gandini et al	1987	39	ns	25	14	64%	both
Gerzof et al	1984	11	acute	9	2	82%	external
Hancke et al	1985	18	chronic	16	2	89%	internal
Hancke et al	1987	31	chronic	28	3	90%	internal
Heyder et al	1988	9	acute	5	4	56%	internal
Ho et al	1984	1	acute	1	-	100%	transgastric
Karlson et al	1982	6	chronic	6	-	100%	external
Kuligowska et al	1985	2	ns	1	1	50%	external
Matzinger et al	1988	12	both	8	4	66%	transgastric
Nunez et al	1985	8	both	8	-	100%	transgastric
Sacks et al	1988	8	acute	7	1	86%	external
Schulze et al	1988	2	both	2	-	100%	external
Stanley et al	1988	27	acute	20	7	74%	external
Torres et al	1986	15	both	10	5	67%	external
van Sonnenberg et al	1985	27	both	20	7	74%	external
van Sonnenberg et al	1989	101	both	91	10	90%	external
TOTAL POST 1982 ASPIRATION + CATHETER DRAINAGE		**369**		**307**	**62**	**83%**	

TABLE 8 Reports in literature of percutaneous **aspiration + catheter drainage** of pseudocysts **after 1982** detailing the number of pseudocysts drained, the type of the antecedent pancreatitis, the overall success of the technique and the approach employed in positioning the catheter.

[ACUTE / CHRONIC = type of pancreatitis
ns = not specified
both = patients with acute or chronic pancreatitis not separated]

Percutaneous methods of drainage have now been refined and modified to include the use of drainage catheters placed into the pseudocyst cavity and led out through the abdominal wall to allow external drainage and also, using a combination of percutaneous and endoscopic manipulations to insert a catheter into the pseudocyst and the stomach and form a catheter "cystogastrostomy" to achieve internal drainage (Table 8). There have been an increasing number of reports recording the experience of percutaneous aspiration of sterile, infected, acute and chronic pseudocysts using ultrasound and/or CT scanning as guidance. Prior to 1982 aspiration only was successful in 42% of patients (Table 6). This has been improved to success in 83% of patients following the addition of catheter drainage techniques (Table 8).

Percutaneous aspiration, even if performed repeatedly, has resulted in only a small increase in successful outcome (Table 7: post 1982). Improvement in the results has, in the main, resulted from the use of prolonged catheter drainage (external or internal) with large diameter or multiple catheters and particularly when the pseudocyst has been infected. Drainage over several weeks or even months has been shown to be important for pseudocysts which communicate with the pancreatic duct (Henriksen and Hancke 1987).

The increasing use of percutaneous drainage techniques has contributed significantly to a change in the management of pseudocysts. There is growing evidence to suggest that sterile collections, particularly "acute pseudocysts" can be managed by percutaneous drainage with the prospect of over 80% success. Infected collections (localised pancreatic abscesses) require a more aggressive and intensive approach (Freeny et al (1988), van Sonnenberg et al (1989) but successful management has been achieved in 90% of patients with catheter drainage. Patients with infected collections not resolved by percutaneous drainage have frequently shown a significant improvement in their general condition so that surgical intervention became less hazardous (van Sonnenberg (1989). The use of percutaneous techniques does not preclude or compromise any subsequent surgical procedure but it does have complications. In particular, infection may be introduced into a sterile pseudocyst.

The results of experience of percutaneous drainage of pseudocysts in two hospitals and the place of this technique in the management of patients with pseudocysts is discussed in Chapter 6.

Complications associated with pseudocyst formation

Pseudocyst formation is an important complication of acute pancreatitis with an associated mortality of between 6 and 16% (Brilhart and Priestley 1951; Grace et al 1976; Hastings et al 1975; Hillis 1963; McConnell et al 1982; Pollak et al 1978; Scharplatz et al 1972; Thomford et al 1969) and further complications occurring in up to 30% of patients.

Problems arise as a consequence of surgical treatment for pseudocysts but there are also complications associated with untreated pseudocysts and these can be considered under 4 headings: 1) infection; 2) obstruction; 3) rupture; and 4) haemorrhage (Bradley 1982).

1) Infection

Pseudocysts are generally regarded as sterile collections (Warshaw (1982)). When a pseudocyst becomes infected it should be regarded as a localised abscess. Such secondary infection occurs in 8-10% of pseudocysts but a positive bacterial culture from aspirated fluid has been reported in as many as 53% of collections (Shatney and Lillehei 1979). Within the base of many pseudocyst cavities lies necrotic tissue (Figure 7) and if this becomes infected there is a significant prospect that localised infection may be converted into a pancreatic abscess or diffuse retroperitoneal sepsis.

FIGURE 7 Portion of necrotic pancreatic and peri-pancreatic tissue removed from the base of a large pseudocyst.

Morbidity is higher in patients in whom the pseudocyst is infected (Warren et al 1958) and the onset of sepsis is often heralded by a deterioration in the general condition of the patient. This clearly influences the choice of surgery, because internal drainage is not always an effective method of treating infected lesions.

2) Obstruction.

Large pseudocysts have been reported causing obstruction to various adjacent structures. The most frequent area obstructed is the duodenum but this is commonly relieved by drainage of the pseudocyst. Obstruction to the stomach (Folk et al 1970), oesophago-gastric junction (Imrie 1980), jejunum (Grace et al 1976) and colon (Jordan and Howard 1966) have been documented. In the situation where a pseudocyst is present in the head of the gland the common bile duct is vulnerable to compression and the resultant jaundice frequently improves following decompression of the collection.

A pseudocyst may not be wholly responsible for such obstruction (Bradley 1982) as there may also be fibrotic changes around the intrapancreatic portion of the duct subsequent to the effects of chronic pancreatitis (Bradley and Salam 1978). Most of the patients in whom this complication has been reported had alcohol associated disease.

The other important structure prone to obstruction is the portal vein (Longstreth et al 1971; McDermott 1960). Grace et al (1976) have reported a fall in portal venous pressure following pseudocyst decompression implying a direct pressure effect on the vein. Decompression of the pseudocyst usually relieved the portal hypertension. The obstructing effect of a pseudocyst can necessitate urgent surgery to relieve the problem.

3) Rupture

One mechanism of pseudocyst resolution occurs when it ruptures into the peritoneal cavity or into a hollow viscus. This occurs in only a small proportion of patients (5%, Hanna 1960) but the mortality following this complication is high.

Becker et al (1968) found a 40% mortality amongst such patients and quoted a figure of 50% from previous literature. If the pseudocyst rupture is sudden the effect can be devastating, with urgent surgical intervention being the treatment of choice (Becker et al 1968). If the leakage is less dramatic pancreatic ascites develops (Bradley 1982).

Rupture into bowel (Bradley and Clements 1974; Bradley and Clements 1975; Grace et al 1976; Hanna 1960), biliary tract (Dalton et al 1970), pleural space (Cameron 1978; Sankaran et al 1975) and portal vein (Zeller and Hetz 1966) have been reported. Decompression as a result of rupture can precipitate rapid deterioration in a patient but occasionally it results in resolution of the collection with clinical improvement and no further

4) Haemorrhage

The reported mortality associated with haemorrhage from a pseudocyst ranges from 43% (Grace et al 1976) to 80% (Trapnell 1971). The most frequent source of bleeding is from vessels (commonly the splenic artery) within the posterior wall of the pseudocyst cavity. Clinically, a sudden increase in the size of the lesion and deterioration in the condition of a patient is suggestive of such a haemorrhagic episode (Pinkham 1945).

Instances of haemorrhage into the pancreatic duct (Leger et al 1976) causing blood loss through the ampulla or into the liver and bile ducts resulting in haematobilia have been reported (Dalton et al 1970, Grace et al 1976). A further major source of bleeding is from the edges of a surgically created internal drainage stoma. There has been considerable debate as to whether the edges should or should not be sutured (Folk et al 1970, Grace et al 1976, Hutson et al 1973, Van Heerden and ReMine 1975).

There is no doubt that irrespective of how the stoma is formed a secondary haemorrhage can occur from the lining of the pseudocyst or from the anastomosis which inevitably requires further surgery to control bleeding. Haemorrhage has also been reported from the gastro-intestinal mucosa overlying a pseudocyst (Bradley et al 1979).

The four categories detailed above account for the majority of complications associated with untreated pseudocysts but post operative complications following drainage procedures also cause considerable morbidity. Drainage of the fluid from a pseudocyst into the stomach can be inadequate treatment since it may not be an effective treatment for the necrotic and potentially infected tissue in the base of a pseudocyst.

Some patients who form a pseudocyst following an episode of severe acute pancreatitis can become significantly catabolic with high protein losses and marked weight loss (up to 1lb per day). Such patients require intensive support with parenteral hyperalimentation. They need to be assessed frequently and every attempt made to stabilise their metabolism if they are to recover from surgical intervention in addition to their pancreatitis. Percutaneous needle aspiration and catheter drainage may be of the greatest value in these patients.

Analysis of pseudocyst fluid

Despite extensive literature on the subject of pancreatic pseudocysts there is a paucity of studies concentrating on analysis of the fluid.

A summary of the literature relating to analysis of pseudocyst fluid is shown in Table 9.

AUTHOR	SUBSTANCES ANALYSED
Aranha et al (1982)	Amylase
Baker et al (1983)	Amylase
Bradley et al (1982)	Amylase, lipase, trypsin, protein, albumin, urea, creatinine, electrolytes, calcium, phosphate, uric acid, cholesterol
Colhoun et al (1984)	Amylase
Freeney et al (1988)	Amylase
Frey et al (1978)	Amylase
Goke et al (1989)	Phospholipase a2
Kane et al (1983)	Amylase
Karlson et al (1982)	Amylase
Kimura et al (1982)	Amylase, isoamylase, alkaline phosphatase, protein, lactate dehydrogenase, carcinoembryonic antigen
Kjaergaard et al (1984)	Amylase, isoamylase
Kuligowska et al (1985)	Amylase
Lasson et al (1989)	Amylase, alpha 1 antiprotease, alpha 2 macroglobulin, alpha 1 protease inhibitor, c1 inhibitor, antithrombin, antichymotrypsin, complement factor c3, albumin, cathodal trypsin, pancreatic elastase, pancreatic secretory trypsin inhibitor
Matzinger et al (1988)	Amylase
Nunez et al (1985)	Amylase
Owens et al (1977)	Amylase
Schwerk et al (1981)	Amylase
Shatney et al (1979)	Amylase
Shetty et al (1980)	Amylase
Tatsuta et al (1986)	Elastase, carcinoembryonic antigen, CA 19-9
Warshaw et al (1985)	Amylase, isoamylase
Weaver et al (1982)	Amylase, isoamylase
Wilson et al (1990)	Amylase. protein, albumin, lipase, tryptic amidase, alpha 1 antiprotease, alpha 2 macroglobulin, free proteolytic activity, trypsin inhibitory capacity

TABLE 9 Details of reports in literature describing analysis of components of pseudocyst fluid, (1977 - 1990).

The amylase content of fluid collected, either at the time of surgery (Aranha et al 1982; Baker et al 1983; Bradley 1982; Frey et al 1978; Kane and Krejs 1983; Kimura 1982; Kjaergaard et al 1984; Lasson et al 1989; Owens and Hamit 1977; Schwerk 1981; Shatney and Lillehei 1979; Shetty et al 1980; Warshaw et al 1985; Weaver et al 1982; Wilson et al 1991) or percutaneous aspiration (Colhoun et al 1984; Freeny et al 1988; Karlson et al 1982; Kuligowska et al 1985; Matzinger et al 1988; Nunez et al 1985) is the most frequently recorded. The range of values is considerable but the high amylase content confirms the pancreatic origin of the fluid (Lasson et al 1989). There has been no correlation between fluid amylase levels and communication of the pseudocyst cavity and the ductal system. The highest levels should occur when a fistula exists.

As a variation on amylase estimation, the isoamylase pattern in pseudocyst fluid has been studied (Kjaergaard et al 1984; Warshaw et al 1985; Weaver et al 1982) and has been correlated with the pattern within serum in the same patients.

Warshaw and Rattner (1985) suggested that the amylase iso-enzyme pattern within pseudocyst fluid can indicate the presence of a persistent fistula between the pancreatic duct and pseudocyst. This observation has not been repeated by other workers.

The proteolytic activity within the cyst fluid has been assessed by Lasson et al (1989) and Wilson et al (1991). Both these authors also measured alpha 1 antiprotease and alpha 2 macroglobulin and Lasson et al (1989) concluded that pseudocyst fluid was a mixture of plasma proteins and pancreatic juice possessing a high proteolytic activity. These authors demonstrated that there was free and bound proteolytic activity and suggested that this could be responsible for some of the complications associated with pseudocysts.

Other enzymes within the fluid, lipase and trypsin (Bradley 1982) and phospholipase A_2 (Goke et al 1989) have been measured and Bradley (1982) reported a detailed analysis of several parameters (Table 9) within 15 specimens of pseudocyst fluid and he compared these with the values in a sample of serum withdrawn around the time the fluid was collected. As expected the amylase, lipase and trypsin values were all greater in pseudocyst fluid.

In the present attempt to differentiate between acute and chronic pseudocysts and to find a marker which may reflect the severity of the inflammatory reaction, acute phase reactants, alpha 1 antiprotease, alpha 2 macroglobulin, interleukin 6, and C-reactive protein have been analysed in samples of pseudocyst fluid from 12 patients. The results are discussed in Chapter 7.

SUMMARY

The development of a pancreatic pseudocyst is a serious complication of acute pancreatitis. Associated problems are common and many patients are very ill. The process that allows collections to form is poorly understood and the natural history of this aspect of the disease requires further clarification. The majority of reports on the subject have been retrospective reviews conducted over several years because the occurrence of pseudocyst is infrequent. Based predominantly on prospective data this thesis sets out to examine current concepts regarding the management and treatment of pancreatic pseudocysts.

CHAPTER 2

PATIENTS AND METHODS

INTRODUCTION

To fulfil the objectives of this thesis, 4 related studies have been performed involving 4 groups of patients:-

1. A group of 100 patients with pseudocysts who presented at Glasgow Royal Infirmary over a period of 23 years (1962-1984). The majority (87) of these patients developed their collection following an episode of acute pancreatitis (Chapter 3). The pseudocyst resolved spontaneously in 22 patients and the clinical differences and final outcome in these patients are compared in detail with those in whom the pseudocyst was drained surgically (Chapter 4).

2. Twenty nine patients from three cities Leeds, Bristol and Glasgow who developed pseudocysts as a result of acute pancreatitis and who were studied prospectively as part of a trial of therapeutic peritoneal lavage used as a method to treat severe acute pancreatitis (Chapter 3). A pseudocyst resolved spontaneously in 15 of these patients and they are also considered in detail in Chapter 4.

3. A group of 21 patients who had their pseudocyst drained by percutaneous needle aspiration or catheter drainage (Chapter 5).

4. Twelve patients from whom samples of pseudocyst fluid have been collected and analysed for acute phase reactants (Chapter 6).

Details of the patients and methods relating to the 100 patients studied in Glasgow Royal Infirmary and the 29 from Leeds, Bristol and Glasgow are given in the present chapter.

100 PATIENTS WITH PSEUDOCYSTS PRESENTING TO GLASGOW ROYAL INFIRMARY BETWEEN 1962 AND 1984.

There are few prospective studies of patients who develop pancreatic pseudocysts following acute pancreatitis. In order to establish the natural history of this complication details of 100 patients with pancreatic pseudocysts presenting consecutively to Glasgow Royal Infirmary between 1962 and 1984 have been reviewed. Fifteen patients from the period 1962 until 1971 were documented retrospectively. Details of episodes of acute pancreatitis have been documented prospectively, as part of a continuing study of this disease and the associated complications, in the other 85 patients since 1971. The 100 patients represent approximately 7% of the total number of patients with acute pancreatitis recorded in the one institution over a 14 year period (1971-1984) (Table 10).

In conjunction with Mr C W Imrie and Miss L Buist details of this 100 patients have been published (Imrie C W, Buist L & Shearer M G 1988) (Appendix 1).

Eighty seven patients developed a pseudocyst after an episode of acute pancreatitis and in the other 13 the pseudocyst was associated with chronic pancreatitis.

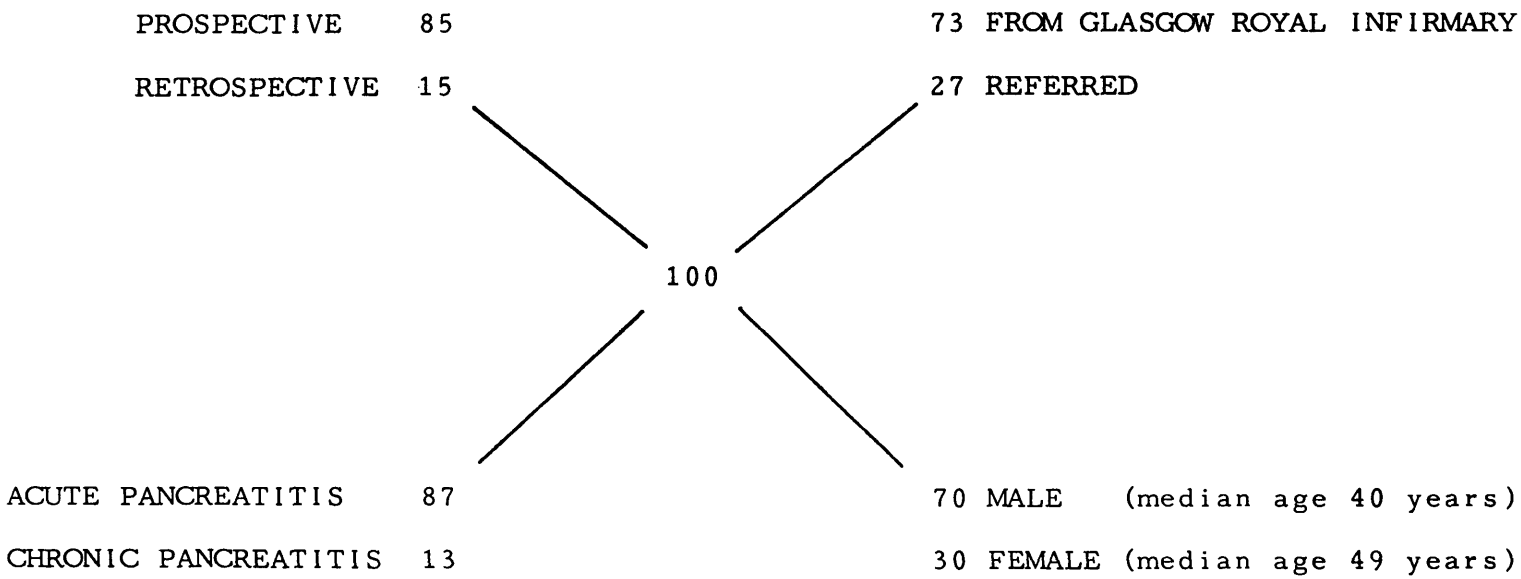


TABLE 10 Details of the 100 patients studied in Glasgow Royal Infirmary.

Data collection:	PROSPECTIVE / RETROSPECTIVE
Preceding pancreatitis:	ACUTE PANCREATITIS / CHRONIC PANCREATITIS
Catchment area:	GLASGOW ROYAL INFIRMARY REFERRED from elsewhere
Sex distribution:	MALE / FEMALE

Twenty eight patients were referred from other hospitals either for further investigations to confirm the presence of a pseudocyst or for surgery for a previously diagnosed collection. In 23 of these patients the pseudocyst followed acute pancreatitis and 5 had been investigated for symptoms of chronic pancreatitis.

Seventy of the patients were male with a median age of 40 years (range 19-77 years). The 30 females had a median age of 49 years (range 21-78 years) (Table 10).

METHODS

The hospital records for all patients were reviewed personally and a detailed proforma relating to the development of the pseudocyst completed. The official records for 12 patients documented retrospectively between 1962 and 1971, or referred from another hospital, were untraceable. However, extracts from their notes had been preserved giving limited information for these 12 patients.

From 1971, details of patients presenting with acute pancreatitis or associated complications have been recorded prospectively on separate proformata. All the relevant files have been reviewed. Despite at least two sources of data for the majority of patients, some information was occasionally lacking, particularly in relation to timing of development and resolution of a pseudocyst.

A summary of the information for each patient was entered into a computer data file to aid analysis. A transcript of the file is given in Appendix 2.

29 PATIENTS WITH PSEUDOCYSTS FROM GLASGOW, LEEDS AND BRISTOL.

The information relating to patients discussed in this section was collected during participation in a multi-centre trial of therapeutic peritoneal lavage for severe acute pancreatitis. The results of the trial have been published (Corfield et al 1985; Mayer et al 1985) (Appendix 1). During this study information was recorded from 418 patients with acute pancreatitis from 24 hospitals (Appendix 3). Consideration of the data has allowed, not only an appraisal of the effect of therapy on patients severely ill with pancreatitis, but also a detailed analysis of delayed complications of acute pancreatitis.

Twenty nine of 418 patients with acute pancreatitis developed a pseudocyst, an incidence of 7% for the whole study. There were 15 male (median age 45 years; range 21-77 years) and 14 females (median age 61 years; range 30-78 years).

All hospital records and trial profomata for these 29 patients have been reviewed personally. Details were again entered into a computer data file and a transcript of the data is given in Appendix 4.

METHODS:
ORGANISATION OF TRIAL THERAPEUTIC PERITONEAL LAVAGE IN PATIENTS WITH SEVERE ACUTE PANCREATITIS

In order to study the effect of treatment on patients with severe acute pancreatitis a multi-centre trial was necessary because no single centre could provide a sufficient number of severely ill patients within a reasonable period.

It was also necessary to document as many patients with acute pancreatitis, of all degrees of severity, as possible. The trial was commenced in Leeds and Bristol in September 1981 and Glasgow patients were entered from October 1982. A standard proforma was used (Appendix 5) and within each centre a coordinator collected the data. Clinicians throughout each city were requested to notify all patients with acute pancreatitis to the coordinator and, from the three centres a total of 24 hospitals cooperated with the study (Appendix 2).

Mr A.P. Dickson acted as the first trial coordinator in Glasgow from September 1982 until July 1983. The patients (51) documented during this period have been included with those collected personally from August 1983 until July 1984 (95 patients).

The criteria for diagnosing acute pancreatitis were, a relevant clinical history and course (acute abdominal symptoms: pain, tenderness, vomiting) and an elevated serum amylase >1200 IU/l (Phadebas technique). All patients included in this analysis fulfilled these criteria.

After referral, patients were visited as soon as possible by the coordinator (usually between 12 and 36 hours after admission) and the trial proforma completed. The patients were visited regularly throughout their hospital stay and the proforma updated. The trial design is shown in Table 11.

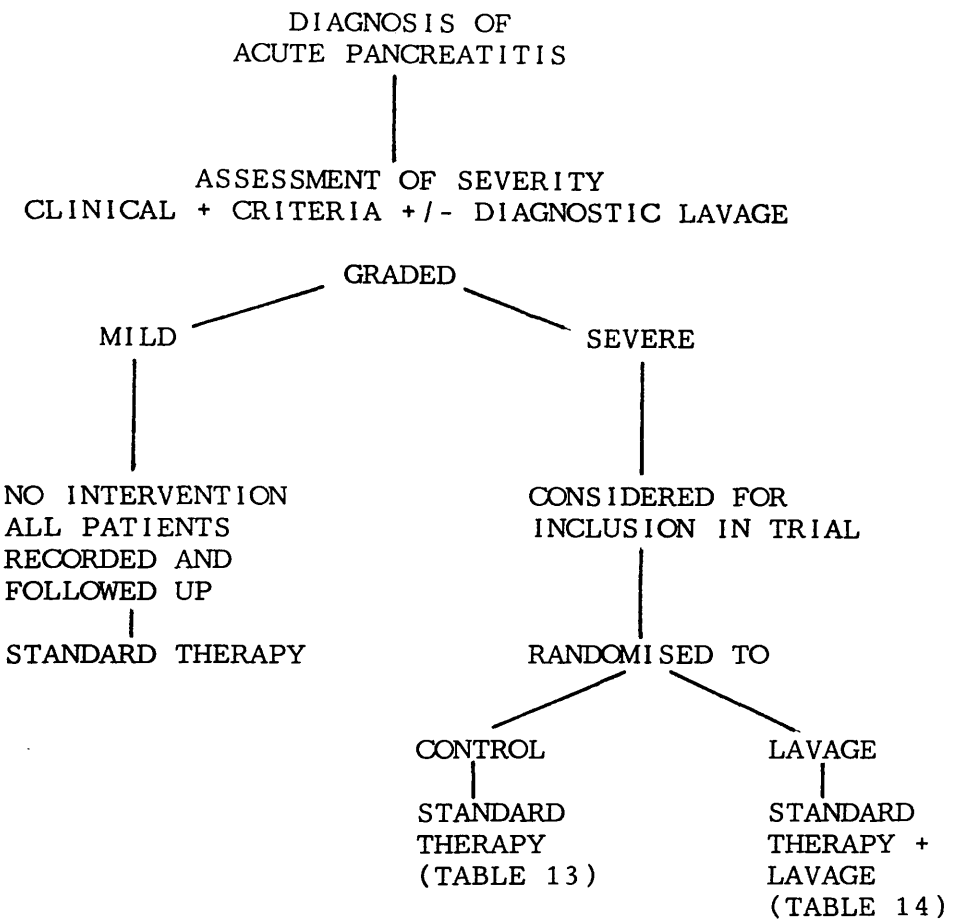


TABLE 11 Protocol for trial of therapeutic lavage in severe acute pancreatitis showing the patient selection and assessment process.

The degree of severity of acute pancreatitis was determined by:-

1) clinical assessment

2) multiple laboratory criteria (Osborne et al 1981) (Table 12)

3) diagnostic peritoneal lavage (Table 13, Figures 8 and 9)(McMahon et al 1980).

Clinical assessment and multiple criteria results were available for all patients studied. In Glasgow, multiple factor grading was the preferred method of assessment and diagnostic lavage was performed in only 30% of patients compared to over 90% in both Leeds and Bristol.

MANAGEMENT

All the patients where managed in the same standard manner and, in addition, 7 patients randomised to receive active treatment were given therapeutic peritoneal lavage.

Standard therapy regimen

This consisted of intravenous fluids, adequate analgesia and measurement of hourly urine output (Table 14). Nasogastric aspiration was used if vomiting was present and controlled oxygen therapy was administered if arterial partial pressure of oxygen was less than 60 mmHg (8 pKa) at any time. Central venous pressure was monitored if urine output (<30ml/hour) indicated impending renal failure thereby necessitating a more accurate assessment of fluid balance.

LEUKOCYTOSIS	greater than 15×10^9 cells/l
ARTERIAL pO_2	less than 60mmHg (8KPa)
BLOOD GLUCOSE	greater than 10mmol/l (no diabetes)
BLOOD UREA	greater than 16mmol/l (no improvement with IV fluids)
SERUM CALCIUM	less than 2mmol/l
SERUM ALBUMIN	less than 32g/l
SERUM GLUTAMIC OXALOACETIC TRANSAMINASE	greater than 200IU/l
SERUM LACTATE DEHYDROGENASE	greater than 600IU/l

Three or more factors positive within 48 hours of admission being regarded as severe

TABLE 12 Early prognostic criteria for assessment of disease severity in patients with acute pancreatitis (Osborne et al 1981).

Three or more factors positive within 48 hours of admission regarded as severe.

INFORMED CONSENT

NASOGASTRIC TUBE INSERTED

URINARY CATHETER INSERTED

PERITONEAL CATHETER (Figure 3) INSERTED

aseptic technique
local anaesthesia (lignocaine 2%)
small midline sub-umbical incision
catheter inserted into the pelvis
free ascitic fluid aspirated
1 litre warm saline instilled

ASSESSMENT

SEVERE pancreatitis if one or more of the following criteria were present:

1. More than 20ml of free ascitic fluid
2. Dark coloured ascitic fluid (darker than number 5 see Figure 4)
3. Return fluid (from litre of saline) darker than number 3 (Figure 4).

TABLE 13 Protocol for assessment of the severity of acute pancreatitis by diagnostic peritoneal lavage.

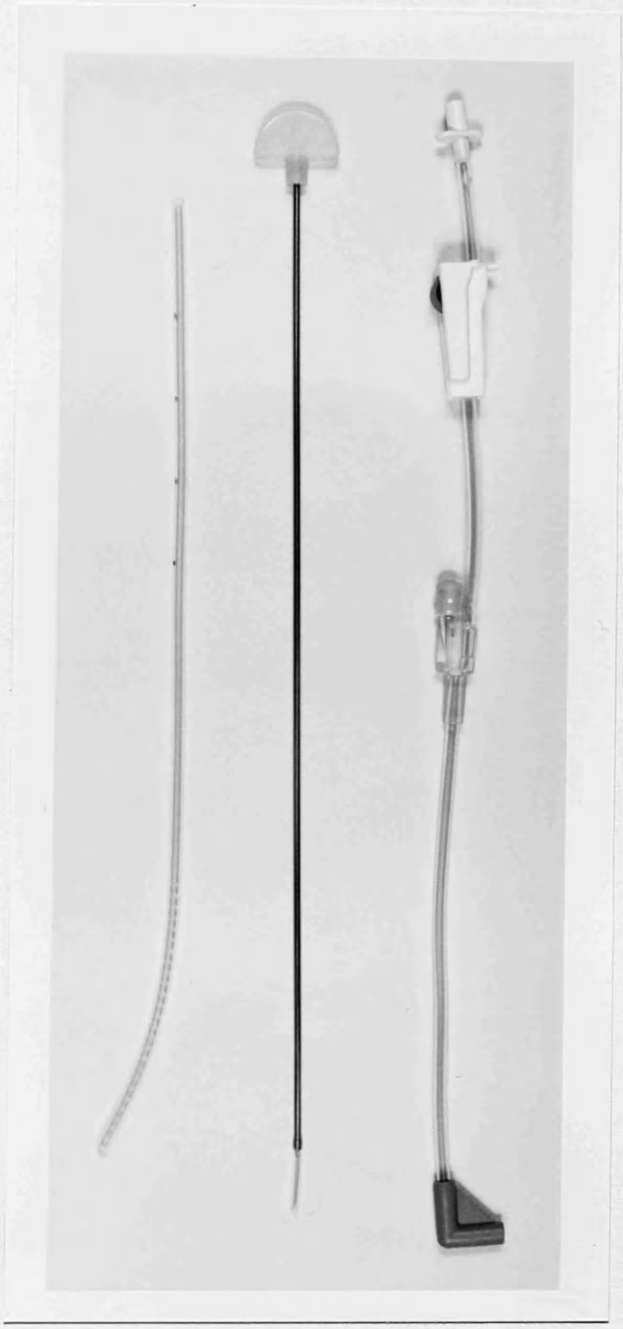


FIGURE 8 Peritoneal dialysis catheter (Trocath, McGraw-Hill). Three components: trocar needle, catheter, extension tube.

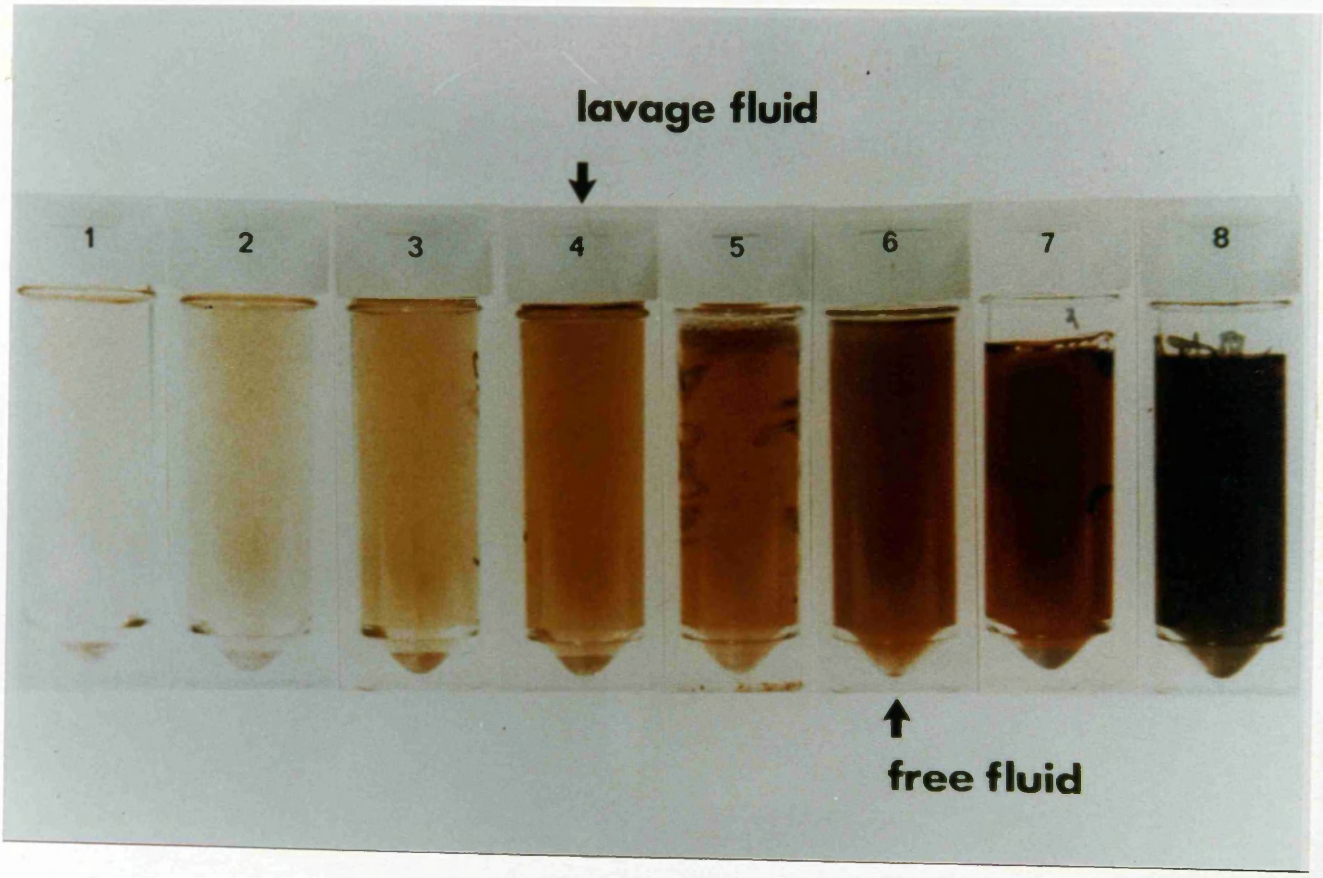


FIGURE 9 Reference fluid colour chart for assessment of free and post lavage ascitic fluid.

INTRAVENOUS FLUIDS:	mainly crystalloid: plasma and other colloid at the discretion of referring clinician.
ANALGESIA:	pethidine (50 - 150mg)
URINARY CATHETER:	to monitor urine output.
NASOGASTRIC ASPIRATION:	when vomiting was a symptom.
CONTROLLED OXYGEN THERAPY:	if arterial oxygen less than 60mmHg.
CENTRAL VENOUS PRESSURE:	for accurate fluid balance monitoring.

TABLE 14 Standard treatment regimen for all patients with acute pancreatitis included in the study.

Therapeutic peritoneal lavage

Seven patients initially assessed as having severe acute pancreatitis were considered for inclusion in the lavage trial. These patients were randomised to lavage or control groups and informed consent obtained (Table 15). Randomisation was achieved by referral to instructions in randomly allocated numbered envelopes provided by an independent statistician.

The management outlined above applied to the time the patients were in hospital with acute pancreatitis. The management of patients subsequent to pseudocyst formation is discussed later (Chapter 3).

STATISTICAL METHODS

When indicated statistical significance was assessed by the Mann Whitney test for non-parametric data and the chi-squared test incorporating Yates' correction.

INFORMED CONSENT

NO CONTRAINDICATIONS (previous abdominal surgery)

NASOGASTRIC TUBE INSERTED

URINARY CATHETER INSERTED

PERITONEAL DIALYSIS CATHETER INSERTED UNDER LOCAL ANAESTHESIA (Table 13)

RETURN FLUID ASSESSED

LAVAGE:- HOURLY CYCLES
2 LITRES OF DIALYSATE
POTASSIUM 4mmol IN EACH LITRE
HEPARIN 250 IU IN EVERY FOURTH LITRE

DISCONTINUED IF a) FLUID CLEAR

OR b) AFTER 72 HOURS

TABLE 15 Protocol for patients randomised to receive therapeutic peritoneal lavage.

CHAPTER 3

RESULTS FOR 100 PATIENTS FROM GLASGOW ROYAL INFIRMARY

INTRODUCTION

This chapter considers the natural history of patients with pancreatic pseudocysts based on the clinical information relating to 100 patients from Glasgow Royal Infirmary. The results for 29 patients from Leeds, Bristol and Glasgow have been analysed in a similar manner and are presented in Chapter 4.

The total of 129 patients constitutes one of the largest recorded studies of patients with pancreatic pseudocysts in the relevant world literature.

100 PATIENTS FROM GLASGOW ROYAL INFIRMARY

Diagnosis

The diagnosis of a pseudocyst was based on a combination of clinical, laboratory, and radiological information. The incidence of the most important clinical signs and symptoms are noted in Table 16. The results are given as a percentage of the total results available for each parameter and compared with results from the literature. All the parameters noted below relate to the point when a diagnosis of pseudocyst was being considered and not to the onset acute pancreatitis.

Pain

Recurrent or persistent abdominal pain following an episode of pancreatitis, was the most common symptom recorded in 89% of patients. It was this symptom that led to further investigations in the majority of patients. The pain was located predominantly in the upper abdomen and epigastrium.

SYMPTOM	LITERATURE REVIEW INCIDENCE (%) MEDIAN	RANGE	RESULTS FOR 100 PATIENTS MEDIAN (%)
Pain	86	63-100	89
Tenderness	64	47-100	69
Nausea/vomiting	60	14-78	39
Mass	54	18-96	59
Anorexia	47	5-83	35
Abdominal distension	44	36-50	22
Pyrexia (>37.5^{o}C)	32	10-81	21
Jaundice	11	4-48	12
Elevated serum amylase (> upper limit of normal)	61	11-100	79
Leukocytosis (>10x10^{9}cells/l)	48	28-90	42

TABLE 16 Incidence (median %) of symptoms, signs, raised serum amylase and leukocytosis in 100 patients with pseudocysts from Glasgow Royal Infirmary compared to cumulative results from relevant literature.

Tenderness

Tenderness on abdominal examination was found in 69% of patients, all but two of whom also complained of pain. The tenderness, as with pain, was most marked in the upper abdomen.

Mass / epigastric fullness

The presence of a discrete mass or fullness in the epigastrium on abdominal examination, was documented in 59% of patients. A mass was palpable in only 1 patient in whom the pseudocyst diameter (by ultrasound) was less than 6cm. In contrast, 64% of those with a minimum diameter of 7cm, as demonstrated by ultrasound scanning, had a clinically palpable mass.

Correlation between the diameter of the lesion and volume of fluid present is difficult to assess, as the volume was only measured in 11 patients at the time of surgery. On the available evidence, a collection containing approximately 1 litre had one diameter of at least 10cm.

Pyrexia

A pyrexia (>37.5°C) was noted in 21% of patients at the time of pseudocyst diagnosis. The pseudocysts in these patients all followed an episode of acute pancreatitis and in 80% of those with a pyrexia the diagnosis of a pseudocyst was made during the same admission as the pancreatitis.

Nausea and vomiting

Nausea and vomiting were noted in 39% of patients. In 3 patients this symptom resulted from significant duodenal obstruction which required a by-pass in the form of a gastroenterostomy. The symptoms of nausea and vomiting per se, were not specifically related to the size of the pseudocyst.

Weight loss / Anorexia

Weight loss was specifically documented in only 35% of all subjects.

Abdominal distension

Diffuse abdominal distension caused by intestinal gas or intraperitoneal fluid was noted in 22% of patients. It was often difficult to differentiate between the presence of a mass and distension resulting from intestinal gas. A prolonged paralytic ileus (persisting for more than 5 days) was noted in two of these patients.

Laboratory information

Jaundice

Obstruction to the common bile duct and subsequent jaundice is a recognised complication of pseudocysts, usually associated with collections situated around the head of the pancreas.

The presence of jaundice (serum bilirubin >30 μmol/l.) at the time of diagnosis was recorded in 12% of patients. The pseudocyst was centred around the head of the gland in 66% of these patients and in the body of the gland in the remainder.

Jaundice was associated with gallstone induced pancreatitis in half these patients and with alcohol in the other 50%.

Hyperamylaseamia

Serum amylase was measured in 82 and urine amylase in 37 patients at the time of pseudocyst diagnosis. In the early part of the study (1962 - 1970) serum amylase was recorded in Wohlgemuth units (6 patients). Although not directly comparable, a value of greater than 10 units was regarded as elevated and one of more than 40 units was equated to a level of 1200 IU/l as measured by the Phadebas method (normal range 70-300 IU/l).

Hyperamylaseamia (>300 IU/l) was found in 64 (78%) patients consisting of 30 (36%) with a value greater than 1200 IU/l and a further 34 (41%) with values between 300 and 1200 IU/l. The frequency of a raised amylase associated with pseudocysts in the published literature varies from 11 to 100% (Table 16).

Twenty five of the 37 patients in whom the urine amylase was also measured had levels greater than 1300 IU/l (the upper limit of the normal range for the Biochemistry laboratory at Glasgow Royal Infirmary) with 17 (68%) of these being greater than 3000 IU/l. Only three patients with an elevated urine amylase had a serum amylase within the normal range (70-300 IU/l).

Leukocytosis

The white blood count was raised above $10x10^9$ cells/l in 42% of patients. Twelve patients (12%) had a level greater than 15×10^9 cells/l and 7 (7%), greater than $20x10^9$ cells/l. As with the amylase levels, the reported occurrence of a leukocytosis (40%-90%) associated with pseudocysts varies considerably in the literature (Table 16).

Radiological information

A barium meal with lateral erect views to show gastric, duodenal or colonic displacement, was performed in 30 patients and significant gastric displacement was detected in 29 subjects. In the one exception the barium study was misleading as it was interpreted as showing a gastric carcinoma with extensive submucosal involvement. At subsequent surgery a large pseudocyst, distorting the stomach was found and drained. There was no evidence of any intrinsic gastric lesion.

Since 1970 ultrasonic scanning has become the diagnostic method of choice for pancreatic pseudocysts. In the present study, at least one ultrasonic scan was performed in each of 77 patients. The dimensions of the pseudocyst were recorded in 66 examinations (85%). In the other 11 patients no comment was made with regard to the size (1) of the pseudocyst, or the radiologist simply described the pseudocyst as "small" (4) or "large" (6). Such descriptive terms are inadequate since, with current ultrasound machines, it requires very little effort to make accurate measurements of a fluid collection while a scan is being performed.

In the remaining 23 patients in whom ultrasonic scanning was not used as the diagnostic method, no size for the pseudocyst was recorded in 19 patients, in 3 it was described as "small" and "large" in 1.

In addition to ultrasound, Computerised Tomographic scanning was employed in 7 patients in order to establish a diagnosis of pseudocyst.

Time to diagnosis of pseudocyst

The median time from acute pancreatitis to the establishment of the diagnosis of a pseudocyst was 27 days. The range in time was considerable (4-479 days) (Figure 10). The time was calculated from the onset of acute symptoms until the time a collection was confirmed by radiology (barium meal, ultrasound or CT scanning) or operation. In patients who had a measureable fluid collection around the pancreas demonstrated by ultrasound at an early stage (within 10 days of acute pancreatitis) and subsequently had further confirmation of pseudocyst formation (repeat scanning or surgery), it was considered valid to regard the earlier period as the time to diagnosis despite the fact that a fibrous, granulating wall may not have formed within the earlier period. Patients who developed transient peripancreatic fluid collections following acute pancreatitis have been excluded from this thesis.

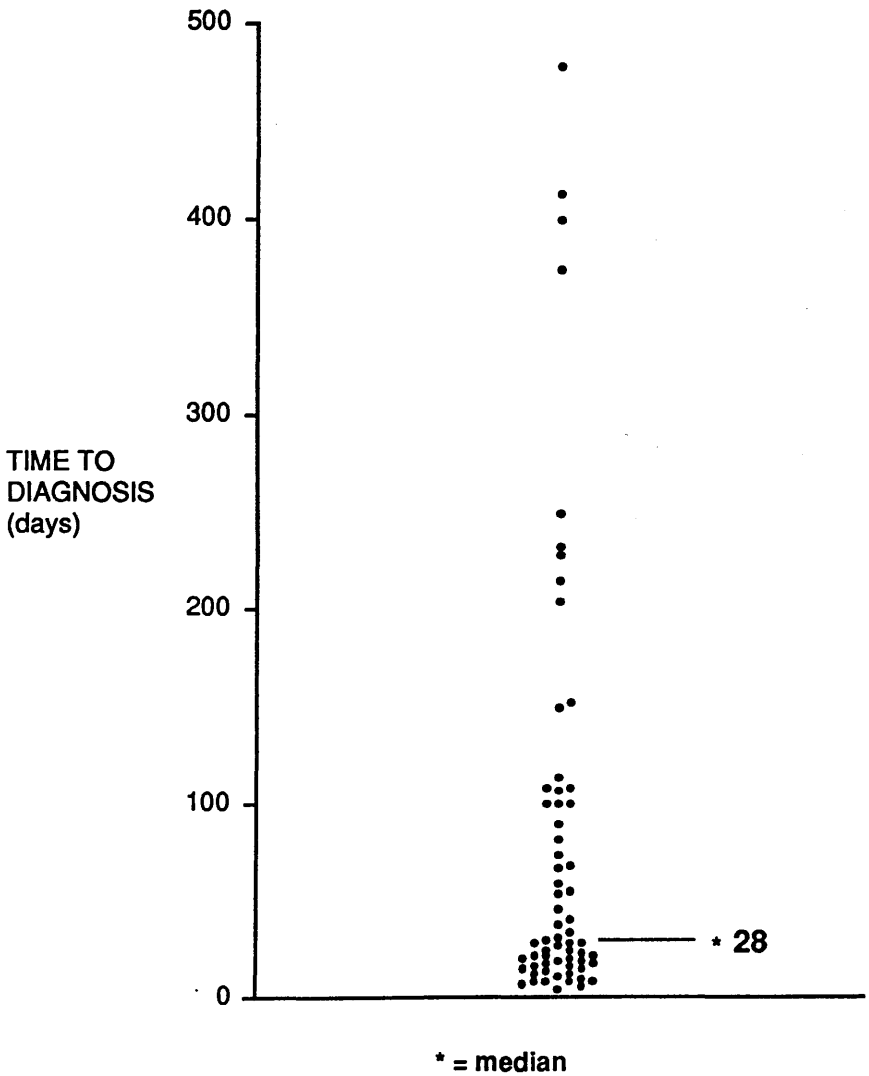


FIGURE 10 Graph illustrating the distribution of the time from acute pancreatitis until diagnosis of a pseudocyst. Glasgow Royal Infirmary patients.

Complete information to allow an accurate assessment of a definitive formation time was only available in 67 patients. The majority of pseudocysts were diagnosed within four weeks. The considerable variation in the time to development of a pseudocyst is a common finding in other studies of patients with pseudocysts. The majority of reports indicate that when there is a high proportion of patients with alcohol induced disease the time from a preceding episode of acute pancreatitis until confirmation of a pseudocyst is often difficult to determine.

Site of Pseudocyst

The site of origin of a pseudocyst in relation to the pancreas as determined by ultrasound scanning or at laparotomy was from the body of the gland in 42% of patients, around the head in 25%, at the neck in 22% and in the tail in 11%.

AETIOLOGY

The principal aetiological factors responsible for the preceding acute pancreatitis are shown in Table 17. Alcohol was the cause in 59 patients; gallstones in 27; trauma in 4; operation in 1; and in only 9 did the cause remain undetermined.

Four patients had both gallstones and alcohol as potential causes of their acute pancreatitis. In two of these patients gallstones have been regarded as the predominant factor and conversely alcohol in the others.

AETIOLOGY	NUMBER OF PATIENTS		
	MALE	FEMALE	TOTAL (= %)
Alcohol	49	10	59
Gallstones	13	14	27
Unknown	6	3	9
Trauma	2	2	4
Post operation	-	1	1
TOTAL	70	30	100

TABLE 17 Aetiology of antecedent acute pancreatitis in 100 patients from Glasgow Royal Infirmary who developed pseudocysts.

4 patients had both gallstones and alcohol as aetiological factors.

Alcohol

In common with previous studies, alcohol was the predominant aetiological factor 59 (%) and this group comprised mainly young men (49) (median age 37 years: range 21-62 years). The 10 females had a median age of 49 years (range 21-58 years). All these patients admitted to drinking significant quantities of alcohol on a regular basis (estimated minimum of 80g alcohol per day). Eleven (19%) had recurrent episodes of severe abdominal pain and were regarded as having chronic pancreatitis.

Gallstones

Twenty seven patients (27%) had gallstone induced pancreatitis. The median age of the 13 males (55 years, range 36-77 years) was greater than that of the 14 females (48 years, range 30-74 years). The presence of gallstones was confirmed at the time of pseudocyst drainage in 26 (96%) patients although only 7 had concomitant biliary tract surgery (cholecystectomy in 5 and cholecystostomy in 2).

The remaining patient had gallstones identified by oral cholecystography during follow up.

Nineteen of the 27 patients with gallstones ultimately had biliary tract surgery. No record of such surgery was found in the other 8 subjects.

One patient later developed chronic pancreatitis because of recurrent bile duct stones which developed after a cholecystectomy.

Traumatic

The pseudocysts were post traumatic in origin, in 4 patients. All 4 suffered blunt abdominal injuries associated with road traffic accidents.

Post operative

One patient developed a pseudocyst as a result of pancreatitis following an elective cholecystectomy at which a per-operative cholangiogram was performed and the common bile duct was deemed to be free of stones.

Idiopathic

The aetiology was regarded as being of an idiopathic nature in 9 (%) patients. All of these patients had biliary tract investigations, serum calcium estimations and the majority (6) had negative viral serology and blood lipid estimations. Repeat investigations were performed in 5 patients during a follow up period but there was no uniformity to these investigations because the patients were under the care different consultants.

One male patient suffered repeated episodes of pancreatitis and developed chronic pancreatic pain. An ERCP demonstrated duct changes consistent with a diagnosis of chronic pancreatitis. He denied any alcohol intake and no other specific cause was found despite repeated investigations.

OUTCOME

The pseudocyst resolved spontaneously in 22 patients (22%). In a further 6 patients there was evidence of resolution of a pseudocyst at a time prior to the event noted for this analysis. All six required surgical drainage of the second or recurrent pseudocyst. These 28 patients are discussed further in Chapter 5.

Surgical drainage was performed in the other 78 patients (78%).

Twelve patients died (mortality 12%), all of whom developed their pseudocysts following an episode of acute pancreatitis.

PATIENTS UNDERGOING DRAINAGE OF A PSEUDOCYST

Drainage procedures were performed in 78 patients (Table 18).

Cystogastrostomy

The most common procedure was a posterior cystogastrostomy, performed in 47 patients. In every patient the stomal edges of the stomach were sutured to the fibrous wall of the pseudocyst.

An accurate measurement of the interval from the episode of acute pancreatitis until surgical intervention was available in 34 of these patients (68%). The median time to surgery was 86 days (range 15-482 days) (Figure 11). The range for the time to surgery is considerable, but no patient had a further documented episode of pancreatitis in the interim period.

	NUMBER OF OPERATIONS RELATED TO AETIOLOGY					
OPERATION	TOTAL	ALCOHOL	GALLSTONES	OTHER	DEATH	
Cystogastrostomy	50*	27	16	4	5	(10%)
External drainage	11	5	3	3	5	(45%)
Distal resection	8	6	-	2	-	
Roux loop	7	4	3	-	1	(14%)
Laparotomy aspiration	4	4	-	-	-	
Cystodudodenostomy	3	3	-	-	-	
Percutaneous drainage	2	2	-	-	-	
Second procedures (all cystogastrostomy)	7					

(* 3 patients underwent 2 cystogastrostomies)

TABLE 18 Drainage procedures for 78 patients from Glasgow Royal Infirmary related to the aetiology of the antecedent acute pancreatitis.

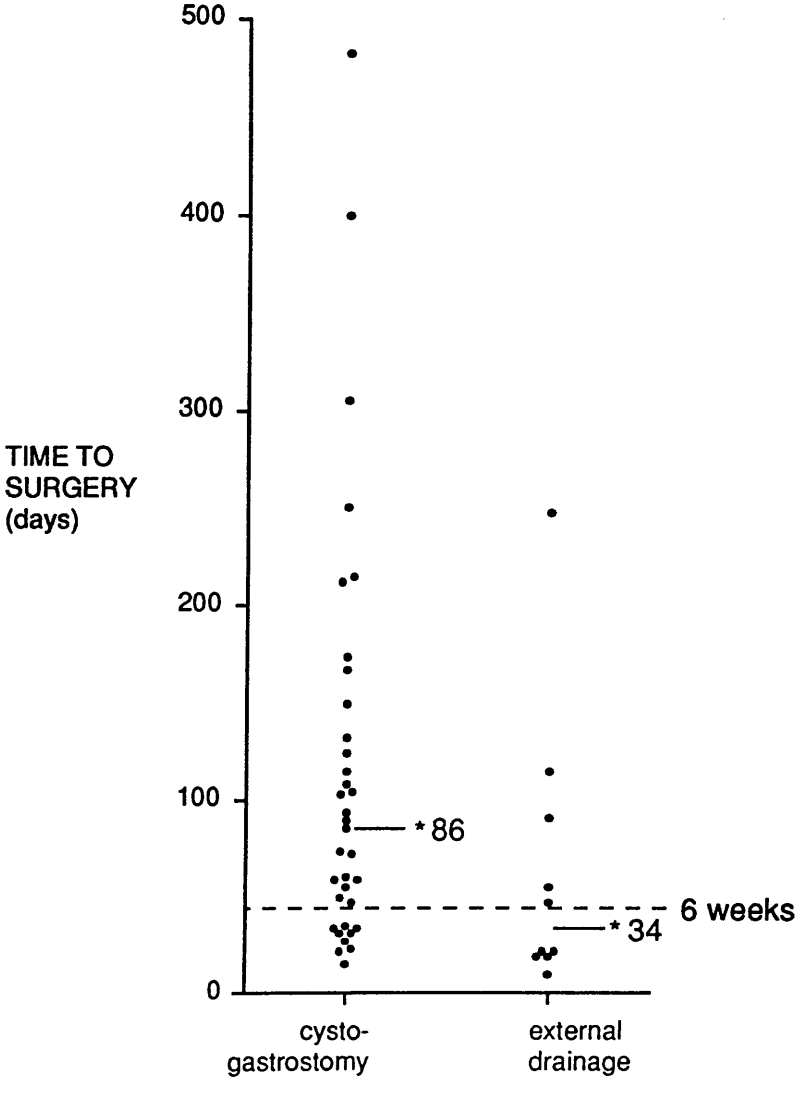


FIGURE 11 **Graph illustrating the distribution of the time from acute pancreatitis until surgical drainage of a pseudocyst. Points grouped according to the type of operation performed.**
Glasgow Royal Infirmary patients.

The patient in whom the time to surgery was estimated to be 482 days had alcohol as the aetiology of his pancreatitis and may well have experienced further minor episodes of acute pancreatic inflammation without attending hospital or his general practitioner.

Eight patients had a cystogastrostomy performed within 6 weeks from a diagnosis of pancreatitis. In all eight, at the time of operation, the pseudocyst wall was regarded as adequately thick ("mature") to allow a cystogastrostomy to be performed safely . Two of these eight patients (25%) died however, both as a result of secondary haemorrhage.

Three (7%), of the other 42 patients undergoing cystogastrostomy six weeks after their acute pancreatitis, died (Table 19). All three (patients CM, JW, WC in Table 20) had been re-admitted electively for surgical drainage of their pseudocyst. The cause of death in each is noted in Table 20.

External drainage

Eleven patients had the pseudocyst dealt with by laparotomy and external drainage with tube drains. The median time to operation in the 10 patients for whom accurate data was available was 34 days (range 9-248 days) (Figure 11). The four patients treated surgically after 47 days had been discharged following the acute episode of pancreatitis and readmitted with recurrent symptoms. The pseudocyst was then diagnosed and treated. Two of the five patients whose pseudocyst was drained after six weeks died compared to 3 of the five drained within six weeks (Table 19).

OPERATION	TIME TO SURGERY FROM ONSET OF ACUTE PANCREATITIS	
	< 6 WEEKS	> 6 WEEKS
Cystogastrostomy	2/8	3/42
External drainage	3/5	2/5

TABLE 19 Number of patients who died related to the time from acute pancreatitis to surgery (before or after 6 weeks) and to the type of surgery performed.

PATIENT	SEX	AGE	AETIOLOGY	OPERATION	CAUSE OF DEATH	COMPLICATIONS
GW	M	40	Alcohol	External drainage	Respiratory failure	Renal infection
JW	F	48	Trauma	External drainage	Sepsis	Venous thrombosis
MR	F	54	Gallstone	External drainage	Sepsis	Duodenal fistula
WD	M	66	Gallstone	External drainage	Sepsis/renal failure	Jaundice/embolous
AS	M	71	Unknown	External drainage	Sepsis/haemorrhage	
CM	M	35	Alcohol	Cystogastrostomy	Sepsis/haemorrhage	Abscess/jaundice
WC	M	57	Gallstone	Cystogastrostomy	Haemorrhage	
JW	M	57	Gallstone	Cystogastrostomy	Cardiac arrest	Myocardial infarct
PP	M	60	Unknown	Cystogastrostomy	Haemorrhage	Anaemia
WB	M	70	Gallstone	Cystogastrostomy	Sepsis/haemorrhage	Chest/jaundice
WB	M	52	Gallstone	Roux en Y	Sepsis	
JB	M	29	Alcohol	Died: no operation	?Sepsis	

TABLE 20 Details of the 12 patients who died including, age, sex, type of operation, cause of death and other complications.

(M = male: F = female)

In all of these patients the surgeon considered external drainage to be the appropriate procedure because of the clinical condition of the patient . All were extremely ill at the time of surgery, and three of the five who had their operation within six weeks of onset of their pancreatitis had developed multiple organ failure prior to surgery (Table 20). The poor outcome was more a reflection of early disease severity and was not necessarily related to the type of operation performed.

Distal pancreatic resection

A distal pancreatic resection was performed in eight patients. In each of the subjects the cavity was in the tail of the pancreas and the pseudocysts were small (<6cm maximum diameter). There were no serious post operative problems in these patients. This type of surgery has a limited place in the management of pseudocysts but can be curative in selected patients.

Four of these pseudocysts in the tail of the pancreas occurred in patients with chronic pancreatitis, an important factor in determining the outcome.

Cystojejunostomy (Roux en Y)

Drainage into a Roux loop of jejunum was performed in 7 patients. In one, the procedure was combined with a cystogastrostomy because a bilocular pseudocyst extended across the head and body of the gland.

One patient from this group died (mortality 14%) as a result of sepsis (Table 20). In the other 6 there was no evidence that the loop had become detached from the pancreas as has been previously reported (Trapnell 1971, Warshaw and Rattner 1985). Two of these patients had associated chronic pancreatitis and one subsequently came to a total pancreatectomy because of continued chronic pain.

Cystoduodenostomy

The pseudocyst was drained into the duodenum in three patients. This method of drainage was chosen because the collection, in the head of the gland, was in close proximity to the duodenum and a direct route of drainage was favoured.

In one patient, cystoduodenostomy was combined with a cystogastrostomy because of the bilocular nature of the cyst in the head and body of the gland. There were no major complications associated with cystoduodenostomy.

Aspiration at laparotomy

Four patients were treated by simple aspiration of a pseudocyst in the head of the gland at the time of laparotomy. In one, the pseudocyst had encroached upon the duodenum to such an extent that a gastroenterostomy was performed. This pseudocyst had been diagnosed by ultrasound and was 8cm in diameter. At the time of the laparotomy it had reduced considerably, and only a small quantity of fluid was aspirated.

In a further patient in this group, the drainage procedure was combined with a transduodenal sphincteroplasty in an attempt to improve the drainage of the pancreatic duct. A third patient developed a second, larger pseudocyst 7 months after aspiration of the original one. This second lesion was successfully drained by a cystogastrostomy. In the final patient in this group, aspiration alone proved successful in dealing with the problem without further intervention being necessary. All four patients had alcohol associated pancreatitis.

In patients with small localised pseudocysts simple aspiration at laparotomy has been surpassed by percutaneous ultrasound guided aspiration which avoids the necessity of a formal operation.

Percutaneous aspiration

Non-operative, percutaneous needle aspiration under ultrasound guidance was used to drain the pseudocyst in 5 patients. Prolonged catheter drainage was attempted in one of these patients. In three subjects the collection refilled within 4 weeks (range 10-28 days) and surgery was required. External drainage was used in one patient and a cystogastrostomy in the other two. Therefore, percutaneous drainage alone was successful in only 2 patients. Neither had any subsequent evidence of refilling of a pseudocyst.

This method of drainage is discussed in more detail in Chapter 6.

MORTALITY AND MORBIDITY

Twelve patients died because of their pancreatic pseudocyst. Details of these patients are given in Table 20. One patient died prior to elective drainage of a recurrent pseudocyst. He had experienced a second severe episode of pancreatitis culminating in the appearance of his second pseudocyst two years after the original lesion. He was admitted for elective drainage and became pyrexial, jaundiced and developed a leukocytosis. On the evening prior to operation he suffered a circulatory collapse and resuscitation was unsuccessful. Acute pancreatitis and a pseudocyst were confirmed on post mortem examination. There was no evidence that the pseudocyst had ruptured and it is possible that the cause of his deterioration was related to a septicaemic event in association with the pancreatitis.

The other 11 patients who died all had surgical drainage of their pseudocysts. Five patients were treated by cystogastrostomy (mortality 10%), five underwent external drainage (mortality 45%) and one a cystojejunostomy (mortality 14%) (Table 20). There were no significant differences in the mean times from operation to death for each operation.

Cause of death: Sepsis

The major factor contributing to death was sepsis which occurred in 8 of the 12 patients who died. It was noted in three patients in association with haemorrhage and was present in a further 5. In four of these patients septicaemia was manifest following a drainage operation. Three had undergone external drainage of sterile pseudocysts but culture of fluid from the drains subsequently grew pathologically significant bacteria in all three. A fourth patient underwent a cystojejunostomy but his condition deteriorated because of continued intraperitoneal sepsis and pneumonia. The median time from operation to death in patients with sepsis was 26.5 days (Table 20) and these patients remained seriously ill throughout their post operative period. Four of these patients had gallstones as the aetiology of their acute pancreatitis (Table 20) but none had biliary tract surgery concomitant with pseudocyst drainage. It is now considered that the failure to eradicate stones for the biliary tree is a serious threat to local and generalised sepsis in such patients (Imrie et al 1988).

The remaining patient in whom sepsis possibly contributed to death was the one described previously who died prior to drainage of a recurrent pseudocyst. With the exception of this last patient, all with septic complications received antibiotic therapy at some time during their illness.

Haemorrhage

Gastrointestinal haemorrhage occurred in 5 patients and was a major factor contributing to death in each. In 3 of these patients the bleeding followed surgical drainage of a pseudocyst and originated from either the cystogastrostomy stoma or from within the pseudocyst cavity. This occurred despite the use of haemostatic stomal sutures at the initial operation. All three had further surgery and secondary suturing of the stoma. One of these three patients died 11 days after the second operation as a result of a further haemorrhage. A second patient developed multiple retroperitoneal abscesses and required six further operations to drain pockets of pus. He was treated in an intensive care unit for most of his illness and eventually his abdominal wound was left open and packed but he succumbed from multi-organ failure and sepsis 47 days after the onset of his acute pancreatitis. The third patient of this group also developed septicaemia following a second operation to re-explore the pseudocyst cavity. He had been referred from another hospital for treatment of established renal failure which developed after the onset acute pancreatitis.

In one of the 2 remaining patients haemorrhage occurred as a spontaneous event associated with an untreated pseudocyst. This patient produced a massive haematemesis 4 days after his pseudocyst had been diagnosed. Upper gastrointestinal endoscopy revealed a large amount of clot within the stomach and a tense swelling distorting the antrum and duodenum. An urgent laparotomy was performed and a ruptured artery was found stretched across the internal diameter of the pseudocyst. The haemorrhage was controlled but over the subsequent week the condition of the patient progressively deteriorated. He developed deep venous thromboses in both legs, renal failure and septicaemia, factors which eventually caused his death.

The remaining patient in whom haemorrhage contributed to death had severe acute pancreatitis of unknown aetiology. He made initial progress following the acute episode but developed persistent vomiting as a result of a large bilocular pseudocyst obstructing the duodenum. At operation this obstruction was relieved by draining the pseudocyst but within a week of surgery he developed haematemesis and melaena. Repeated blood transfusion was required to maintain his haemoglobin at a satisfactory level. He was regarded as unfit for further surgery and he died 20 days after his operation. No post mortem examination was performed.

Other causes of death

Three other patients died. One following a cardiac arrest precipitated by a myocardial infarction on his first post-operative day. Coronary artery disease was confirmed at post mortem examination. The pseudocyst in this patient was filled with thick green fluid which was sterile on culture. A second patient died 4 days after surgery as a result of acute renal and respiratory failure. Post mortem examination revealed a residual pseudocyst, bronchopneumonia and pyelonephritis.

The third patient died because of persistent pancreatic inflammation and a duodenal fistula following external drainage of a small collection in the head of the pancreas. It is possible that infection also contributed to this death.

Other complications

Ten other patients who underwent cystogastrostomy experienced a variety of complications (Table 21). Similarly, 3 of those whose pseudocyst was drained externally experienced significant problems. One of the seven patients who had a Roux en Y cystogastrostomy drainage died but there were no major complications in the other 6. Although the numbers are small, this type of drainage procedure can produce satisfactory results and is favoured by some surgeons. Those who had a cystoduodenostomy or a distal resection were without significant problems in the post operative period. The complications occurring in the group of 22 patients in whom the pseudocyst resolved spontaneously are also detailed in Table 21. All were relatively minor.

	CYSTO-GASTROSTOMY	EXTERNAL DRAINAGE	ROUX EN Y DRAINAGE	SPONTANEOUS RESOLUTION
NUMBER WITH COMPLICATIONS	10	3	0	7
Haemorrhage	-	1	-	-
Pleural effusion	3	-	-	5
Wound dehiscence	3	-	-	-
Ascites	1	-	-	1
Deep venous thrombosis	1	-	-	-
Skin nodules	2	-	-	-
Doudenal obstruction	1	-	-	-
Subphrenic abscess	1	1	-	-
Jaundice	-	-	-	1
Axillary vein thrombosis	-	1	-	-

TABLE 21 Details of the complications in patients who survived following surgery and those in whom a pseudocyst resolved spontaneously.

MORTALITY RELATED TO AETIOLOGY

When considered in relation to the aetiology of the preceding pancreatitis the mortality figures assume considerable importance (Table 22). (Imrie et al 1988). In six (50%) of the 12 patients who died, a pseudocyst developed following an episode of gallstone induced acute pancreatitis. The mortality related to this aetiology was therefore, 22% (6 of 27 patients) compared to only 5% (3 deaths) from the 59 patients with alcohol induced acute pancreatitis. This difference was significant ($p < 0.05$ Chi squared test) and may, in part, be attributed to a difference in age of the patients with gallstone pancreatitis (median age of those dying 57 years, range 52-66 years) when compared to those with alcohol associated disease (median age of those dying 35 years, range 29-40 years). Two of the three deaths related to alcohol were caused by sepsis and/or haemorrhage. The third patient died of respiratory and renal failure. Of the 6 gallstone related fatalities, 5 were caused by sepsis and/or haemorrhage. The remaining patient died as a result of a myocardial infarction. None of the patients with gallstones had definitive biliary tract surgery at the time of surgical drainage of their pseudocyst. It is possible that persistent infection within the biliary tree contributed to the sepsis in these patients.

AETIOLOGY	NUMBER OF PATIENTS	DEATHS	%
Gallstones	27	6 (5M:1F)	22*
Alcohol	59	3 (3M)	5*
Unknown	9	2 (2M)	22
Trauma	4	1 (1F)	25
Post operation	1	-	-
TOTAL	100	12	

TABLE 22 Number and percentage of patients with a pseudocyst who died related to the aetiology of acute pancreatitis.

(* significant difference between the mortality amongst those with an alcohol aetiology compared to those with gallstones as the cause. Chi squared test, $p=<0.05$)

(M = male: F = female)

RECURRENT PSEUDOCYSTS

After surgical drainage or spontaneous resolution of the pseudocyst, a second collection developed in 12 patients (12%). In this group of patients the preceding acute pancreatitis was caused by alcohol in 7, gallstones in 3, trauma in 1 and the aetiological factor remained unknown in the remaining patient. Six of these occurred within four weeks of drainage of the original collection. The initial drainage procedure had been by percutaneous aspiration in 3 of these patients and cystogastrostomy in the other three. Four of these six patients were treated successfully by a cystogastrostomy on a second occasion and one required external drainage. The remaining patient required external surgical drainage 18 days after percutaneous aspiration. He developed major complications (sepsis and haemorrhage) and ultimately died.

In the six remaining patients, the second collection developed between 7 months and 3 years after the initial lesion. The first pseudocyst had been drained surgically in five of these patients and it had resolved spontaneously in the other patient. It is difficult to determine whether these second collections were recurrences of the original or new pseudocysts at a different site.

The second collection was treated successfully by cystogastrostomy in three patients, spontaneous resolution occurred in a further two patients and the final patient died on the day prior to surgery.

SUMMARY

1. This review is an analysis of data on 100 consecutive patients with pancreatic pseudocysts. They were unselected and form the major part of the experience encountered in one institution over a period of 23 years. A pseudocyst formed following acute pancreatitis in 87 patients.
2. Seventy eight pseudocysts required drainage and 22 resolved spontaneously. The overall mortality was 12% and in 11 of these 12 patients surgery was undertaken as part of their management. The mortality amongst patients undergoing external drainage (45%) was greater than that amongst those drained by other procedures (10%), and the mortality amongst patients in whom surgery was performed within six weeks of pseudocyst development was greater than that of those in whom drainage was performed following this period.
3. Various complications occurred in a further 13 patients (13%), and a second pseudocyst developed in a further 12 (12%) at various times.

4. Only four patients suffered complications caused by the presence of a pseudocyst (3 duodenal obstruction requiring gastroenterostomy: 1 gastro-intestinal haemorrhage). Delayed surgery, beyond 6 weeks was, therefore, found to be an adequate method of pseudocyst management in this study.

5. The complications of delayed rupture, and fistula formation did not occur; haemorrhage occurred in only one patient. This is in contrast to the findings of Bradley et al (1976) who reported that the incidence of complications directly related to a pseudocyst increased after 6 weeks from the time of diagnosis and these authors advocated surgical drainage around this time.

6. With few delayed complications occurring beyond 6 weeks and the median time to surgery (for internal drainage procedures) being greater than 12 weeks from the time of pseudocyst diagnosis it is recommended that this period is a more appropriate waiting time before considering some form of intervention.

7. Alcohol was the predominant aetiological factor (59%) initiating the acute pancreatitis which preceded pseudocyst formation. Gallstones were responsible in 27%. However, the mortality associated with gallstone induced pseudocysts (22%) was significantly greater than that in patients with pseudocysts forming after alcohol induced acute pancreatitis (mortality 5%).

8. Irrespective of the aetiology, sepsis and haemorrhage were the most important factors contributing to death in at least 8 patients. Sepsis associated with cholelithiasis and a partially obstructed biliary system are also important factors and on the basis of these results Imrie et al (1988) have advised that patients forming pseudocysts as a result of gallstone induced pancreatitis should have biliary tract pathology dealt with at the time of pseudocyst drainage.

9. The clinical sign of a palpable abdominal mass correlated with the presence of a pseudocyst of at least 6cm diameter. Seventy four percent of the patients with a palpable mass had a pseudocyst of this size and all these underwent surgical drainage.

CHAPTER 4

RESULTS FOR 29 PATIENTS FROM LEEDS, BRISTOL AND GLASGOW

INTRODUCTION

The details for the group of 29 patients from Leeds, Bristol and Glasgow who developed pseudocysts after acute pancreatitis are presented in the same format as in the preceding chapter and the same definitions of the clinical features are used. This study represents one of the largest prospective series of patients forming a pseudocyst after an episode of acute pancreatitis. The information collected in the 3 cities (Chapter 2) provided an unique opportunity to analyse the complications associated with acute pancreatitis.

CLINICAL FEATURES

The clinical signs and symptoms of patients at the time of diagnosis of the pseudocyst are summarised in Table 23.

ASSESSMENT OF SEVERITY OF ACUTE PANCREATITIS

In this group of 29 patients Glasgow multiple prognostic factors (Table 12) predicted only 10 (34%) as being "severe" within 48 hours of admission. Diagnostic lavage, (Table 13. McMahon et al 1980) performed in 24 patients was a better predictive procedure, but still only identified 13 (54%) as severe (Chapter 2). No study to date has found a consistent indicator to predict the patients suffering acute pancreatitis who are likely to form a pseudocyst.

SYMPTOM / SIGN	NUMBER OF PATIENTS	%	GRI STUDY (%)
Pain	29	100	89
Tenderness	27	93	69
Pyrexia (> 37.5°C)	18	62	21
Mass	15	50	59
Nausea/vomiting	8	28	39
Distension	9	30	22
Jaundice	5	17	12
Paralytic ileus	2	7	2
Anorexia	1	3	35
Hyperamylaseamia (>300IU/l Phabedas)	22	76	77
Leukocytosis ($>10 \times 10^9$ cells/l)	23	79	42

TABLE 23 Incidence of symptoms, signs, raised serum amylase and leukocytosis in 29 patients with pseudocysts from Leeds, Bristol and Glasgow compared to the result for patients from Glasgow Royal Infirmary.

The intention of initial severity assessment, however, is to identify at an early stage of illness, those patients who are likely to become severely unwell and require intensive management. The formation of a pseudocyst is a serious but delayed complication of acute pancreatitis and as such early assessment can not necessarily be expected to predict it. Estimation of acute phase reactants (e.g. C-reactive protein) may be more valuable in assessing delayed complications.

LABORATORY INFORMATION

Jaundice

The serum bilirubin was elevated (> 30 μmol/l) in only five patients (17%), three of whom had gallstones as the underlying cause of their acute pancreatitis. No specific aetiological factor was found in the other two (idiopathic).

Hyperamylaseamia

At the time of pseudocyst diagnosis the serum amylase was greater than 300 IU/l in 22 patients (76%) and greater than 1200 IU/l in 11 (38%).

Leukocytosis

The white blood cell count was greater than $10x10^9$ cells/l in 23 (79%) of the 29 patients with the level being greater than $15x10^9$ cells/l in 10 (34%).

RADIOLOGICAL INFORMATION

The pseudocysts were detected by ultrasonography in 26 patients (90%) and by CT scanning in the other three. This latter form of imaging was also used in three other patients to confirm ultrasound findings.

Dimensions of the pseudocyst were recorded in 19 (65%) of the 29 patients, the largest diameter being taken as the most significant. In an additional 5 (19%) patients, the lesion was simply described as "large" which has been regarded as implying a diameter of at least 5cm. The remaining 5 patients did not have the dimensions of the pseudocyst recorded. Three of the pseudocysts in these 5 patients were of sufficient size and clinical importance to warrant surgical drainage. Repeated ultrasonic scans showed resolution in the other two.

Following admission with acute pancreatitis, the median time to clear identification of a collection by ultrasound or CT scanning was 19 days (range 2-49 days) (Figure 12). Six (21%) patients had been discharged after the acute episode of pancreatitis without a pseudocyst being diagnosed despite ultrasound scanning in 4. All six patients developed further abdominal pain and five were readmitted as emergencies at a median time of 14 days (range 3 - 23 days) following original discharge form hospital. A pseudocyst was diagnosed during the second admission. The remaining patient had the diagnosis made by a CT scan performed as an out patient.

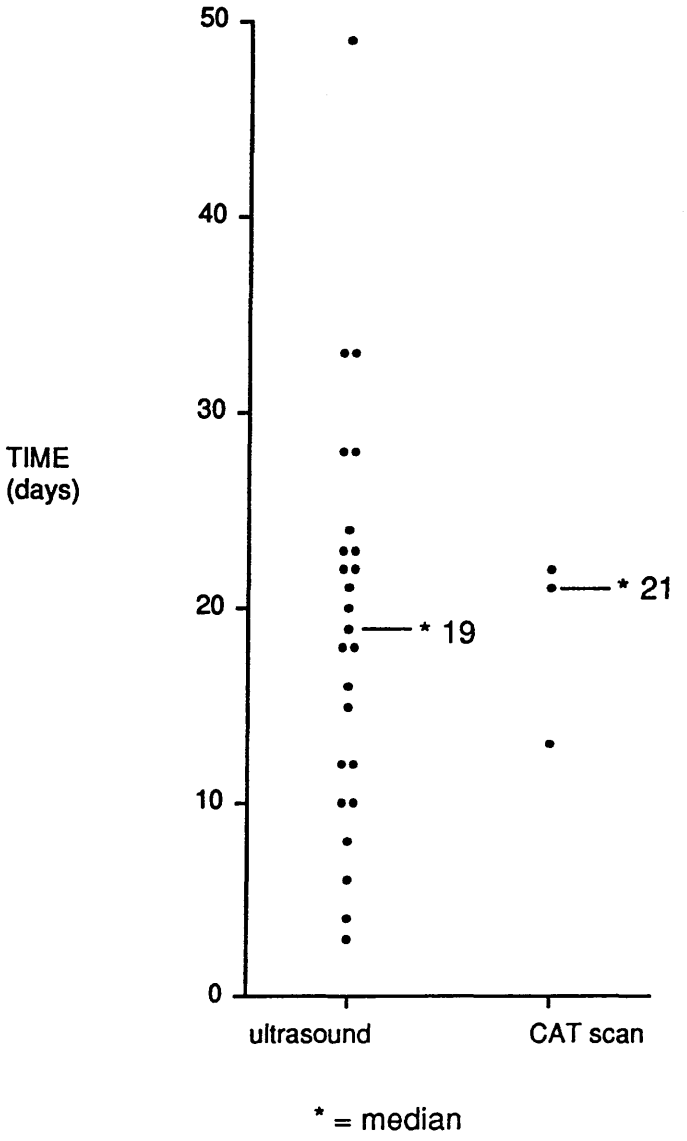


FIGURE 12 **Graph illustrating the distribution of the time from acute pancreatitis until detection of a pseudocyst by ultrasound or CT scanning.**
Leeds, Bristol & Glasgow patients.

AETIOLOGY

Fourteen (48%) of the episodes of acute pancreatitis were caused by gallstones, 7 (24%) by alcohol, 1 (3%) by a proven ampullary carcinoma, and in the remaining 7 (23%), no specific cause was found (Table 24) despite repeated investigations. The predominance of gallstones as the most common aetiology was unexpected when compared to the results from the earlier Glasgow Royal Infirmary study in which alcohol was, by far, the most common causal factor.

The distribution of aetiological factors noted above was similar to that of all 418 patients with acute pancreatitis (54% gallstones: 20% alcohol: 27% idiopathic) (Corfield et al 1985) studied in Leeds, Bristol and Glasgow.

Eleven patients (78%) with gallstones had biliary calculi confirmed at the time of cholecystectomy or post mortem. Of the other 3 (20%), two had the stones confirmed by ERCP and the other by ultrasound scan alone.

Seven patients had alcohol induced pancreatitis. One male patient developed acute pancreatitis following a solitary bout of excess consumption of alcohol. The other six drank a minimum of 5 pints of beer per day (90-120g alcohol) on most days of the week. One patient from this group developed chronic pancreatitis following his original pancreatic pseudocyst. He ultimately required a distal pancreatectomy to remove a small chronic cyst from the tail of the gland, four years after his initial acute pancreatitis.

AETIOLOGY	MALE	FEMALE	TOTAL	%	DEATHS	% AETIOLOGY IN ALL 418 PATIENTS
Gallstones	5	9	14	48	1	50
Alcohol	7	-	7	24	-	20
Idiopathic	2	5	7	24	1	27
Ampullary carcinoma	-	1	1	3	-	-

TABLE 24 Distribution of 29 patients from Leeds, Bristol and Glasgow according to aetiological factors of acute pancreatitis.

The results for the 29 patients were very similar to those of the total number of 418 patients with acute pancreatitis documented in the 3 cities.

One other patient had small pseudocysts (<3.5cms) detected by ultrasound scan on more than one occasion over a period of three years. None of the patients with alcohol as the underlying cause for their pancreatitis had evidence of gallstones.

Six of the seven patients in whom the aetiology remained unknown had repeated imaging of the biliary tract without gallstones being detected, but none underwent ERCP. Ideally all these patients should have had this investigation performed.

TREATMENT

The initial, standard management for all patients has been described earlier (Table 13). In addition, 14 patients (48%) had a period of parenteral or enteral hyperalimentation. The duration of feeding ranged from 3 to 44 days with a median of 8 days. Antibiotics were administered to 23 patients (77%) at some time during their illness.

The other specific treatment used was therapeutic peritoneal lavage. This was performed as an initial therapy in 6 patients. None of these six patients died compared to 2 of the 23 patients who did not receive lavage (Table 25). The mortality results were not significantly different but these two groups of patients were not strictly comparable. All patients treated with lavage were graded as having severe disease at the time of admission, whereas, only 7 of the other 23 were similarly graded. The acute pancreatitis in other 16 patients was categorised as mild.

	NUMBER	DEATHS	%
LAVAGE (All severe)	6	0	0
NO LAVAGE	23	2	9
NO LAVAGE (severe)	7	1	14

(Difference in mortality not significant, Chi-squared test)

TABLE 25 Number of patients and mortality in those treated with 48 hours of peritoneal lavage compared to the patients in whom this treatment was not employed.

With such small numbers it would be inappropriate to make firm conclusions regarding the effect of peritoneal lavage therapy upon the development of a pseudocyst.

OUTCOME

Eleven (38%) of the 29 patients required surgical drainage of the pseudocyst and there was one death (mortality of 9%) (Table 26).

The pseudocyst resolved spontaneously in 15 (52% of all the patients)(discussed in Chapter 5) of the other 18 patients, in a further 2, the collection was still present at the time of the last documented follow up but in both these patients no further admissions to hospital were noted over a 4 year period.

The remaining patient died without surgery, giving a mortality of 5% for those without drainage.

SURGERY

Surgical drainage of the pseudocyst was performed in 11 patients. In six, a posterior cystogastrostomy was performed in a standard fashion with a stoma size of at least 4cm and the stomal edges oversewn. No patients died in this group and there were few complications.

Roux en Y cystojejunostomy was performed in 3 patients, all of whom were from Bristol. Two were treated in the same surgical unit reflecting a preference for this type of drainage. The third patient was referred to a surgical unit in London. She had a bilocular pseudocyst extending across the body and head of the pancreas. The Roux en Y technique was chosen to achieve adequate drainage of both collections.

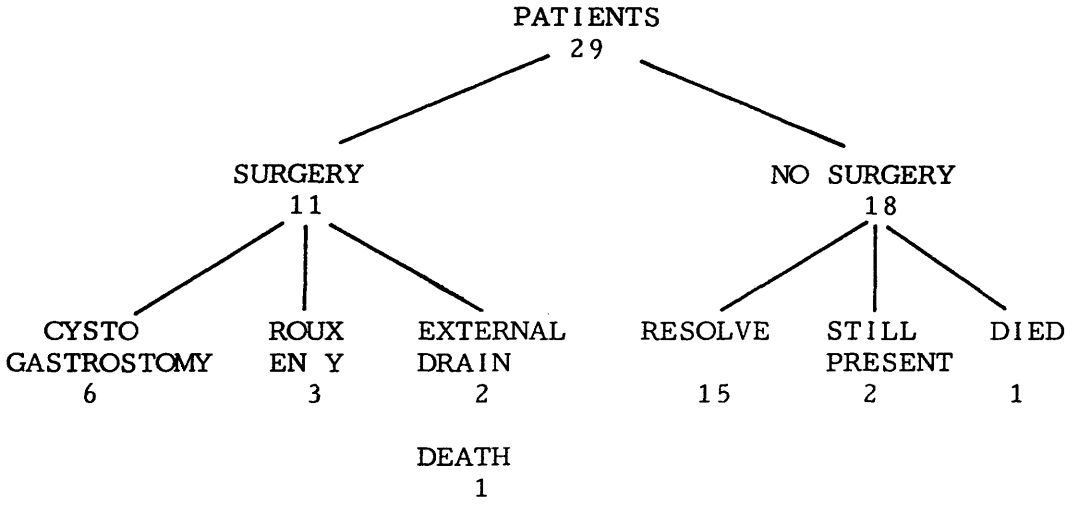


TABLE 26 Clinical outcome and surgical operations in 29 patients with pseudocysts from Leeds, Bristol and Glasgow.

External drainage of a pseudocyst was employed in two patients. Intraperitoneal rupture of the pseudocyst had occurred in both. One of these, a 56 year old man, had been discharged following his acute pancreatitis but was readmitted 17 days later with symptoms of increasing abdominal pain and was found to have a pseudocyst. His symptoms did not settle and at laparotomy (33 days after the onset of acute pancreatitis) the pseudocyst was found to have ruptured. There was a large amount of serosanguinous fluid, with a high amylase concentration, within the peritoneal cavity. This was drained via large diameter plastic drains but abdominal packing was necessary to control haemorrhage encountered during the surgery. On removal of these packs a pancreatic fistula became established but, over a period of 6 months, this gradually resolved without surgical intervention.

The second patient requiring external drainage initially appeared to be recovering from his pancreatitis, but, 21 days after the onset of acute pancreatitis, he developed an epigastric mass which suddenly decreased in size in association with severe abdominal pain, tenderness and hypotension. Laparotomy, at this time, revealed a ruptured pseudocyst with pockets of fluid in the right upper quadrant and right paracolic gutter. The peritoneal cavity was drained but post-operatively the patient developed cardiac failure, pneumonia and suffered a gastro-intestinal haemorrhage, which proved fatal, 2 weeks after his operation. A post mortem examination was not performed and no source of the bleeding was identified.

The aetiology of his acute pancreatitis also remained unknown. This patient was the only one who died after surgical drainage of a pseudocyst giving a mortality of 9% (1 of 11 patients) for all those undergoing surgery. However, mortality associated with rupture of a pseudocyst and external drainage was 50% (1 of 2 patients).

The median time to surgery for all 11 patients was 49 days (range 21-266 days) (Figure 13) from the time of acute pancreatitis. Only three operations (27%) were performed within six weeks of the detection of the pseudocyst and of these 2 were external drainage. The other early operation was a cystogastrostomy performed without complication at 28 days.

PATIENTS WHO DID NOT UNDERGO SURGERY

Eighteen patients did not have their pseudocysts drained. In 15 (i.e. 52% of the 29 patients with a pseudocyst from, Leeds, Bristol and Glasgow) the pseudocyst resolved spontaneously. In two patients a collection was still present and asymptomatic at the time when last seen at follow up. The remaining patient died without undergoing surgery. This patient who died was an elderly lady whose initial peri-pancreatic fluid collection (? pseudocyst) was delineated by ultrasound six days after being admitted to hospital with acute pancreatitis. She developed several complications viz: bilateral pleural effusions, hyperglycaemia, renal failure and was regarded as unfit for surgery. Other methods of drainage such as percutaneous aspiration were not employed.

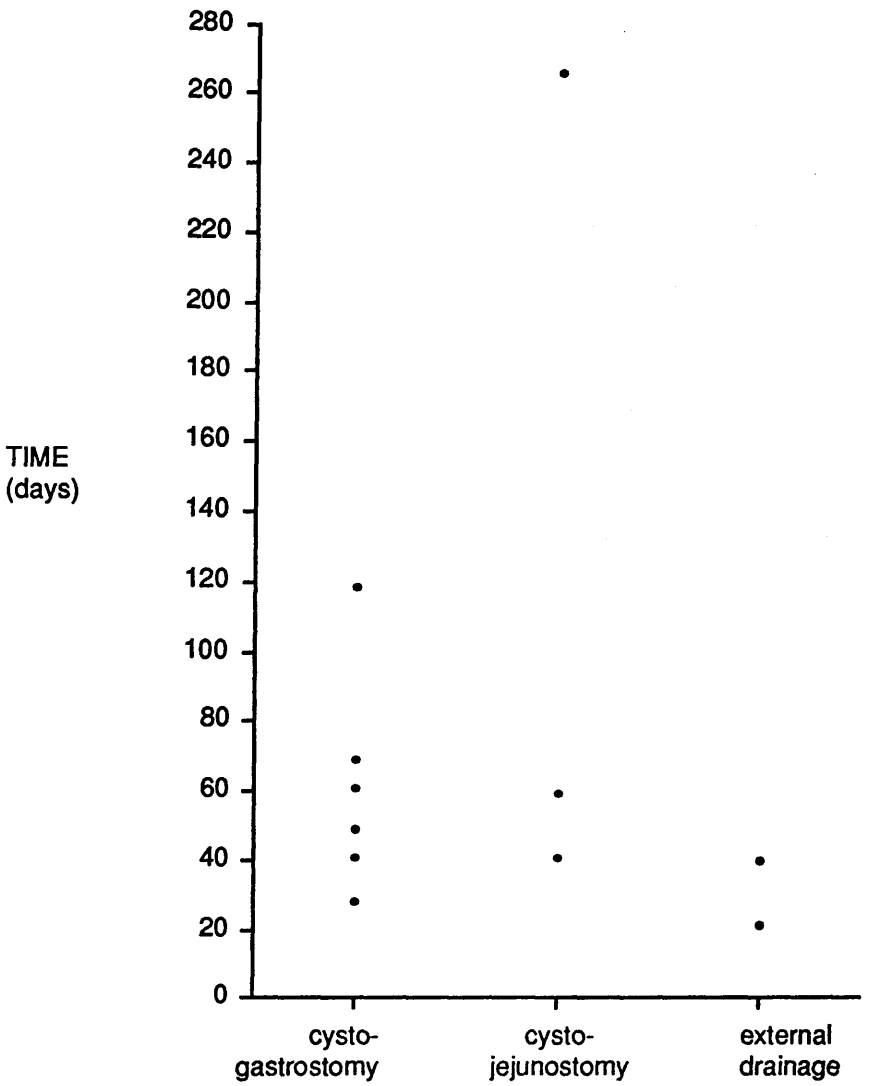


FIGURE 13 **Graph illustrating the distribution of the time from acute pancreatitis until surgical drainage of a pseudocyst. Points grouped according to the type of operation performed.**
Leeds, Bristol & Glasgow patients.

Her respiratory condition deteriorated and she had a fatal cardiac arrest on the 25th day of her illness. Post mortem examination confirmed acute pancreatitis with pseudocyst formation, and coronary artery disease.

In two patients, the pseudocyst was still present at the last documented follow up. In one of whom, the continued presence of a pseudocyst was identified by ultrasonic examination over a period of six months but this patient refused to undergo surgery. He was discharged and no further episodes of pancreatitis were recorded during a follow up time of 4 years.

The second patient had a 5x7.5cm pseudocyst identified, by ultrasound scan, 1 month after her episode of acute pancreatitis. She failed to attend for follow up but no further admissions were traced over a period of four years.

FOLLOW UP

Three of the 27 patients available for follow up died. Two succumbed from causes unrelated to acute pancreatitis or pseudocyst formation and the third as a result of widespread metastases from an ampullary carcinoma which had initially caused acute pancreatitis.

Four of the remaining 24 patients experienced recurrent abdominal symptoms. Two, in whom the pseudocyst had initially resolved spontaneously, developed further cystic lesions. In one of these a second large pseudocyst formed in the body of the pancreas 3 years after the first.

This patient had gallstone induced acute pancreatitis and a renal adenocarcinoma was coincidentally discovered by ultrasound scan during his initial admission. Treatment of this latter condition was given priority and a nephrectomy was performed. His gallbladder was not removed at this time. At the last noted follow up, the recurrent pseudocyst had refilled following percutaneous aspiration and surgical drainage was being considered.

The second patient with a further cystic lesion had alcohol induced chronic pancreatitis. He had recurrent chronic pain and a small cyst formed in the tail of the pancreas 3 years after the first episode. A distal pancreatectomy was successfully performed resulting in an improvement of his symptoms.

Recurrent abdominal pain developed in two further patients both of whom had a cystojejunostomy as the method of drainage of their pseudocysts. Both required readmission to hospital on at least one occasion but there was no evidence of a recurrent pseudocyst and neither had elevated serum amylase levels.

COMPLICATIONS

The importance of the aetiology causing acute pancreatitis complicated by a pseudocyst was noted earlier in this chapter. Amongst the present group of 29 patients there were no deaths in those with alcohol induced disease but one (7%) of the gallstone induced group died.

Complications directly related to the pseudocyst itself were not common in this series but two did rupture spontaneously with an associated mortality of 50%.

A period of six weeks has been suggested as the optimum time to delay prior to surgery to allow the lining of the pseudocyst to mature (Chapter 1). One cystogastrostomy was performed 28 days after detection of the pseudocyst without difficulty and with adequate tissue fibrosis to effect a satisfactory drainage stoma. There were no technical problems with the delayed drainage procedures.

SUMMARY

1. All 29 patients detailed in this section developed a pseudocyst following acute pancreatitis. They were recorded during a study involving 418 patients with acute pancreatitis. The distribution of aetiological factors amongst the patients with pseudocysts was very similar to that in all 418 patients studied. This implies that no single aetiology is more likely to result in pseudocyst formation. This is contrary to the results in the world literature and this is the first study to show such a relationship. All previous studies, including the 100 patients from Glasgow Royal Infirmary noted earlier, have shown a striking preponderance of alcohol induced pancreatitis leading to pseudocyst formation.

2. The higher risk of death associated with gallstone acute pancreatitis complicated by pseudocyst formation (7%) compared to alcohol induced disease (mortality nil) was noted again but the numbers of patients are small.
3. The median time to surgery (internal drainage) was 60 days (Figure 6). This again confirms that a "waiting" period of 6 weeks is inappropriately brief when considering the ideal time for intervention.

CHAPTER 5

SPONTANEOUS RESOLUTION OF PANCREATIC PSEUDOCYSTS

INTRODUCTION

Having considered the natural history of the development and outcome of pseudocysts following pancreatitis in a total of 129 patients the present chapter focuses on spontaneous resolution of pseudocysts. The background information on this aspect of pseudocysts was presented in Chapter 1.

PATIENTS FROM GLASGOW ROYAL INFIRMARY STUDY

As noted in Chapter 3 spontaneous resolution of a pseudocyst occurred in 22 patients and in addition, in a further 6 a pseudocyst had resolved prior to the reference event recorded in the study, giving a total of 28 patients. Details for three of the patients presenting between 1962 and 1971 were very limited and their official hospital records are now untraceable. These patients have been excluded from further analysis.

Sixteen of the 25 patients with sufficient information for analysis were male (median age 43 years, range 20-84 years). The median age of the 9 females was 44 years (range 30-73 years).

Diagnosis

In addition to clinical and biochemical information, the diagnosis of a pseudocyst was confirmed by ultrasound scanning in 24 of the 25 patients and by CT scanning in the other. CT scanning was used in 3 other patients, ERCP in 2 and a barium meal in 6 to confirm the findings of ultrasonic scanning.

Aetiology / Acute and Chronic Pancreatitis.

Alcohol was the cause of the pancreatitis in 14 (56%) (12 male, 2 female) of the 25 patients : gallstones in 7 (28%)(2 male, 5 female) and in the remaining 4 (16%)(2 male, 2 female) no specific cause was found. The distribution of aetiological factors within this group of 25 patients with resolving pseudocysts was similar to that in the 100 patients as a whole (chapter 3).

A pseudocyst developed after an episode of acute pancreatitis in 23 of the 25 patients (92%). The other two were known to have proven chronic pancreatitis at the time their collection formed. A further 3 patients ultimately developed chronic pancreatitis despite the fact that their pseudocysts formed as a result of their first episode of acute pancreatitis. Three of these 5 patients with pseudocysts associated with chronic pancreatitis developed second collections and all 5 had alcohol induced disease.

Time to Diagnosis of a Pseudocyst

The period from acute pancreatitis to the confirmation of a pseudocyst by ultrasound, CT scanning or barium studies, together with appropriate clinical and laboratory findings has been regarded as "the time to diagnosis".

The median time to diagnosis of 21 patients was 18 days (range 4-74 days) (Figure 14). Three of the remaining four patients formed their pseudocysts associated with chronic pancreatitis. An accurate time to diagnosis was impossible to calculate in one subject and in the other two the period between a proven episode of acute pancreatitis and pseudocyst formation was 13 and 14 months respectively.

The fourth patient in this group in which there was no precise time to diagnosis experienced 5 episodes of acute pancreatitis over a period of 9 months. The first episode was alcohol induced but the others were not related to this aetiological factor. A pseudocyst, 5cm in diameter, formed in the tail of the pancreas 3 months after the second episode of acute pancreatitis. This collection resolved over a period of 2 months. A pseudocyst later recurred in the tail of the pancreas and was removed by distal pancreatic resection (Figure 15). Histological examination confirmed the specimen to be a pseudocyst (Figure 16).

Maximum Size of Pseudocyst

The maximum sizes of the pseudocysts in 19 patients, as measured by ultrasound or CT scanning are displayed in Figure 10. No measurements were made on the scans of the other 6 patients and the collections were merely reported as "small" (4) or "large" (2). Such poor scan reporting is unsatisfactory. The maximum diameter in twelve (48%) pseudocysts was 6cm or greater. The median size was 7cm.

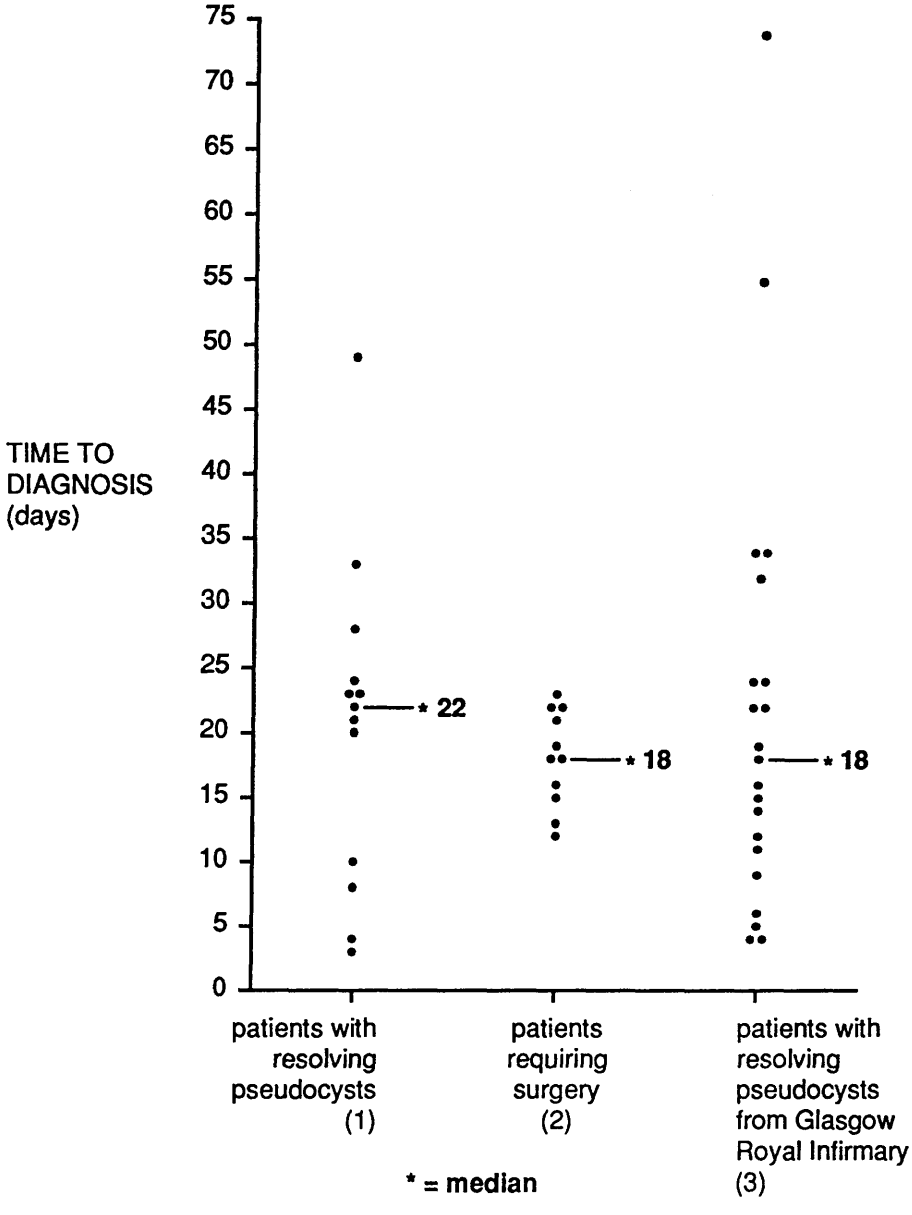


FIGURE 14 **Graph of time from acute pancreatitis until diagnosis of the pseudocyst in :**
1) patients from Leeds, Bristol and Glasgow in whom a pseudocyst resolved spontaneously
2) patients from Leeds, Bristol and Glasgow who underwent surgical drainage
3) those from Glasgow Royal Infirmary in Whom a pseudocyst resolved spontaneously

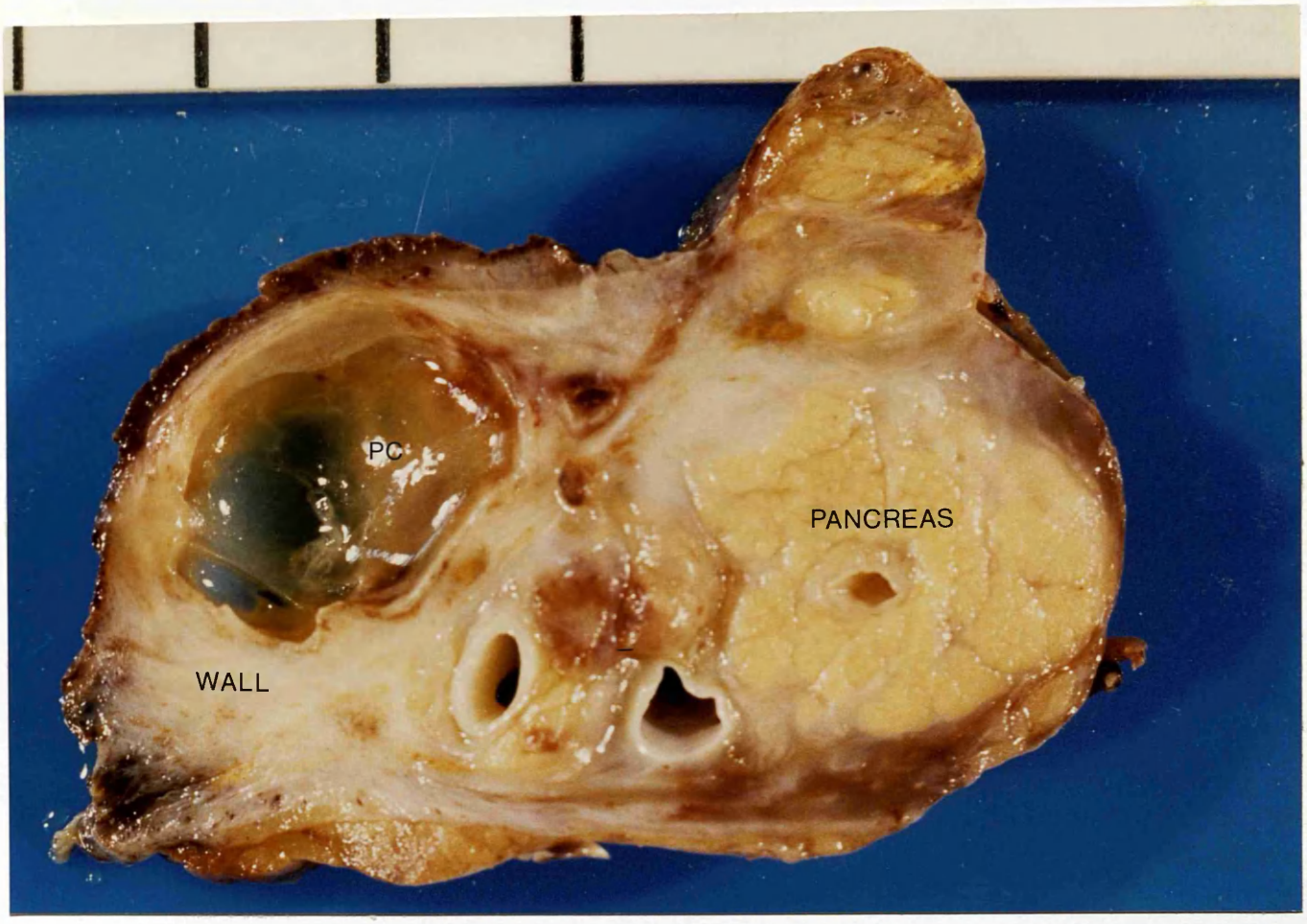


FIGURE 15 Gross operative specimen of a distal pancreatic resection showing a portion of pancreas and a pseudocyst with surrounding fibrosis.

PC = pseudocyst
WALL = thick fibrous wall of pseudocyst

Measure in centimetres.

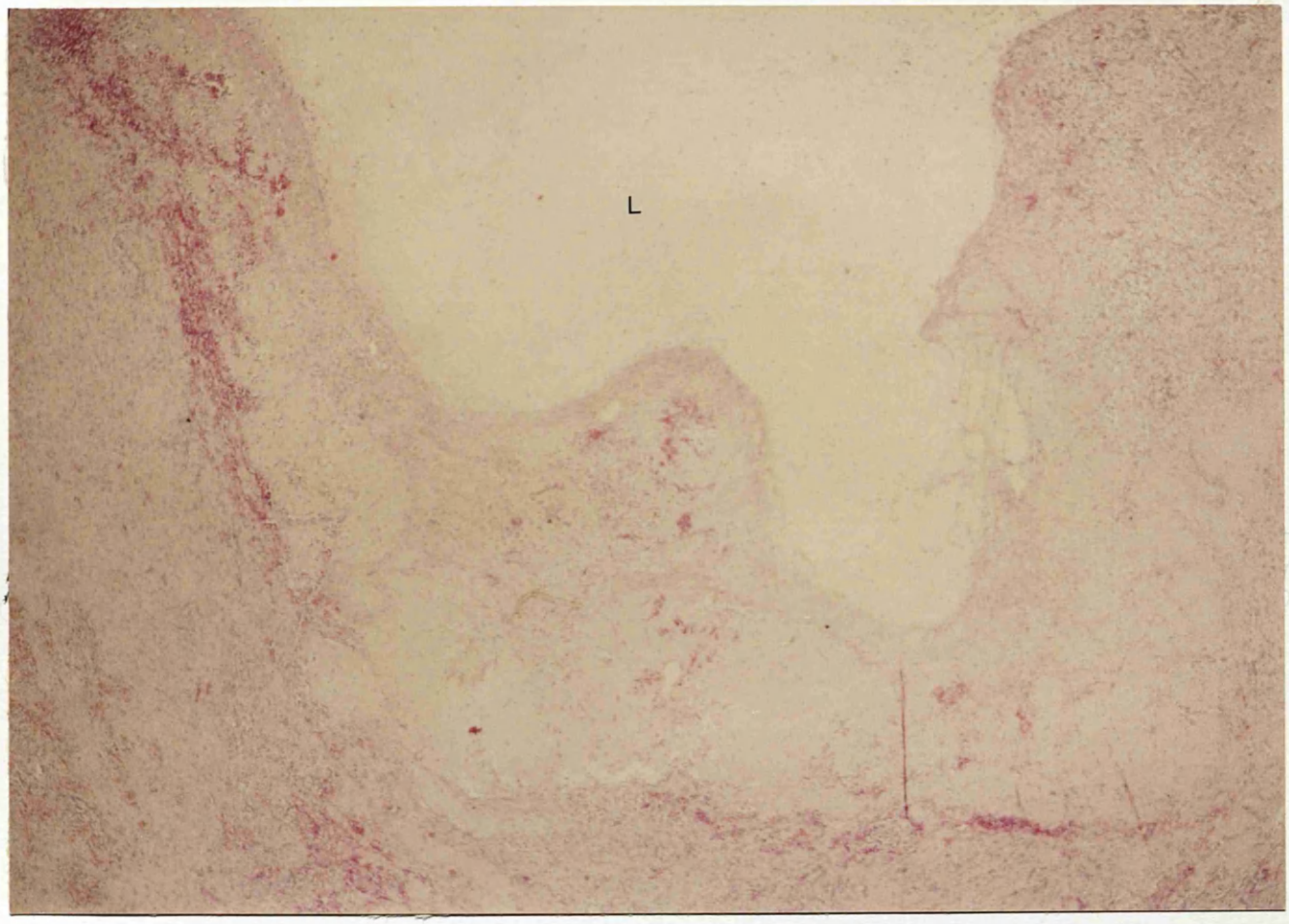


FIGURE 16 Distal pancreatic resection:
Histology of the resected specimen showing dense fibrous tissue surrounding the pseudocyst cavity and no true epithelial lining.

L = Lumen of pseudocyst.

Haemotoxylin and eosin x100.

The sizes of pseudocysts requiring surgery are also displayed in Figure 17. The median diameter for these collections was 10cm (range 4-20cm) but the difference between these and the size of the pseudocysts which resolved was not significant (Mann Whitney test) although there was a trend for the larger pseudocysts to be more likely to require surgery.

Clinical and Laboratory Information

Table 27 summarises the important clinical signs and symptoms in patients in whom a pseudocyst resolved spontaneously and those who required surgery for their pseudocyst. The most striking difference was the presence of a mass. Only 16% of the pseudocysts which resolved spontaneously were recorded as being clinically palpable, despite the fact that 48% of them were at least 6cm in diameter. In contrast 68% of those pseudocysts which required surgical intervention were palpable. Vomiting and anorexia were more common in this latter group but otherwise, the clinical and laboratory findings were similar.

Hyperamylaseamia (>300 IU/L) was more frequent in patients who required surgery but a leukocytosis was present in almost the same proportion (Table 27). The presence or absence of these features in a patient with a pseudocyst was not helpful in determining which collections would resolve.

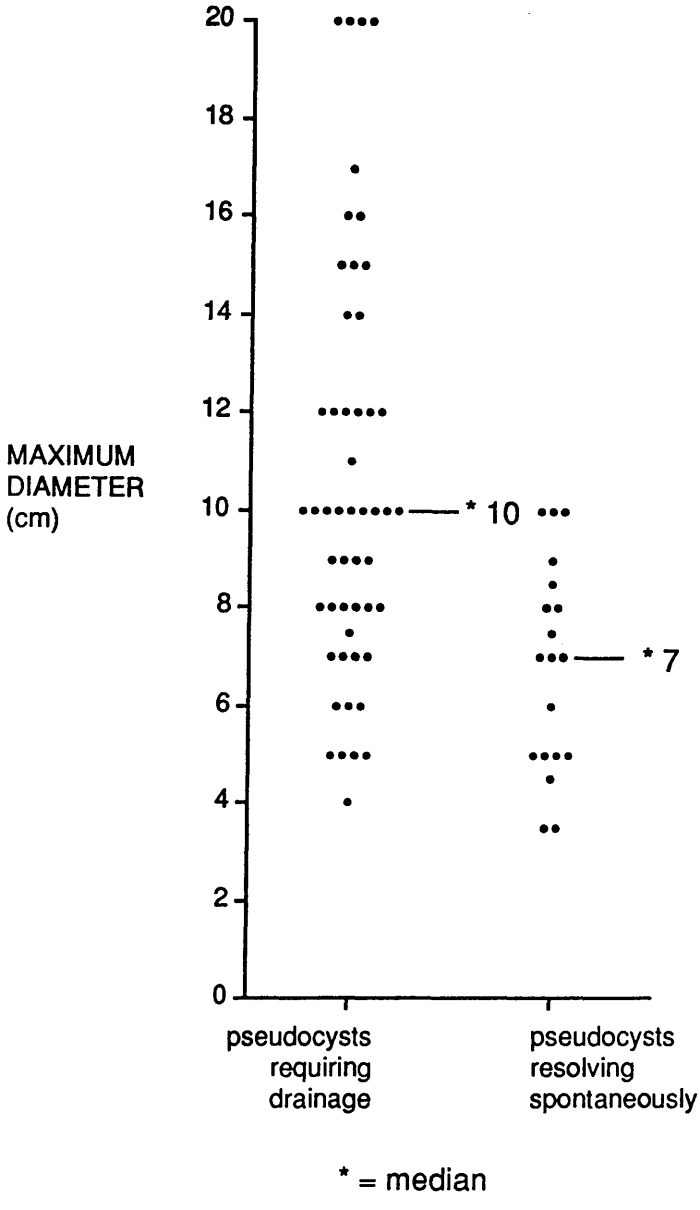


FIGURE 17 **Graph illustrating the distribution of the maximum diameter (cm) of a pseudocyst as recorded by ultrasound. Points grouped into the pseudocysts which underwent surgical drainage and those which resolved spontaneously.**

	OPERATED		RESOLVED	
	number	%	number	%
Pain	57	93	24	96
Tenderness	43	69	19	72
Pyrexia (>37.5^{0}C)	12	20	5	20
MASS	**41**	**67**	**4**	**16**
Vomiting	26	43	7	28
Anorexia	26	43	5	16
Distension	11	18	6	24
Ileus	2	3	3	12
Jaundice	8	13	3	12
Serum amylase				
>300 IU/l	50	81	17	68
>1200 IU/l	25	40	8	32
Leukocytosis				
>10x10^{9}cells/l	26	46	9	36
>15x10^{9}cells/l	9	16	5	20

TABLE 27 Incidence of symptoms, signs, increased serum amylase and leukocytosis in patients from Glasgow Royal Infirmary whose pseudocyst required surgery compared to those in whom a pseudocyst resolved spontaneously.

There was a significant difference in the results (%) for the presence of a palpable abdominal mass in the patients whose pseudocyst resolved spontaneously compared to those which required operation ($p=<0.05$ Chi squared test).

Time to Resolution

The time to complete resolution for all 25 pseudocysts is shown in Figure 18. Clinically, all patients were improved at the time of resolution. Ultrasound scanning confirmed resolution in 19 patients but in the other 6 clinical findings alone were accepted as evidence of resolution. All 6 patients were reviewed as outpatients for between 3 and 43 months (median 12 months) before being discharged.

Three of these 6 pseudocysts resolved within a period 6 weeks from the time of diagnosis of a pseudocyst and three after this time. Therefore, if the data for these patients were to be disregarded, the median time to resolution would remain unaltered.

The median time to complete resolution was 3 months (range 14 days to 26 months), with only 9 pseudocysts (36%) resolving within or around 6 weeks (14 to 44 days) from the time of diagnosis of a pseudocyst. A typical example of spontaneous resolution is shown in figures 19 and 20. The ultrasonic scans demonstrated a fluid collection (7.5 x 4cm) cephalad to the pancreas developing within 7 days after acute, alcohol induced pancreatitis (Figure 19). The patient with this pseudocyst had persistent abdominal pain, which prolonged his hospital stay to 17 days at the time of his original emergency admission with pancreatitis. His clinical condition gradually improved and after 5 weeks a repeat scan (Figure 20) demonstrated reduction in the collection to 2.8 x 2.5cm.

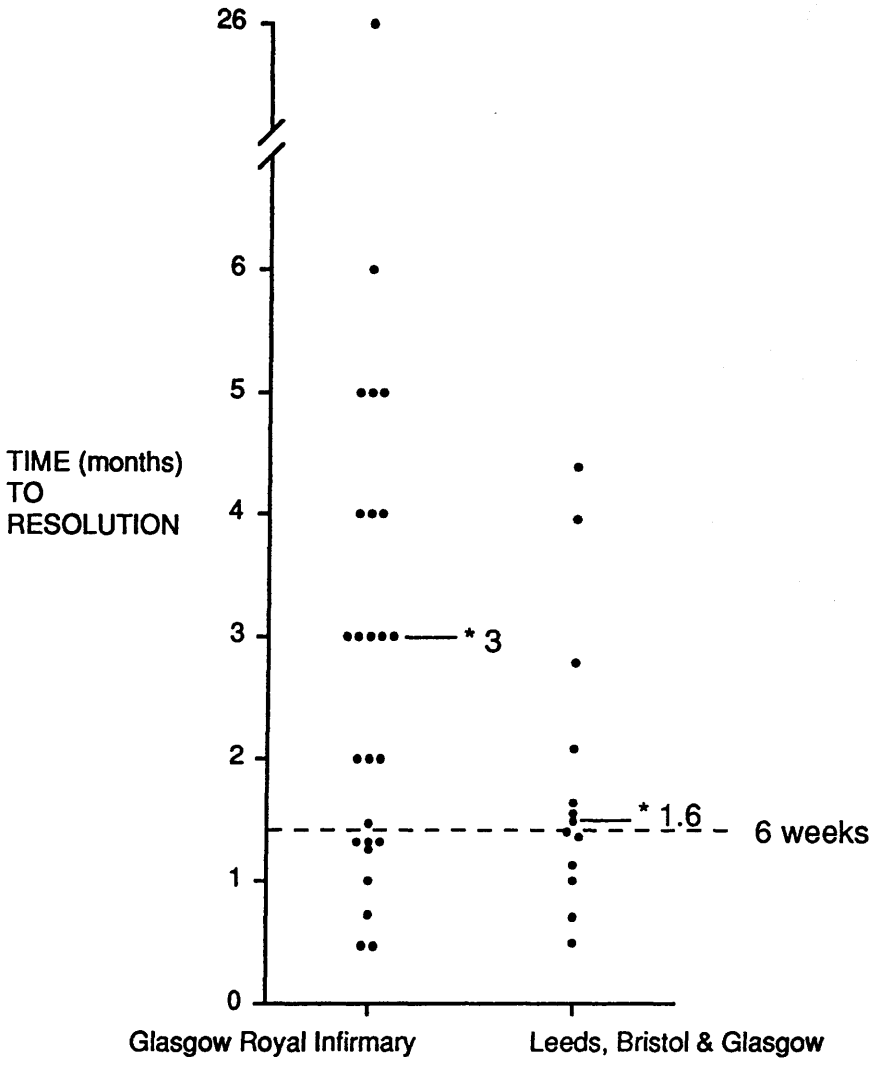


FIGURE 18 **Graph illustrating the distribution of times from acute pancreatitis to complete resolution of a pseudocyst. Results plotted in two groups, Glasgow Royal Infirmary patients and those from Leeds, Bristol and Glasgow.**

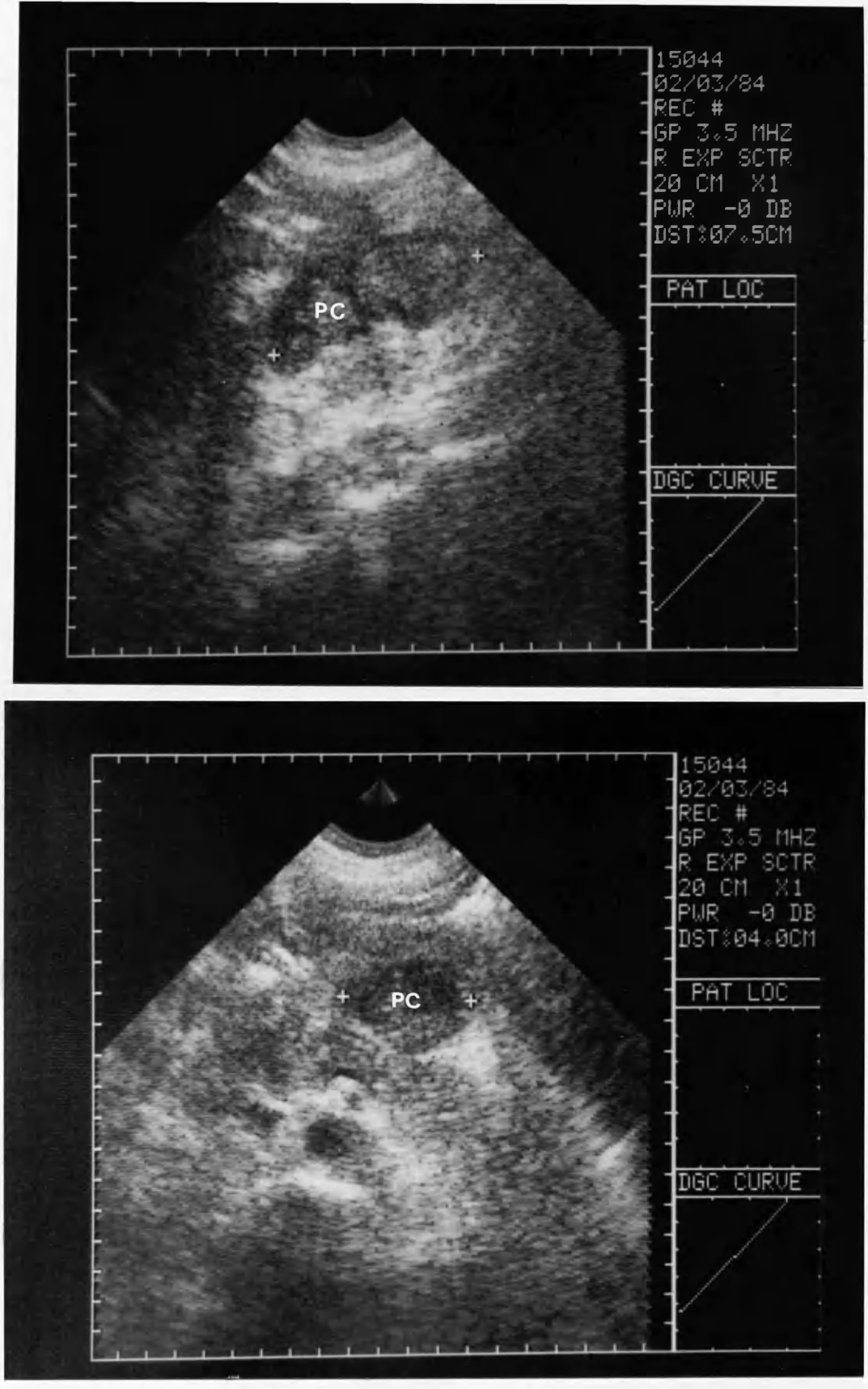
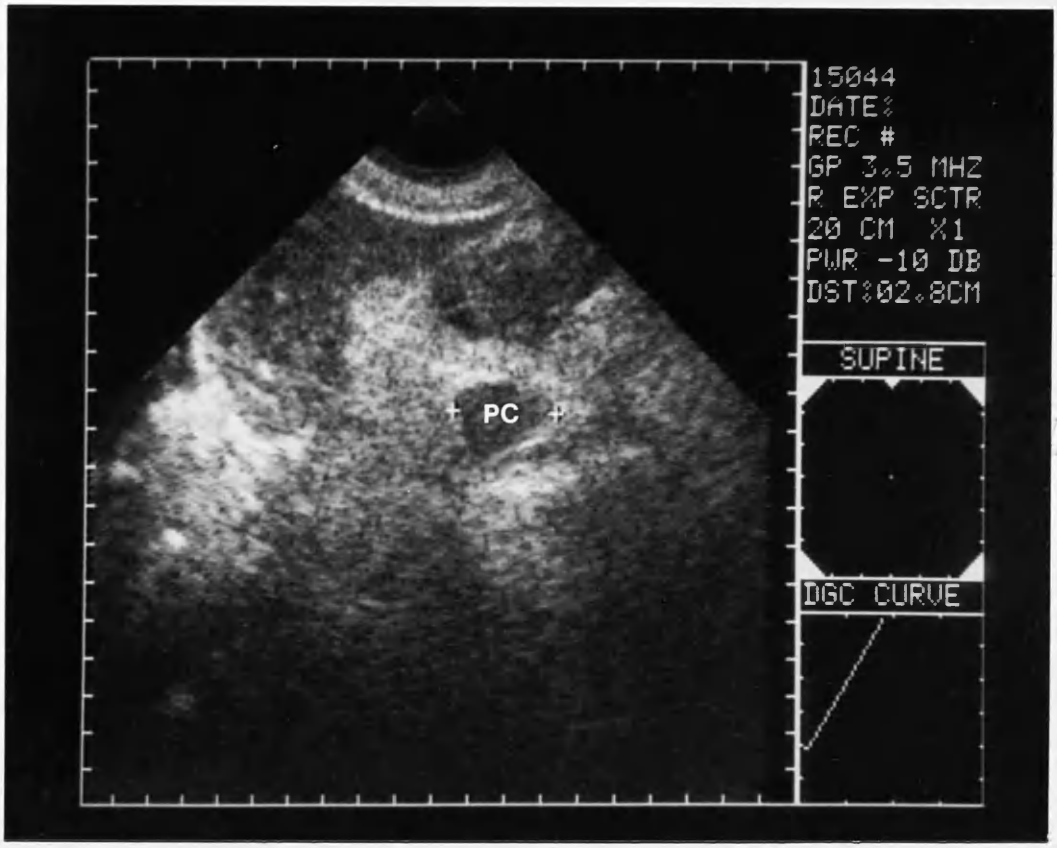


FIGURE 19 Ultrasound scans of a pseudocyst with dimensions 7.5 x 4cm prior to spontaneous resolution. (dimensions measured between crosses).

PC = pseudocyst



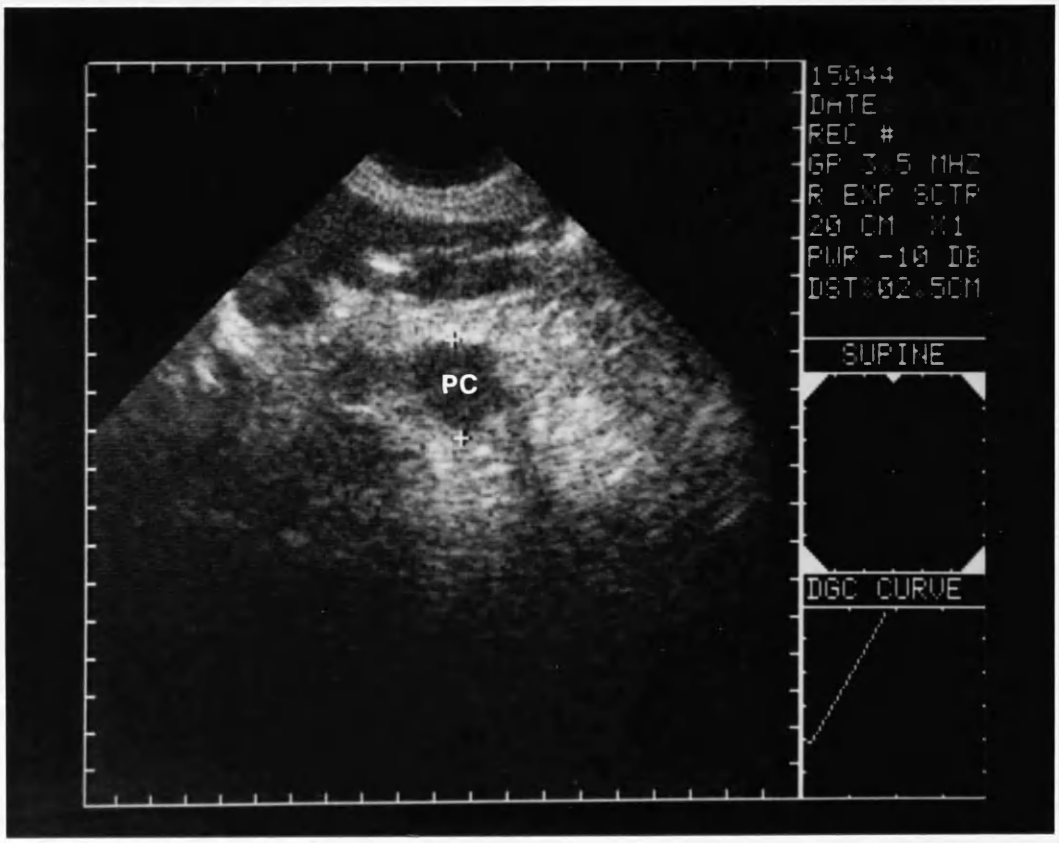


FIGURE 20 Ultrasound scans of same pseudocyst as Figure 19 but after a period of 5 weeks. The collection has now decreased in size to 2.8 x 2.5cm. (dimensions measured between crosses).

PC = pseudocyst

The greatest time of 26 months to complete resolution was in a patient who, after her gallstone induced pancreatitis, attended as an out patient for over 2 years during which time repeated ultrasound scanning showed a persistent 5 cm pseudocyst. This eventually disappeared and she underwent cholecystectomy. There was no evidence of a collection at the time of surgery.

The maximum pseudocyst size is plotted against the time to resolution in Figure 21. The graph illustrates that there is no direct correlation between the two parameters and small pseudocysts do not necessarily resolve rapidly.

Follow Up

The median period of outpatient follow up was 19 months (2 to 136 months). Six patients (24%) developed a second pseudocyst, five within six months of the original collection. In one patient the second collection resolved spontaneously but the others required surgical drainage. Three of the five patients with chronic pancreatitis produced a second pseudocyst and had continuing clinical problems but all the other patients were well, without further pancreatic disease, at the time of last follow up.

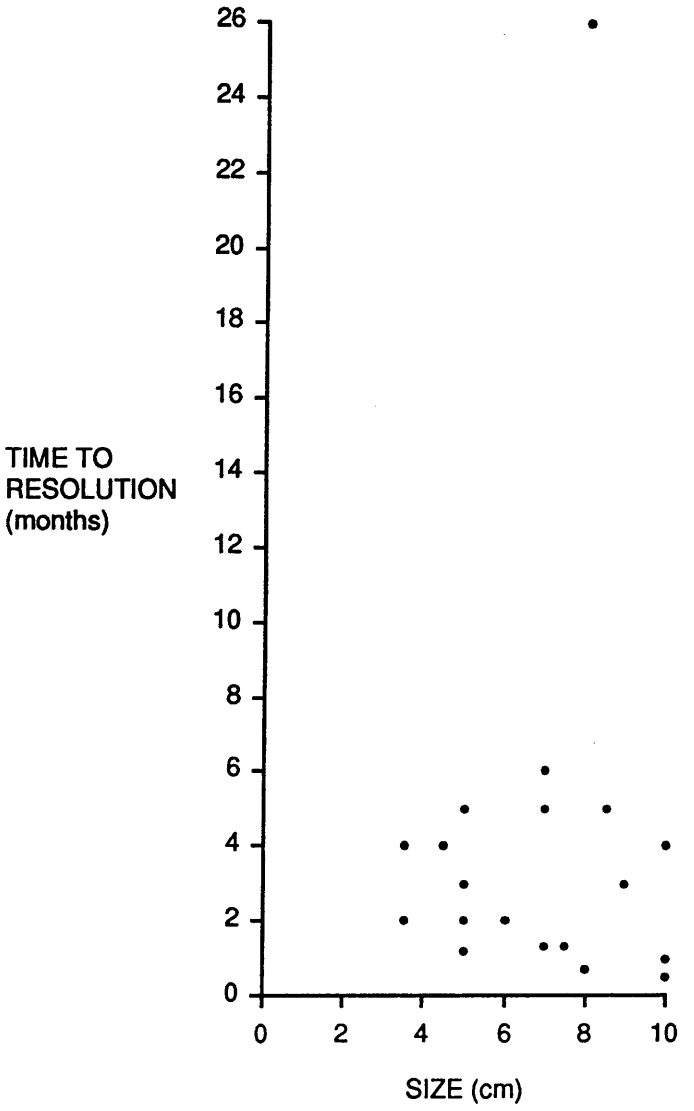


FIGURE 21 **Graph of maximum pseudocyst size (by ultrasound) against time to complete resolution for 19 pseudocysts showing that large collections do not necessarily take the greatest time to resolve.**

PATIENTS FROM LEEDS, BRISTOL AND GLASGOW.

A pseudocyst resolved spontaneously in 15 (52%) of the 29 patients in this study. The diagnosis of a pseudocyst was confirmed by ultrasound in 13 patients and CT scanning in two.

Aetiology / Acute and Chronic Pancreatitis

In contrast to the previous group of patients from Glasgow Royal Infirmary, biliary disease was the most frequent cause of acute pancreatitis complicated by a pseudocyst (8 patients, 53%. 4 male and 4 female): alcohol was the aetiology in 5 (33%) (all male) and a specific cause remained undetermined in the other 2 patients (13%).

All the pseudocysts formed as a result of an episode of acute pancreatitis. Only one patient had previous episodes of pancreatitis caused by alcohol and in this subject a small pseudocyst had been noted previously.

Time to Diagnosis of a Pseudocyst

The times to diagnosis of a pseudocyst are shown in Figure 14 and these values from the patients in Leeds, Bristol and Glasgow are compared with those from the Glasgow Royal Infirmary study. The median time was 22.5 days (range 3 - 49 days). Collections diagnosed early (within 10 days) could not, at that stage, have been considered true pseudocysts but comparison of the time to diagnosis with the time to resolution (Figure 22) illustrates that 3 of the 4 "pseudocysts" diagnosed by ultrasound scanning within this period persisted for longer than 6 weeks and only one apparently resolved in 21 days.

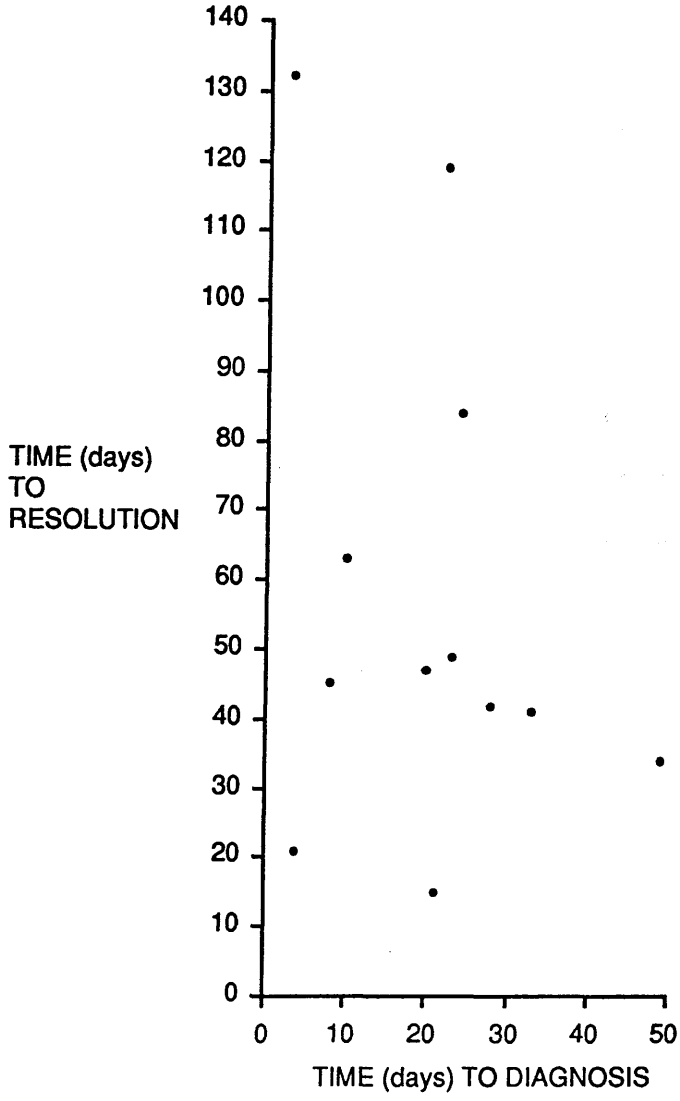


FIGURE 22 **Graph of time from acute pancreatitis to diagnosis of a pseudocyst against time to complete resolution for 12 pseudocysts. Of the 4 pseudocysts diagnosed within 10 days of acute pancreatitis only one resolved within 21 days and could therefore have been a transient effusion.**

One patient with chronic pancreatitis had a small (3.5cm) pseudocyst present at the time of acute pancreatitis and a time to diagnosis was not estimated. There was no significant difference (Mann Whitney test) in the times to diagnosis between pseudocysts which resolved spontaneously (median time 22 days; range 3-49 days) and those that ultimately required drainage (median 18 days; range 12-23 days).

Maximum Size of Pseudocyst

The maximum size of 10 of the pseudocysts is shown in Figure 23. Three of the other 5 were described as "large" and there was no size recorded on the ultrasound scans of the other 2 patients. Only 3 (30%) were 6cm or greater and the median size was 5cm. This was 3cm smaller than the median size of those treated surgically a difference which was not statistically significant (Mann Whitney test).

Clinical and Laboratory Information

The data for the clinical signs, symptoms and laboratory information are given in Table 28 and compared with the results in the patients whose pseudocysts were drained surgically.

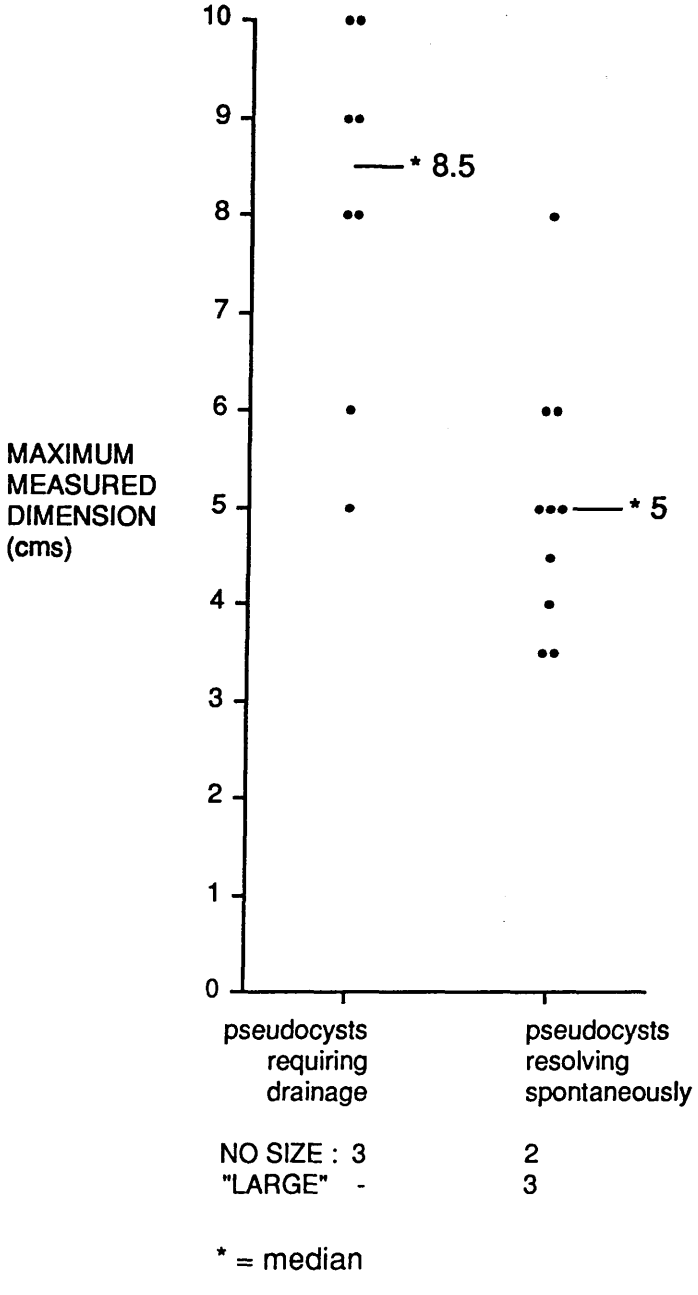


FIGURE 23 **Graph illustrating the distribution of the maximum diameter (cm) of a pseudocyst as recorded by ultrasound. Points grouped into the pseudocysts which underwent surgical drainage and those which resolved spontaneously.**
Patients from Leeds, Bristol and Glasgow.
Note that no size was given for 5 of the collections and in 3 others the pseudocyst was described as "large".

	OPERATED		RESOLVED	
	number	%	number	%
Pain	11	100	15	100
Tenderness	10	91	14	93
Pyrexia (>37.5^{0}C)	6	55	10	67
MASS	**9**	**82**	**4**	**27**
Vomiting	4	36	3	20
Anorexia	1	9	-	-
DISTENSION	**8**	**73**	**1**	**7**
Ileus	2	18	-	-
Jaundice	1	9	2	13
Serum amylase				
>300 IU/l	10	91	10	67
>1200 IU/l	7	64	4	27
Leukocytosis				
>10x10^{9}cells/l	**10**	**91**	**8**	**53**
>15x109cells/l	5	45	4	27

TABLE 28 Incidence of symptoms, signs, increased serum amylase and leukocytosis in patients from Leeds, Bristol and Glasgow whose pseudocyst required surgery compared to those in whom a pseudocyst resolved spontaneously.

The results (%) for the presence of a palpable abdominal mass, abdominal distension and leukocytosis >10x10^{9}cells/l were significantly different (all p=<0.05 Chi squared test) in the patients whose pseudocyst resolved compared to those in whom operation was necessary.

As in the group of 25 patients from Glasgow Royal Infirmary, the presence of a mass on clinical examination was significantly more common in the patients requiring surgery and in the present group there were also significant differences in incidence of abdominal distension and the number with a leukocytosis of greater than $10x10^9$ cells/l (Table 28). These two latter differences were more pronounced than in the larger group of Glasgow patients.

Assessment

By multiple factor assessment at the time of admission with acute pancreatitis, 11 of the patients (73%) in whom a pseudocyst resolved spontaneously were deemed to have mild and 4 severe acute pancreatitis. Amongst the patients requiring surgery 6 (54%) were considered as having mild and 5 severe acute pancreatitis.

Diagnostic peritoneal lavage was performed in 24 of the 29 patients with a pseudocyst but again only 13 (54%) of episodes of acute pancreatitis were graded as severe. Early assessment of severity of acute pancreatitis was not a useful indicator of those likely to develop pseudocysts. To date there is no specific marker that allows prediction of possible pseudocyst formation early during an episode of acute pancreatitis (Chapter 4).

Time to Resolution

The median time to complete resolution was 45 days range (15-132 days) in 13 patients (Figure 18).

Resolution was confirmed by repeated ultrasound scans in 7 patients, by CT scanning in 3 and in a further three patients, the reduction in size was confirmed at the time of subsequent cholecystectomy.

Of the 2 patients with no accurate time of resolution recorded one was found, incidentally, to have a renal adenocarcinoma (see above). When he had recovered from his pancreatitis he was transferred to the care of a urologist and the precise time to resolution of his pseudocyst was not documented. This patient subsequently developed a second pseudocyst 2 years later. This collection was initially drained by percutaneous aspiration but ultimately required surgery. The remaining patient had resolution of his pseudocyst confirmed solely by clinical examination without further ultrasonic or CT scans being performed. He was followed up for 19 months without further symptoms.

Follow Up

The median period of follow up of all 15 patients was 5.5 months (range 2-54 months). Two patients developed further pseudocysts. One, the patient with a renal tumour, is reported above. The second patient had a 4cm pseudocyst revealed by CT scanning within one month of proven resolution of a similar sized collection. The second pseudocyst eventually resolved spontaneously after a period 14 months.

SUMMARY

There were some differences in this group of 15 patients when compared to the 25 from Glasgow Royal Infirmary in whom a pseudocyst resolved (Table 29) but there were important similarities summarised below:-

1. The median times to resolution were 45 and 90 days confirming that the majority of pseudocysts resolved after a period of 6 weeks. The background to this particular time is discussed in Chapter 1. From the present data it is recommended that "waiting period" before considering intervention should be 12 weeks with the proviso that the clinical condition of the patient is not deteriorating.

2. Both studies produced a 3cm difference in the median maximum pseudocyst diameter between the collections which resolved spontaneously and those which underwent surgery. Despite the fact that these differences did not achieve statistical significance there was a trend for pseudocysts greater than 6cm in diameter to be more likely to require some form of surgical drainage.

	Glasgow Royal Infirmary Results	Leeds Bristol Glasgow Results
Median time to resolution (days)	90	45
Median maximum size (cm) on ultrasound	7	5
% resolving > 6 weeks	64%	52%
% size > or = 6cm	48%	30%

TABLE 29 Comparison of the time to complete resolution of a pseudocyst, the maximum diameter by ultrasound scan, the percentage of collections resolving after six weeks and the percentage of resolving pseudocysts greater than 6 cm between the patients from Glasgow Royal Infirmary and those from Leeds, Bristol and Glasgow.

3. In the study of patients from Leeds, Bristol and Glasgow spontaneous resolution occurred in the majority (52%). This is an important finding and should strengthen the argument for delay in intervention and careful and repeated monitoring of patients forming a pseudocyst after acute pancreatitis.

4. The clinical presence of a palpable abdominal mass in a patient with a pseudocyst indicates that the collection is at least 6cm in diameter and is more likely to require drainage than resolve spontaneously.

5. The other significant clinical differences (abdominal distension, leukocytosis $\geq 10 \times 10^9$ cells/l) between patients with resolving pseudocysts and those requiring surgery noted in the study from Leeds, Bristol and Glasgow were more pronounced than in the 100 patients from Glasgow Royal Infirmary alone. These features have been included in a new assessment system for the prediction of outcome in patients who develop a pseudocyst after acute pancreatitis (Chapter 8).

6. Late recurrence of a pseudocyst following spontaneous resolution occurred in a total of 7 patients and surgical drainage was necessary for the second collection in 5 (71%) of these.

7. No patient from either group experienced significant delayed complications associated with the pseudocyst.

CHAPTER 6

PERCUTANEOUS ASPIRATION OF PANCREATIC PSEUDOCYSTS

INTRODUCTION

Despite the fact that a majority (52%) of pseudocysts in patients from the Leeds, Bristol Glasgow study resolved spontaneously when all the 129 patients are considered together the majority (89, 61%) required some form of surgical drainage. Although internal surgical drainage procedures are relatively safe there is still a morbidity and mortality associated with surgical intervention. A method of drainage that avoids operation but achieves resolution with minimal morbidity has appeal. Percutaneous drainage procedures have been considered as a solution to this problem (Chapter 1).

The present chapter considers the experience of percutaneous needle aspiration of pancreatic pseudocysts in two Glasgow hospitals (The Royal Infirmary and Stobhill General Hospital).

PATIENTS

Between 1981 and 1988, 21 patients with pancreatic pseudocysts from Glasgow Royal Infirmary and Stobhill General Hospital, Glasgow have undergone percutaneous drainage procedures. There were 14 males (median age 37 years; range 23-77 years) and 7 female patients (median age 47 years; range 30-78 years). A total of 26 aspirations were performed. In sixteen patients a pseudocyst was drained once. The remaining five patients had two aspirations. In two instances aspiration was repeated within 7 days and in a further two patients a second separate collection was identified and aspirated at 6 months and 2 years respectively after the original pseudocyst.

The remaining patient had a collection aspirated followed by an attempt at catheter drainage after 4 weeks (Table 30).

The diagnosis of a pseudocyst was confirmed by ultrasonic scanning in all patients. The collection developed following acute pancreatitis in 13 patients and was associated with chronic pancreatitis in 8. The aetiologies of the preceding pancreatitis are shown in Table 30.

Three of the patients did not present to hospital as an emergency but were referred to a surgical clinic for investigation of abdominal pain. The presence of a pseudocyst was subsequently detected by ultrasound scanning.

METHODS

All percutaneous aspirations were performed with ultrasound guidance and the procedure undertaken using local anaesthesia. A preliminary ultrasound scan was performed (Figure 24) to assess the size of the pseudocyst and to determine the most direct route to the collection avoiding the colon, liver and spleen. A fine gauge needle (19-22 gauge) was then introduced into the cavity and the position confirmed. Fluid was aspirated (Figure 25) and specimens sent for biochemical and bacteriological examination. As much fluid as possible was then withdrawn and the needle removed. Scanning was repeated to assess the completeness of aspiration and the size of the empty cavity. Another scan was performed after 5-7 days (Figure 26) to assess whether the pseudocyst had refilled or not.

NUMBER OF PSEUDOCYSTS
21

	ASPIRATION THERAPY SUCCESSFUL	ASPIRATION THERAPY FAILED
	6	15
Median time from pancreatitis to aspiration (range days)	18 days (14-21)	29 days (11-120)
Median maximum pseudocyst diameter (range cm)	11cm (8-11.5)	10cm (6-22)
Aetiology of pancreatitis		
Alcohol	3	10
Gallstone	2	4
Post operation	1	-
Carcinoma	-	1
Bacteriology of fluid		
Sterile	5	13
Infected	1	2
Surgical drainage following unsuccessful aspiration		
Cystogastrostomy		10
External drainage		2
Distal pancreatectomy		1
Refill no surgery		2

TABLE 30 Details of time to aspiration, maximum pseudocyst size, aetiology of pancreatitis and bacteriology of fluid in pseudocysts in which aspiration was succesful and those in which it failed.

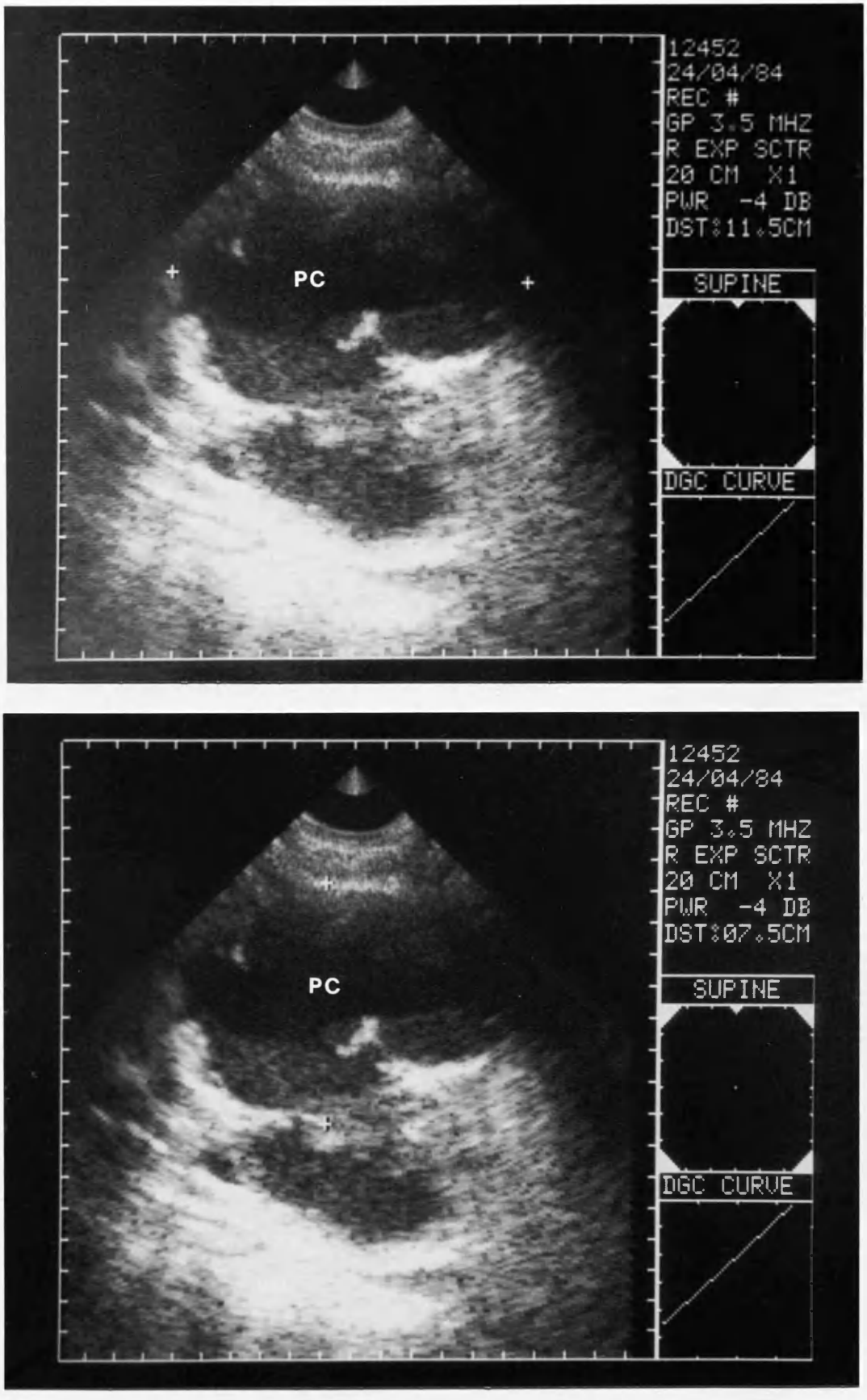


FIGURE 24 Ultrasound scans of a pseudocyst (11.5 x 7.5cm) prior to percutaneous aspiration. (dimensions measured between crosses).

PC = pseudocyst

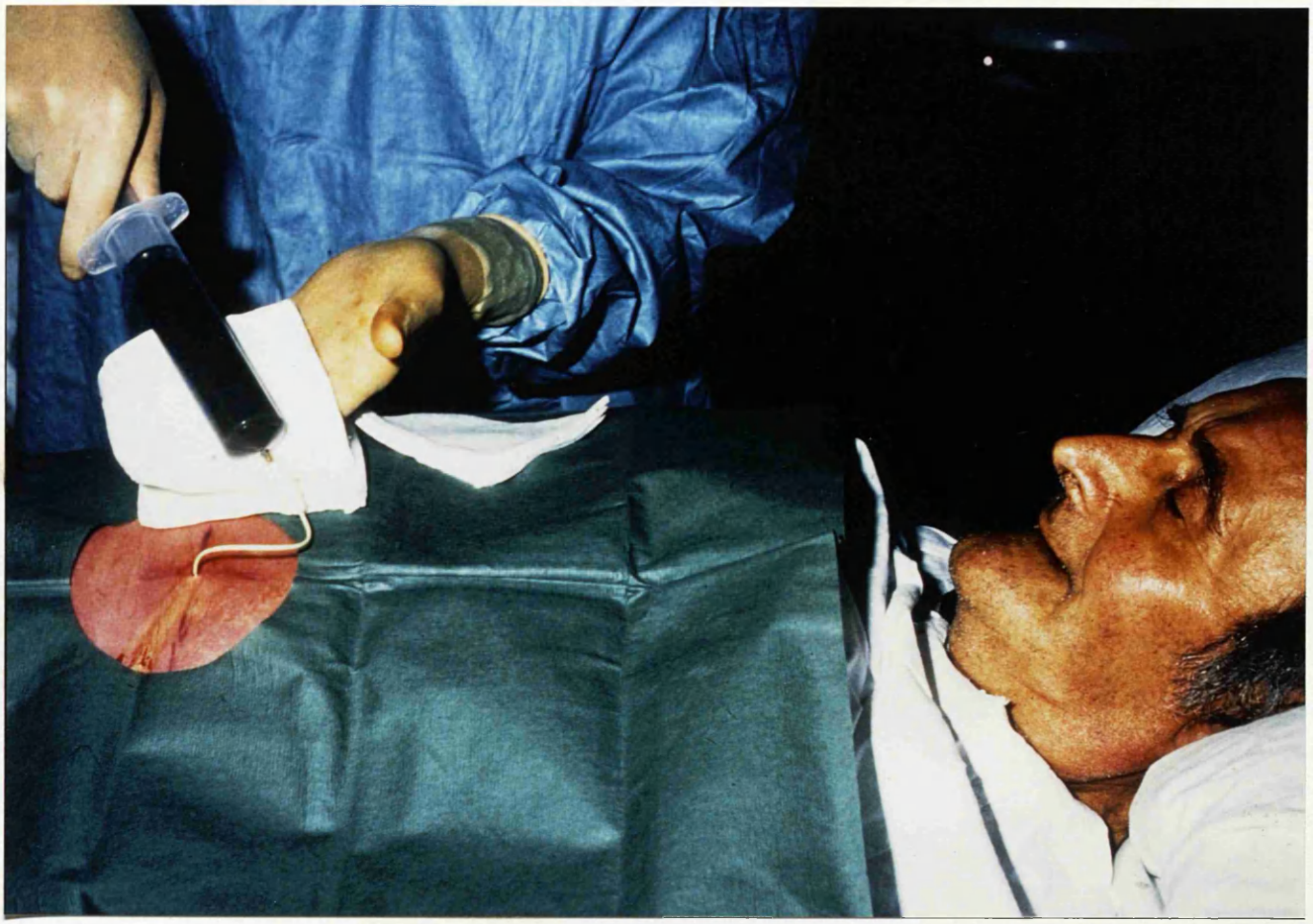


FIGURE 25 Photograph of patient undergoing percutaneous drainage of a pseudocyst by catheter.
Procedure has been performed using local anaesthetic.
Note the colour of the aspirated fluid.

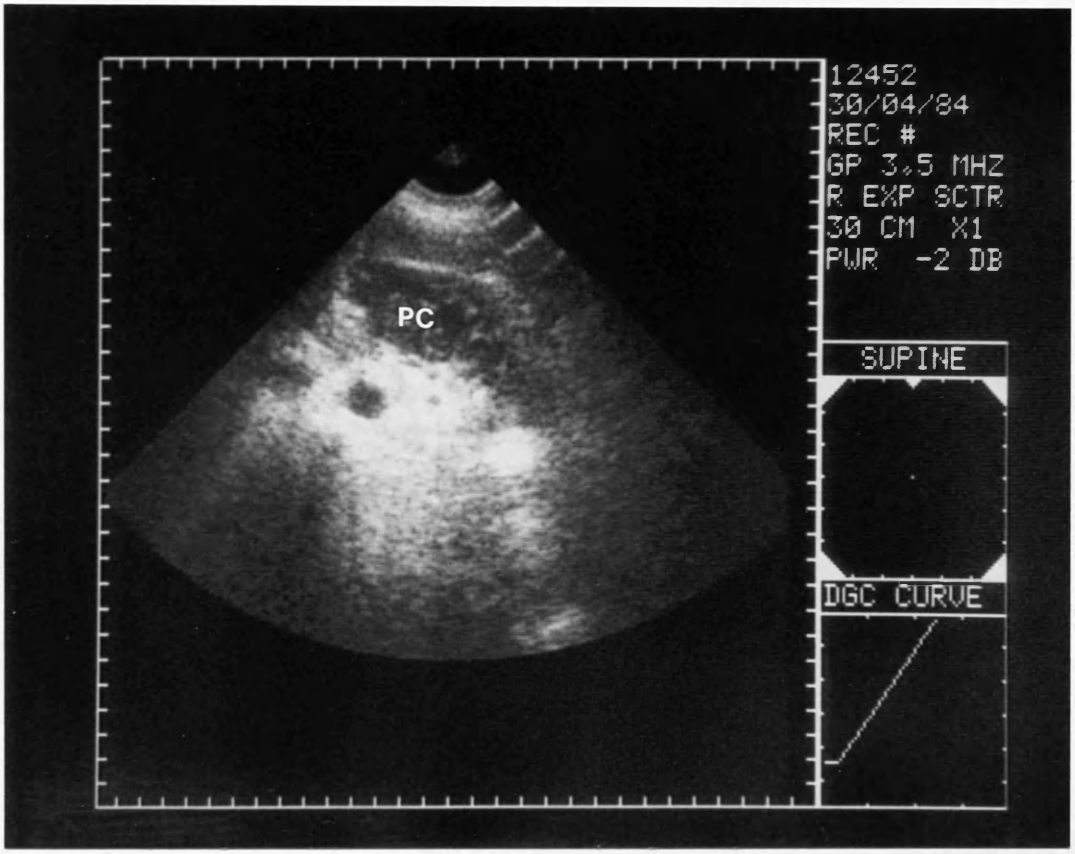


FIGURE 26 Ultrasound scan of a pseudocyst (same patient as Figure 24) following percutaneous aspiration. (dimensions not marked but echolucent area is obviously smaller than in figure 24).)

PC = site of aspirated fluid

A drainage catheter were used in only three patients. In two patients the catheter was allowed to drain from the pseudocyst cavity and out through the anterior abdominal wall. Unfortunately these catheters both fell out after 2 and 4 days respectively. In the third patient an attempt was made to establish a catheter cystogastrostomy (Hancke and Henriksen 1985). This involved passing a fine bore hollow needle through both walls of the stomach and into the pseudocyst. A guide wire was then inserted down the needle and a double pigtail catheter slid over the wire until one of the curled ends lay within the pseudocyst cavity. A gastroscopy was then performed and the catheter was grasped and the other end placed in the lumen of the stomach thereby creating a communication between the pseudocyst and the stomach via the catheter. This catheter unfortunately, migrated into the pseudocyst cavity after 2 days and the patient developed signs and symptoms of infection. At this time surgery was performed in order to remove the catheter and drain the pseudocyst. With the exception of this last patient, there were no immediate complications of the procedures.

RESULTS

The median time from the onset of an episode of acute pancreatitis to aspiration of a pseudocyst was 21 days (range 11-120 days) in 13 patients. It was not possible to calculate this period accurately in the other 8 patients.

Six of these suffered chronic pancreatitis and had no clear precipitating event of acute pancreatitis, a further patient was referred to a surgical out patient clinic and had no acute symptoms and the sixth patient developed a small pseudocyst in the tail of her pancreas associated with metastatic carcinoid tumour elsewhere in the gland. Details of the results are summarised in Table 30.

Percutaneous aspiration was successful in reducing and eventually contributing to the resolution of a pseudocyst in 6 (29%) patients. There was no evidence of recurrence within a minimum follow up period of 10 months in 4 of these patients. Of the other two, one failed to attend and the other patient died within 5 weeks of aspiration as a result of her metastatic colonic carcinoma. There was no evidence that her pseudocyst had refilled within that period.

The aspiration failed to resolve the pseudocyst in the other 15 patients (71%). Thirteen of these patients underwent surgical drainage; 10 cystogastrostomy, 2 external drainage and one distal pancreatectomy at a median time of 21 days (range 2-330 days) from the time of aspiration. In the other two patients repeated ultrasound scanning showed the continued presence of a pseudocyst of similar size to the original collection.

The pseudocyst refilled within 10 days in 10 (67%)of these 15 patients and by 21 days in another 2. In two further patients with alcohol induced chronic pancreatitis percutaneous aspiration could be regarded as being partially successful in that their pseudocysts did not refill within a period of 6 months from the procedure. Aspiration of the second collection in one of these patients proved inadequate and he then underwent a cystogastrostomy. The other required a distal pancreatectomy for a recurrent pseudocyst in the tail of the pancreas. The one remaining patient who was treated with surgery had a small (5cm) cystic lesion in the tail of her pancreas which probably developed as a result of metastatic carcinoid tumour within the pancreas. The exact time that this refilled was not clear but it caused her no symptoms over a follow up period greater than 2 years. It was interesting to note that the amylase level in the fluid of this cyst was only 143 IU/l, compared to levels ranging from 8600 IU/l to 460400 IU/l in the samples from the other pseudocysts.

The median maximum pseudocyst diameter in this group of patients as measured by ultrasound was 11cm (range 8-11.5cm) for those which resolved after aspiration compared to a median of 10cm (range 6-22cm) for those which required to be drained by operation or in which the pseudocyst refilled. There was no significant difference in these diameters (Mann Whitney test).

The volume of fluid aspirated varied from 50ml to 1400ml (median 350ml) and did not correlate directly with the maximum measured diameter. During all procedures the immediate post aspiration scan showed satisfactory evacuation of the cavity which would suggest that the early recurrence of fluid was genuine refilling rather than missed fluid at the time of aspiration.

Specimens from the pseudocysts were sterile in 18 patients but contained bacteria in 3. One sample grew a Streptococcus species, one Staphylococcus aureus and another grew both a Proteus species and Escherichia coli. This last collection resolved following aspiration and systemic antibiotics without the patient experiencing any major complications.

After surgical drainage only one patient (8%) experienced complications. He underwent external drainage of his pseudocyst 18 days after aspiration but became septicaemic, despite the collection being sterile on aspiration, and eventually died of respiratory failure. Although not proven in this patient, it is possible that the percutaneous intervention resulted in infection being introduced into this pseudocyst.

SUMMARY

1. The results presented show rather a low success rate of 29% for percutaneous aspiration of a pancreatic pseudocyst. This figure is similar to that recorded in the world literature which considers aspiration alone as a method of treatment for pancreatic pseudocyst (Table 6).

2. Three patients in whom the collection responded to this form of treatment (50% of the successes) presented to the hospital without significant acute symptoms. All three had alcohol associated pancreatitis and one had chronic symptoms.

3. One infected collection was successfully treated by aspiration and systemic antibiotic therapy but, in contrast, infection was probably introduced into one pseudocyst ultimately leading to retroperitoneal sepsis and death of the patient. The technique is not without risks.

CHAPTER 7

ANALYSIS OF ACUTE PHASE REACTANTS IN PSEUDOCYST FLUID

INTRODUCTION

Despite extensive literature on the subject of pancreatic pseudocysts there is a paucity of studies concerning analysis of pseudocyst fluid. This chapter describes analysis of acute phase reactants Interleukin 6, alpha 1 antiprotease, alpha 2 macroglobulin and C reactive protein in pseudocyst fluid from 12 patients.

The present study was undertaken in the light of the clinical information obtained in the other parts of this thesis and in an attempt to find a marker which might reflect the severity of the inflammatory reaction within a pseudocyst and differentiate between acute and chronic pseudocysts.

A summary of the literature relating to analysis of pseudocyst fluid is given in Chapter 1.

PATIENTS

Samples of pseudocyst fluid were collected from 12 patients at the time of surgical drainage (9) or percutaneous needle aspiration (3). All patients eventually underwent surgery. Details of the patients are given in Table 31. Fluid was collected from 9 male (median age 46 years; range 37 - 66 years) and 3 female patients (median age 41 years; range 26 - 72 year).

Eight of the pseudocysts were regarded as "acute". Six of these collections immediately followed an episode of acute pancreatitis. The aetiological factor of the pancreatitis was alcohol in 2 of these 6 patients, gallstones in 1 and the aetiology was undetermined (idiopathic) in the other 3 patients.

PATIENT	SEX	AGE	PSEUDOCYST ACUTE/ CHRONIC	AGE AT SAMPLE	SIZE (cm)	PANCREATITIS AETIOLOGY	SAMPLE TAKEN AT	TYPE OF DRAINAGE
NB	M	66	acute	7 dys	9x5	alcohol	aspiratiopn	cystogastrostomy
EB	M	44	acute	?	large	alcohol	operation	cystogastrostomy
DC	M	46	acute	?	huge	alcohol	aspiration	external drainage
SH	M	37	acute	21 dys	10x6	alcohol	aspiration	cystogastrostomy
EL	F	26	acute	50 dys		unknown	operation	cystojejunostomy
CM	F	72	acute	120 dys	10x7	gallstones	operation	cystogastrostomy
GS	M	53	acute	60 dys	10	unknown	operation	cystogastrostomy
IS	M	43	acute	60 dys	8	unknown	operation	cystoduodenostomy
JL	M	42	chronic	24 mth	9	alcohol	operation	distal pancreatectomy
MM	F	41	chronic	12 mth	6x4	alcohol	operation	cytojejunostomy
JM	M	47	chronic	?		alcohol	operation	external drainage
RW	M	47	chronic	?	6	post trauma	operation	cystogastrostomy

TABLE 31 Details (age, sex) of 12 patients whose pseudocyst fluid was analysed.
Details of pseudocyst:- acute or chronic: age at time of fluid sample: size: aetiology of preceding pancreatitis.
Surgical procedure ultimately used to drain pseudocyst.

(dys = days : mth = months
M = male : F = female)

The fluid samples were obtained by percutaneous needle aspiration in two of these six patients at 7 and 21 days after the collection had first been identified by ultrasound scan. The other four samples were collected during surgical drainage at a median time of 60 days (range 50 - 120 days) after pseudocyst formation. The remaining two of the 8 patients with "acute" pseudocysts presented with symptoms of abdominal pain and hyperamylaseamia associated with the presence of a large, established pseudocyst. Both patients regularly drank large quantities of alcohol but neither had previous evidence of pancreatic disease and the precise time of development of the pseudocyst could not be determined. The fluid sample was obtained by needle aspiration after 3 days in one of these patients and at the time of surgery in the other.

The pseudocysts in the remaining four patients were regarded as chronic (Table 31). All four had experienced previous episodes of pancreatitis induced by alcohol in 3 and following abdominal trauma in the other. In two of these patients the age of the pseudocyst could not be determined accurately. The other two collections had been present for 12 and 24 months prior to drainage and sample collection.

METHODS OF SAMPLE ANALYSIS

All the fluid samples were collected in sterile containers and were stored at -20°C for variable periods (Table 32). All assays were performed in the Pathological Biochemistry Department of Glasgow Royal Infirmary. The amylase was measured on a separate sample at the time of collection.

Interleukin 6

This was assayed using a sensitive colourimetric cell culture assay using Interleukin 6 dependent mouse hybridoma cells (7TDI cells). The amount of cell growth and replication is proportional to the level of Interleukin 6 present within a sample or standard solution. Cell growth following a set period of incubation was estimated using a fluorescent cell probe (MTT = 3-[4,5-dimethykthiazol-2-yl]-2,5,diphenyltetrazolium bromide thiazolyl blue).

All serum samples were heat treated (56°C for 30 minutes) and diluted to provide a final sample volume of 50µl. Each sample and standard was added to 50µl ($2x10^3$) 7TDI cells giving a total volume of 100µl in each well of a tissue culture plate. The plates were then incubated for 4 days at 37°C with an atmosphere of 8% carbon dioxide. After this the fluorescent probe (MTT) was added to each well and allowed to equilibrate for 4 hours. The cells were then disrupted using 50µl of Triton X. The resultant released fluorescence was measured the following day by determining the absorbance at 540nm. The Interleukin 6 levels for the test samples were derived by reference to a standard curve.

PATIENT	PANCREATITIS ACUTE/ CHRONIC	IL6 units	CRP mg/l	A1AP g/l	A2MG g/l	AMYLASE IU/l	SAMPLE AGE (months)
EB	acute	<10	35	1.9	<0.2		27
DC	acute	<10	75	2.3	0.9	4480	27
SH	acute	<10	29	1.6	<0.2	36200	26
JL	chronic	<10	<10	1.9	0.3	67600	23
MM	chronic	<10	<10	0.5	<0.2	64500	19
JM	chronic	<10	16	0.8	0.3		23
NB	acute	<10	<10	<0.2	<0.2	460400	26
EL	acute	<10	<10	<0.2	<0.2		26
CM	acute	<10	<10	<0.2	<0.2	9570	3
GS	acute	<10	<10	<0.2	<0.2		19
IS	acute	<10	<10	<0.2	<0.2	151800	13
RW	chronic	<10	<10	<0.2	<0.2		18

TABLE 32 Results of acute phase reactant analysis of fluid samples from pseudocysts in 12 patients (Table 30). The normal laboratory range for each reactant is given in the text.

All the acute phase reactant results for lower 6 patients are at the minimum limit of sensitivity for each test.

[IL6 = Interleukin 6
CRP = C-Reactive Protein
A1AP = Alpha 1 Antiprotease
A2MG = Alpha 2 Macroglobulin]

Alpha 1 Antiprotease / Alpha 2 Macroglobulin

These were measured on an Encore Centrifugal Analyser using a turbimetric immunoassay with appropriate anti-sera (Atlantic Antibodies). Diluted serum samples and specific antisera to the test protein are pipetted separately onto a transfer disc. The disc is then placed into the centrifugal analyser where the sample and antisera are mixed and the resulting turbidity, which is proportional to the amount of specific protein present, is measured.

C Reactive Protein

This was analysed on the Abbot TDX fluorimeter using a fluorescent polarisation immunoassay employing a commercial reagent pack. The pack contains an antibody to C-reactive protein (CRP), a fluorescing labelled CRP and a pretreater.

The principle of the test is based on the fact that the Abbot TDX fluorimeter produces a plane, polarised light which excites the labelled CRP (the fluorophore) and raises it to a higher state. After excitation the fluorophore returns to a steady state and a light of a different energy level and wavelength is emitted.

The sample, antibody and labelled CRP are mixed together and the labelled CRP competes with the CRP in the sample for binding sites on the antibody. The unbound labelled CRP is free to rotate and, within the analyser, it depolarises the exciting light and polarisation is decreased. This change is inversely proportional to the level of CRP within the sample.

Amylase

This was measured using the Phadebas test (Pharmacia Diagnostics, Sweden). The technique is based on the ability of amylase to split a starch polymer. A water insoluble cross-linked starch molecule carrying a blue dye is provided in tablet form in the test kit. The starch is hydrolysed by amylase resulting in water soluble blue fragments. The absorbance of the blue solution is measured in a photometer and is proportional to the amylase activity.

RESULTS

The results for each patient are shown in Table 32. In samples from six patients all results were at the lower limit of sensitivity of all the assays. The implications of this finding will be discussed subsequently.

Interleukin 6

In all 12 samples the values of this parameter were less than the lower limit of the assay indicating Interleukin 6 could not be detected within these specimens of pseudocyst fluid.

Alpha 1 Antiprotease (normal serum values 1.3 - 2.1 g/l)

In 6 samples the values were <0.2g/l (lower limit of test) implying that there was no alpha 1 antiprotease present within the fluid. Four of the results were within the normal serum range (3 acute pseudocysts and 1 chronic). The other 2 results were lower than normal (both chronic pseudocysts).

Alpha 2 Macroglobulin (normal serum range 1.1 - 3.9g/l)

Alpha 2 macroglobulin was detectable in samples from only 3 of the 12 patients. Interestingly all three also had alpha 1 antiprotease in the specimen (Table 32). All three patients had alcohol associated disease and 2 had chronic pancreatitis.

C Reactive Protein (normal serum value < 20 mg/l)

Only 4 fluid samples contained detectable levels of C reactive protein. Three of these were elevated and associated with acute pseudocysts. All three patients with these elevated levels had large areas of pancreatic necrosis and two subsequently had prolonged infection. The fourth result was within the normal serum range and was from a chronic pseudocyst.

DISCUSSION

The results obtained in this study reveal that levels of the analytes above the lower sensitivity of the assays occurred in 6 of the 12 patients.

At the time of the Interleukin 6 analysis it was observed that almost all test cells became non-viable. With high levels of proteases within the pseudocyst fluid it is likely that a cell culture assay is inappropriate for analysis of this type of specimen. The continuing enzymic action may also have been responsible for the other low results. The fluid samples were stored at -20^{o}C within 1 hour of collection but even at this temperature protease activity continues.

One possible solution to this problem would be to inhibit protease activity rapidly at the time of sample collection by adding inhibitors such as aprotinin to the fluid.

Another possible explanation for the apparent lack of Interleukin 6 is that it was truly absent from pseudocyst fluid. This substance is produced by various lymphoid and non-lymphoid cells, T cells, B cells, monocytes and fibroblasts and has a multitude of functions. One of which is its action as an intermediary substance in the acute phase response (Kishimoto 1989). Interleukin 6 stimulates the biosynthesis of acute phase proteins and induces the production of C reactive protein and alpha 1 antiprotease in human hepatocytes (Castell et al 1988). Serum levels correlate well with those of C-reactive protein in patients with severe burns (Nijstein et al 1987) strongly suggesting a contributory role in the acute phase response.

Patients developing pseudocysts, especially following acute pancreatitis, exhibit elevated serum levels of C-reactive protein (Mayer et al 1984). The local inflammatory response within a pseudocyst is likely to produce Interleukin 6 and, prior to the present analysis it was reasoned that the levels of this reactant would be elevated within cyst fluid particularly that obtained from acute pseudocysts. The results do not fit this hypothesis. Further analysis with simultaneous fluid and serum sampling is necessary.

Data from two studies (Lasson et al 1989, Wilson et al 1991) reporting levels of alpha 1 antiprotease and alpha 2 macroglobulin estimated by both immunological and functional assays has shown that levels of alpha 1 antiprotease in pseudocyst fluid are commonly within the normal serum range but that alpha 2 macroglobulin levels tend to be low. This finding is similar to the serum response of this substance in acute pancreatitis (Lasson and Ohlsson 1984; McMahon et al 1984). The current results recorded for alpha 1 antiprotease and alpha 2 macroglobulin are consistent with these other studies. It was, however, observed that more than half the results for alpha 2 macroglobulin were at the limit of assay sensitivity.

In the case of alpha 2 macroglobulin the low levels are probably a true reflection of events within pseudocyst. In view of the rarity of analysis of this substance in pseudocyst fluid further observations are necessary.

The C-reactive protein results were elevated (>20 mg/l) in 3 of the four samples with values greater than the lower limit of the assay. The four pseudocysts from which these samples were taken developed as a result of alcohol induced pancreatitis. The 3 patients whose specimens recorded raised levels of C-reactive protein all had large pseudocysts with considerable amounts of tissue necrosis. Two of these patients went on to develop abscesses.

In common with analysis of serum C-reactive protein in patients with acute pancreatitis, the elevated values of C-reactive protein within pseudocyst fluid were associated with severe acute pancreatitis. Clearly, the numbers in this study are very small but further studies are merited to confirm this positive finding.

SUMMARY

1. Overall, this analysis of acute phase proteins within pseudocyst fluid has been, to some extent, disappointing but it represents a preliminary study which has attempted to quantify the differences between acute and chronic pseudocysts in terms of a marker of severity of the inflammatory response.
2. The results for C-reactive protein within the fluid were the most positive feature in three of the acute pseudocysts but if these are paralleled by the serum response of this reactant then analysis of the fluid may be superfluous.

CHAPTER 8

CONCLUSIONS AND DISCUSSION

INTRODUCTION

In this concluding chapter the important findings of this thesis are discussed and a new approach to the assessment and management of patients who form pancreatic pseudocysts is presented.

THE NATURAL HISTORY OF PANCREATIC PSEUDOCYSTS

Which patients are likely to form a pseudocyst ?

Because the majority of studies of patients with pseudocysts have come from medical centres where alcohol was, by far, the most common aetiological factor causing acute pancreatitis there has been a tendency to regard patients with this cause as being more likely to develop a pseudocyst (Anderson 1972; Aranha et al 1983; Becker et al 1968; Bradley et al 1976; Caravati et al 1966; Crass and Way 1981; Erb and Grimes 1960; Folk and Freeark 1970; Frey 1978; Gonzalez et al 1976; Grace and Jordan 1976; Hastings et al 1975; Judd et al 1931; Kaiser et al 1964; McConnell et al 1982; Sankaran and Walt 1975; Scharplatz and White 1972; Thomford and Jesseph 1969; Tucker and Webster 1972).

Pseudocysts forming with a background of chronic pancreatitis are almost all alcohol associated, primarily because alcohol is the major cause of this type of pancreatitis. When considering pseudocysts which develop as a result of acute pancreatitis, the results from the study of 29 patients from Leeds, Bristol and Glasgow (Chapter 4), clearly demonstrated that no single aetiology was predominant. The distribution of causal factors in the patients who formed a pseudocyst was almost identical to that of the 418 patients with acute pancreatitis.

This finding is not unexpected if the pathogenic factors for pseudocyst formation (Figure 1) are regarded as common to all types of inflammatory pancreatitis, no matter the cause. There are no differences in the histological appearances of acute inflammatory pancreatitis whether caused by the two common aetiologies, gallstones or alcohol. Periductal necrosis is the common histological feature of the pancreatitis induced by either of these aetiologies (Foulis 1980). There are some differences in the distribution of pancreatic damage in ischaemic pancreatitis when compared to other causes but the net effect however, is still areas of necrosis that can potentially produce leakage of fluid from the ductal system into the surrounding tissues and cause pseudocyst formation.

The formation of a pseudocyst is not confined to patients of one sex or age group. Seventy of the 100 patients from the Glasgow Royal Infirmary study were male, 49 (70%) of whom had alcohol associated disease. The median age of these 70 males was 40 years (range 19-77 years) and that of the 30 females was 49 years (range 21-78 years). In the Leeds, Bristol and Glasgow study of 29 patients, the sex distribution was almost equal with 15 males (median age 45 years: range 21-77 years) and 14 females (median age 61 years: range 30-78 years).

There has been considerable research into assessment and grading of disease severity in patients with acute pancreatitis (Williamson 1984) but the information provided in this thesis indicates that initial assessment either by multiple factor grading (Table 12) or diagnostic peritoneal lavage (Table 13) at the onset of acute pancreatitis gives no indication as to the eventual development of a pseudocyst (Chapter 4). There were similar proportions of patients who formed a pseudocyst whose acute pancreatitis was graded as mild or severe. The information from the 418 patients with acute pancreatitis from Leeds, Bristol and Glasgow revealed that of the 113 whose pancreatitis was graded as severe by prognostic criteria 10 (9%) developed a pseudocyst whereas of those 305 patients with "mild" pancreatitis 19 (6%) formed a pseudocyst.

There are no specific features which allow early prediction of this complication in patients with acute pancreatitis. Even the repeated measurement of acute phase reactants, C-Reactive protein in particular, whilst reflecting continued inflammatory reaction, is a non-specific indicator of impending complications (Buchler et al 1986; Mayer et al 1985)

When do pseudocysts develop ?

The advent of ultrasonic scanning has greatly enhanced understanding about the natural history of the development and course of pancreatic pseudocysts (Bradley 1982).

Ultrasound can easily identify fluid around the pancreas following acute pancreatitis and whilst such a collection may progress to become a true pseudocyst with the development of a fibrous, granulation wall, it could potentially resolve and therefore be regarded as a transient pancreatic effusion (Bradley et al 1976, Bradley 1982). To prove that a collection is a "true" pseudocyst it would be necessary to confirm the pancreatic origin by fluid analysis, nature of the surrounding wall by biopsy and a communication between the collection and the pancreatic duct by ERCP in all patients. These procedures might be inappropriate and be an unnecessary intervention in patients whose pseudocysts resolve spontaneously. There is, as yet, no study which utilises such thorough confirmation. In recent years improvements in the resolution of CT scanners have resulted in enhanced tissue definition to an extent where the morphology of a pseudocyst and the thickness of the wall can be assessed without recourse to biopsy.

One important factor in differentiating between an effusion and a true pseudocyst is the time a collection has persisted. The majority of effusions will resolve quickly, within 3-4 weeks of formation but true pseudocysts persist for longer (Bradley et al 1976). Experimental evidence suggests that it takes 4 to 6 weeks for a fibrous, granulating wall to form (Warren et al 1957).

The validity of this evidence in relation to pseudocyst formation in man has been discussed in Chapter 1. The experience in the present work indicates that, on occasion, a definitive fibrous wall may be formed within 2 to 3 weeks. Throughout this study considerable care has been taken to avoid including patients with transient effusions in the analysis of results.

The median time from an episode of acute pancreatitis to confirmation of a pseudocyst by imaging or surgery was 19 days (range 3-49 days) for the patients from Leeds, Bristol and Glasgow and 27 days (range 4-479 days) for those from Glasgow Royal Infirmary. A pseudocyst was therefore, most frequently diagnosed between the second and fourth weeks following an episode of acute pancreatitis. At this time a collection was more likely to be a pseudocyst than a transient effusion.

The diagnosis of a pseudocyst was based, not only on imaging evidence, but also on clinical and laboratory information. The majority of patients studied had symptoms and signs such as abdominal pain, a palpable mass or distension and a raised serum amylase or leukocytosis at the time of pseudocyst diagnosis. Such a combination of factors is less frequently found when a simple transient effusion is present.

When clinical, laboratory and imaging criteria are all positive, diagnosing a pseudocyst is not difficult. Occasionally, however, a pseudocyst forms insidiously without major systemic upset. Indeed, of 29 patients in the Leeds, Bristol and Glasgow study, 6 (20%) had been discharged from hospital, apparently recovered from their acute pancreatitis only to be readmitted, within 2-3 weeks with a well developed pseudocyst.

The presence of a communication between the pancreatic ductal system and the surface of the gland is an important feature in the pathogenesis of a pseudocyst (Chapter 1). The progression of events: acute pancreatitis - areas of necrosis - duct communication - fluid release - sequestration, is critical to pseudocyst formation. The fact that the majority of pseudocysts do not seem to form until the second to fourth weeks after acute inflammation suggests that a communication may not always form immediately but rather it takes some time for an area of necrosis to break down completely and allow fistula formation. It had been hoped that analysis of acute phase reactants within pseudocyst fluid may have provided information about the presence of a fistula but the results were not helpful (Chapter 7).

A potential method of interrupting the progression of this sequence of events is to remove the accumulated fluid using percutaneous needle aspiration of the pseudocyst. Experience shows that, to be effective, catheter drainage has to be employed or the aspiration repeated on several occasions (Chapter 6) and these techniques are not without complications.

Can spontaneous resolution of a pseudocyst be predicted ?

It would be of considerable value to be able to select patients in whom it could be confidently predicted that their pseudocyst would resolve spontaneously and without complication. The differences in clinical and laboratory results between patients with resolving pseudocysts and those in whom surgical drainage was performed have been stressed in Chapter 5.

The clinical features of abdominal distension, a palpable mass, a raised serum amylase and leukocytosis occurred in a greater proportion of those undergoing surgery and in addition, more of the pseudocysts which were drained surgically were greater than 6cm in diameter on ultrasound scan.

It has been suggested that if a combination of large diameter, raised serum amylase and elevated white blood cell count was present then spontaneous resolution was unlikely to occur (Bradley 1982). The data in this thesis has been further examined taking into consideration five important features of pseudocyst formation viz. a diameter of 6cm; a serum amylase of 450 IU/l; a leukocytosis of 12×10^9 cells/l; a palpable abdominal mass; abdominal distension (Table 33) in an attempt to create an assessment system for predicting spontaneous resolution. The features listed in Table 33 have been derived from the results in this thesis and were based on information available at the time of pseudocyst diagnosis. The pseudocyst diameter, as determined by ultrasound scanning, is the central feature of this assessment system.

	LEVEL CHOSEN
PSEUDOCYST DIAMETER ON ULTRASOUND	> 6cm
SERUM AMYLASE (IU/L) AT DIAGNOSIS	>= 450 IU/L
LEUKOCYTOSIS AT DIAGNOSIS	>= $12x10^9$ cells/l
ABDOMINAL MASS ON EXAMINATION	
ABDOMINAL DISTENSION ON EXAMINATION	

TABLE 33 5 criteria for assessment of outcome of patients with pseudocsyts.

3 OR MORE criteria positive indicating that surgical drainage is likely to be necessary.

The results for this system as applied to the 100 patients from Glasgow Royal Infirmary and the 29 from Leeds, Bristol and Glasgow are detailed in Table 34.

The sensitivity and specificity of the system with respect to predicting spontaneous resolution if less than 3 criteria were positive, were greater in the Leeds, Bristol and Glasgow patients when compared to those from Glasgow Royal Infirmary. Confirmation of the value and potential use of this system will only come when it is applied prospectively to patients who form pseudocysts.

An other important feature in relation to spontaneous resolution of a pseudocyst is the time for which a collection has been present. The relevance of a period of six weeks has been discussed in Chapter 1. The median times to complete resolution were 45 and 90 days respectively for the Leeds, Bristol and Glasgow and Glasgow Royal Infirmary studies. These results suggest, that in the majority of patients, a pseudocyst may be safely observed for at least 12 weeks whilst waiting for spontaneous resolution to occur and before some form of surgical drainage becomes mandatory. During this waiting period it is essential that the pseudocyst is repeatedly assessed by ultrasonic or CT scanning. A progressive increase in size of a collection or any deterioration in the clinical condition of a patient may hasten surgical intervention.

	100 PATIENTS FROM GLASGOW ROYAL INFIRMARY		29 PATIENTS FROM LEEDS BRISTOL GLASGOW	
POSITIVE CRITERIA	<3	3 or more	<3	3 or more
RESOLVING PSEUDOCYSTS	11	7	12	3
DRAINED PSEUDOCYSTS	20	37	1	11
SENSITIVITY	61%		80%	
SPECIFICITY	65%		92%	

TABLE 34 Results of assessment system applied to data from 100 patients from Glasgow Royal Infirmary and 29 from Leeds, Bristol and Glasgow.

Can complications of pseudocysts be predicted and avoided?

Pseudocyst formation is a serious complication of pancreatitis be it acute or chronic. The mortality of 10% recorded in both groups of patients studied for this thesis is consistent with that recorded in the established literature which shows a range of mortality of 6-16% (Brilhart and Priestley 1951; Grace and Jordan 1976; Hastings et al 1975; Hillis 1963; McConnell et al 1982; Pollack et al 1978; Scharplatz et al 1972; Thomford and Jesseph 1969). The majority of deaths in the patients studied in this thesis resulted from at least one of the important complications viz. haemorrhage, sepsis, rupture, or obstruction all of which were stressed by Bradley (1982).

Measurement of acute phase reactants, C-Reactive protein in particular (Buchler et al 1986; Mayer et al 1985), and the use of contrast enhanced, dynamic CT scanning (Clavien et al 1988; Jeffrey et al 1982; Kivisaari et al 1982; Lawson 1983; Mainwaring et al 1989; Siegleman et al 1980; van Sonnenberg et al 1985; White et al 1986) are two important techniques of disease assessment that have been used with increasing frequency in the last few years in patients suffering acute pancreatitis. Both modalities give an indication of disease severity and CT scanning can reveal the morphology of a pseudocyst and the retroperitoneal area around the pancreas. The information available from this type of imaging has become an important adjunct in the management of patients with severe acute pancreatitis.

Contrast enhanced dynamic CT scanning was performed in only 10 of the 129 patients considered in this thesis. With such a limited experience of this technique no comment can be made on its value in the management of these patients but this technique becoming a valuable assessment tool in the management of patients with severe, complicated acute pancreatitis .

There are no reports of successful prophylactic measures designed to prevent the major complications caused by pancreatic pseudocysts. Theoretically, early percutaneous pseudocyst drainage could potentially protect against spontaneous rupture and obstruction by removing the fluid. Decompression of a large pseudocyst could also decrease the likelihood of haemorrhage from within the cavity.

The reported incidence of complications occurring in untreated pseudocysts varies between 18 and 42% (Becker and Pratt 1968; Gillman et al 1974; Thomford and Jesseph 1969; Sankaran and Walt 1975). Bradley et al (1979) reported that an increasing proportion of patients developed complications when a pseudocyst had been present for more than 6 weeks. These authors used this data to support a policy of surgical intervention around this time.

The majority of their patients suffered alcohol induced pancreatitis and although their results have been quoted by others to support similar management (Beebe et al 1984; Wade 1985), there is little additional evidence for the concept that the longer the delay to definitive treatment, the more likely complications will occur (Agha 1984; Andersson et al 1989; Aranha et al 1983; Beebe et al 1984; Lasson et al 1988; O'Malley et al 1985; Wade 1985). Indeed, the data in this thesis does not support the findings of Bradley et al (1979) which demonstrated an increasing proportion of patients suffering complications the longer a pseudocyst remained untreated.

Although complications can occur in any patient with a pseudocyst the results in Chapters 3 and 4 have highlighted the importance of the aetiology of the antecedent acute pancreatitis. The mortality in the Glasgow Royal Infirmary study was significantly greater in patients with gallstone induced acute pancreatitis (22% mortality) when compared to those with alcohol (5% mortality) as the causal factor. Consideration must be given to concomitant biliary tract surgery at the time of pseudocyst drainage and prophylactic antibiotic therapy to reduce the incidence of septic complications (Imrie et al 1988).

MANAGEMENT OF PATIENTS WHO DEVELOP A PSEUDOCYST

The management of patients forming a pseudocyst has, in the main, been a policy of "wait and see" and, if necessary intervene. This thesis has focussed on patients in whom such a policy has been adopted. There is some hope, however, that, in future, a change in management may decrease patient mortality and morbidity.

What should be regarded as a basic plan of management for patients with pseudocysts is outlined in Table 35. This scheme is based on conservative management of patients with a pseudocyst using repeated ultrasound or CT scanning and clinical assessment over a period of 4 to 6 weeks then deciding the need and timing of intervention aimed at draining the collection. Complications are dealt with as they arise.

Employing an assessment system as described in this chapter would be of value if it could reliably predict patients in whom a pseudocyst was eventually going to resolve spontaneously without complication or the need for any form of intervention. In addition, for those patients in whom early estimation of outcome predicts that they will ultimately not resolve spontaneously, there is a place for an improvement in management involving planned intervention with the aim of reducing mortality and morbidity and decreasing the number of patients ultimately being subjected to formal operation. As suggested earlier such intervention could be achieved by percutaneous drainage and a proposed scheme of management incorporating early assessment and outcome prediction combined with percutaneous drainage is given in Table 36.

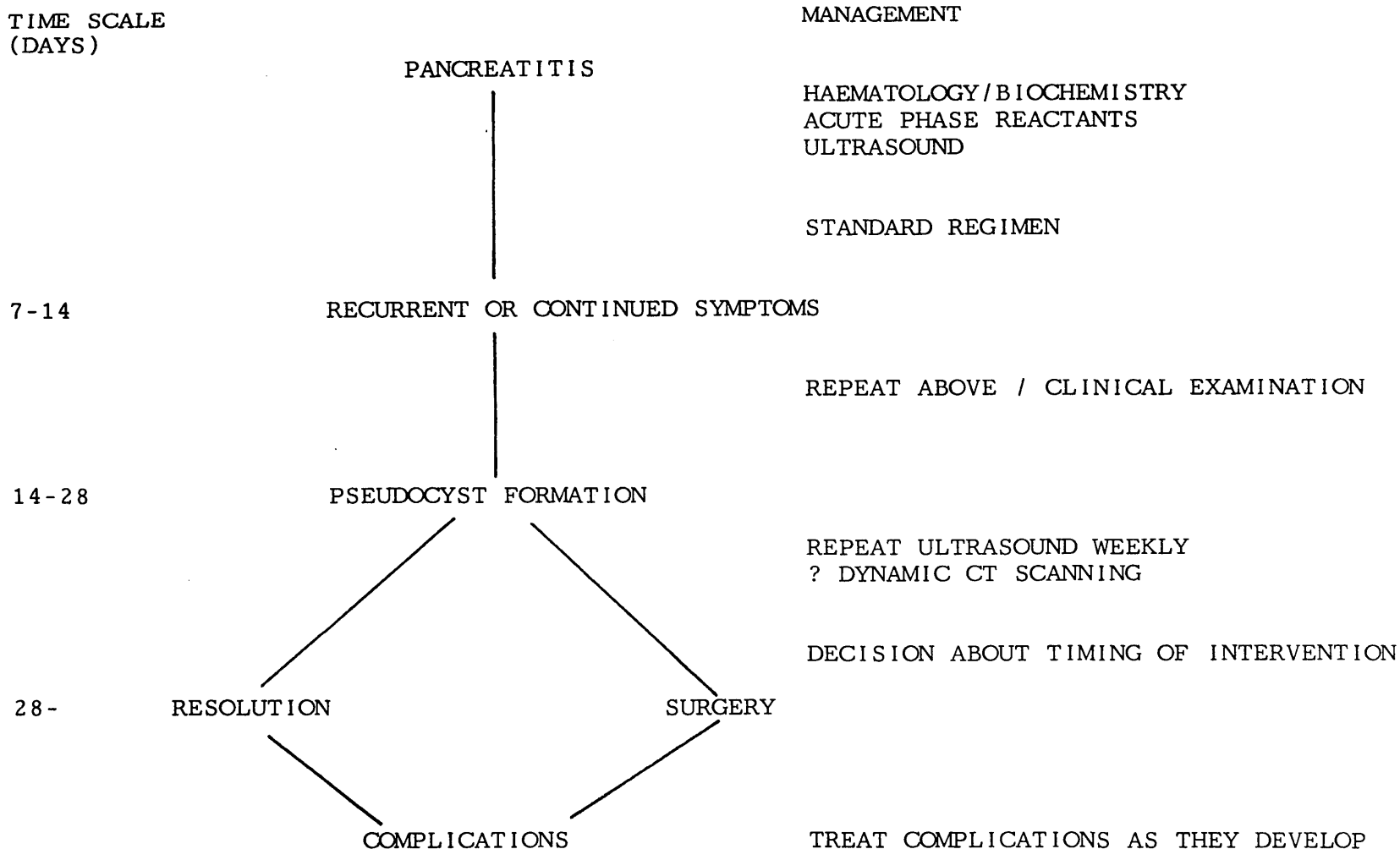


TABLE 35 Outline of basic management of patients with pancreatic pseudocysts.

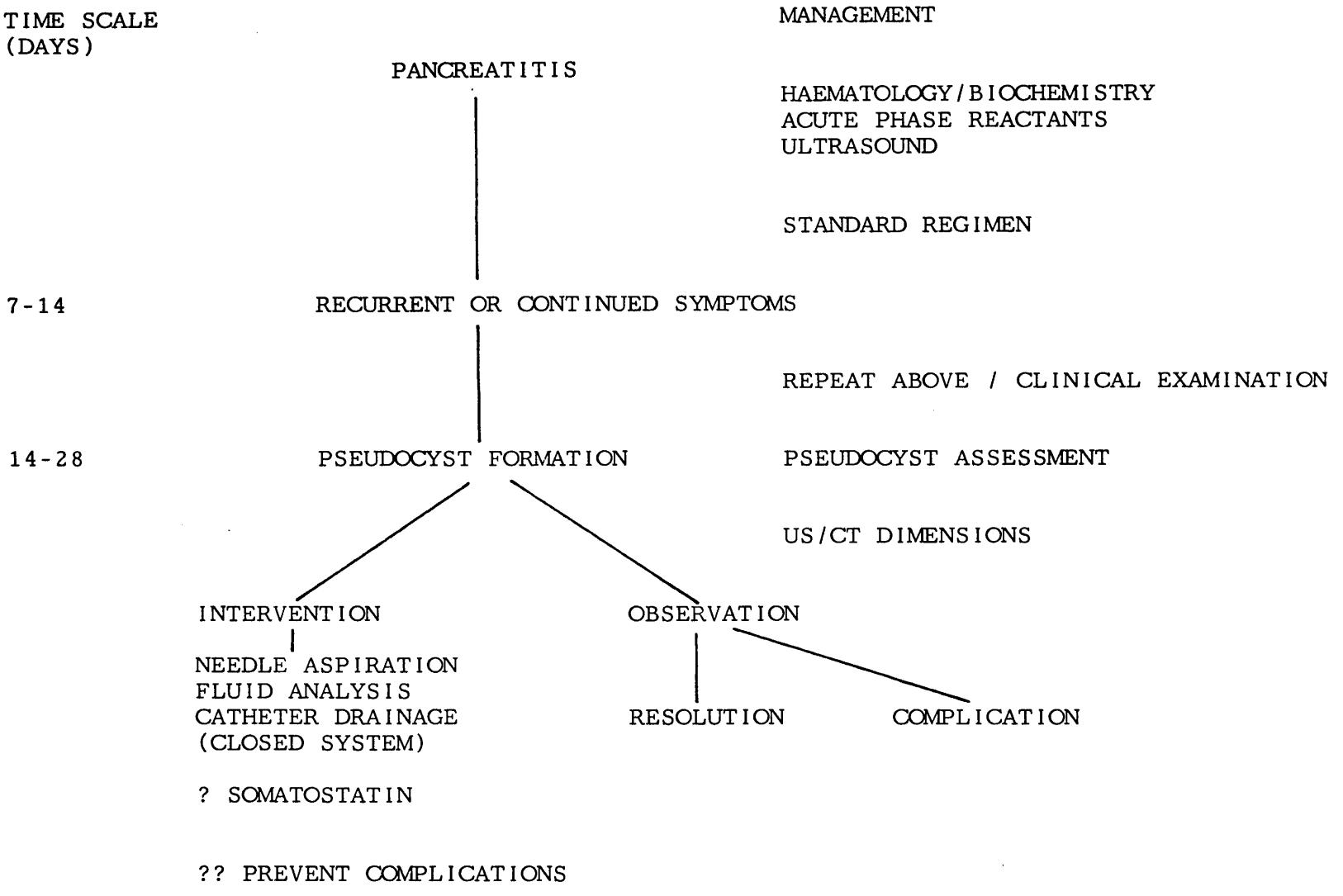


TABLE 36 Outline of suggested future management of patients with pancreatic pseudocysts.

A plan of this nature relies, to a considerable extent, on close cooperation between enthusiastic clinicians and radiologists to provide a complete investigative and therapeutic service at all times.

Percutaneous aspiration and drainage may not obviate the need for surgery in all patients and the technique is not without risk, but there is evidence to suggest that decompression of a fluid collection leads to clinical improvement which allows time to plan elective drainage with the patient in a more favourable condition (Freeny et al 1988, van Sonnenberg et al 1989).

In future, the success of more aggressive management of patients with pseudocysts will depend on refinement of methods of assessment and interventional techniques.

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Journal of the American Medical Association, **195**, 869-871.

APPENDIX 1

LIST OF PUBLICATIONS RELEVANT TO THESIS

APPENDIX 1

PAPERS PUBLISHED FROM WORK ASSOCIATED WITH THIS THESIS.

The importance of etiology in the outcome of pancreatic pseudocyst.

Imrie CW, Buist LJ, **SHEARER MG.**

American Journal of Surgery 1988, 156; 159-162.

A controlled clinical trial of peritoneal lavage for the treatment of severe acute pancreatitis.

Mayer AD, McMahon MJ, Corfield AP, Cooper MJ, Williamson RCN, Dixon AP, **SHEARER MG**, Imrie CW.

New England Journal of Medicine 1985, 312; 399-404.

Prediction of severity in acute pancreatitis: Prospective comparison of three prognostic indices.

Mayer AD, McMahon MJ, Corfield AP, Cooper MJ, Williamson RCN, Dixon AP, **SHEARER MG**, Imrie CW.

Lancet 1985, 2; 403-407.

PHOTOCOPIES OF THESE PAPERS ARE ON THE FOLLOWING PAGES.

Importance of Cause in the Outcome of Pancreatic Pseudocysts

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Among 100 consecutive patients with pancreatic pseudocysts, a biliary cause for the preceding acute pancreatitis was found in 27, for a mortality rate of 22 percent. Patients with alcohol abuse as the cause had a more favorable prognosis, with a 5 percent mortality rate among 59 patients ($p < 0.05$, chi-square test). Despite an age difference between the two groups, we consider that this feature of patients with pancreatic pseudocyst warrants attention and we make recommendations herein with respect to therapy. Pseudocysts developed in 86 patients consequent to an episode of acute pancreatitis, and all 12 deaths (14 percent) were in this group. None of the remaining 14 patients whose pseudocysts were a feature of chronic pancreatitis died. Of the 81 patients in whom amylase levels were measured, 76 percent had an increased level.

Although pancreatic pseudocyst is a well-documented and interesting complication of pancreatitis, the literature on the subject is beset by two major problems. The first is that differentiation between pseudocysts associated with chronic pancreatitis and those consequent to an attack of acute pancreatitis is infrequently stressed [*1–5*]. One study particularly emphasized the higher mortality rate associated with acute pancreatitis compared with the chronic condition [*6*]. The second problem is that the cause of the pancreatitis in relation to the disease's outcome has not been studied previously. This may partly be because gallstones were considered a causal factor in only a small proportion of the total number of patients in the majority of studies, with 17 to 25 percent being the highest figures encountered [*1–3,5,7,8*]. The major purpose of the present study is to focus on the various outcomes in patients with pancreatic pseudocysts associated with alcohol abuse, gallstones, and trauma, using data derived predominantly from prospective studies of patients with acute pancreatitis seen from 1971 to 1984 in the Glasgow Royal Infirmary. In addition, more light is shed on the incidence of hyperamylasemia among these patients. We also discuss the lower mortality rate when pseudocysts were an incidental finding in patients with chronic pancreatitis compared with pseudocysts found as a consequence of acute pancreatitis.

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PATIENTS AND METHODS

Eighty-five patients (85 percent) were documented as having pancreatic pseudocysts during prospective studies commencing in January 1971, and 15 cases were documented in a mainly retrospective study between 1962 and 1970 [*9*]. Pseudocysts developed in 86 patients (86 percent) after emergency hospital admission for an episode of acute pancreatitis. Only 14 pseudocysts were detected in patients with chronic pancreatitis. They were documented during elective admission for pseudocyst treatment. Symptoms of chronic pancreatitis subsequently developed during the follow-up period in two other patients.

Of the patients studied, 62 of the 86 with pseudocysts consequent to acute pancreatitis derived from our own hospital catchment area, in which 879 patients with acute pancreatitis were admitted during the same time period. The incidence of pseudocysts as a complication of acute pancreatitis was therefore 7 percent overall, being more common in those with an alcohol-related cause (11.5 percent) than in those with gallstones (4 percent). The 14 patients with chronic pancreatitis and pseudocysts represented only 7 percent of those screened at the hospital over this period.

The management of patients with acute pancreatitis at our hospital is initially conservative in patients with gallstones and in those with alcohol abuse as the causes [*10,11*]. Only those with trauma as the cause undergo immediate laparotomy. A minority of gallstone patients in this period were operated on early in the course of the disease, but the hospital policy from 1978 onward has favored definitive biliary surgery during the same admission. This has been detailed in previous publications [*12,13*], including the earlier policy of delayed intervention in patients with gallstones, those patients being usually readmitted for elective or semielective surgery [*14*].

The diagnosis of pancreatic pseudocyst was only accepted if there was a combination of clinical findings together with positive biochemical data, imaging data, or both. The most frequent and significant clinical signs were pain, abdominal distention and epigastric fullness, vomiting, anorexia, and weight loss. Other symptoms of obstructive jaundice and gastrointestinal hemorrhage occurred infrequently. A secondary or persistent increase in the serum amylase level, urinary amylase level, or both was the most frequent biochemical abnormality. In the early years of the study, a barium meal study with lateral erect views was the most common imaging technique, but with the introduction of ultrasonography, the latter became the method of choice. The value of ultrasonography in this situation has been frequently stressed, not only for its facility in detecting pseudocysts, but for monitoring

TABLE I
Causes of Pseudocysts

Cause	Total	Men	Women
Alcohol abuse	59	49	10
Gallstones	27	13	14
Unknown	9	6	3
Trauma	4	2	2
Postop	1	...	1
Total	100	70	30

their progression or regression [*15–17*]. In a few instances, computerized tomographic scanning was also used to provide supplementary information, but this was not a routine procedure.

In most patients (78 percent), the pseudocyst was confirmed at operation or at the time of drainage by other methods. In others, it was monitored by ultrasonographic scans or barium meal study. In 97 percent of patients, the pseudocyst had a minimum diameter of 5 cm, the exceptions being three patients with smaller cysts occurring in the head of the pancreas.

The Student's t test and the chi-square test were the statistical methods used.

RESULTS

There were 70 male and 30 female patients, the men having a mean age of 43.7 years and the women, 47.7 years. Forty-nine of the 59 patients (83 percent) in whom alcohol abuse was considered the primary cause of pancreatitis were men, whereas just under 50 percent of the 27 with gallstone-associated disease were men (Table I). Those considered to have alcohol abuse as the cause all drank in excess of 80 g of alcohol per day, and had done so for many years. In many, heavier bouts of drinking immediately preceded the episode of acute pancreatitis.

Blunt abdominal trauma was considered to be the cause of pancreatitis in four patients. The pseudocyst developed in one patient after an episode of postcholecystectomy pancreatitis. The remaining nine patients had no clear cause identified. A history of moderate alcohol intake was obtained in two of the patients with a gallstone cause and in three of the patients in the trauma group. Four of the 59 patients who had alcohol abuse as the primary cause had another factor identified as well. Two were subsequently found to have stones in the gallbladder only, whereas one had positive viral titers for Coxsackie B infection. In addition, an annular pancreas was identified at a later date in another patient.

In 81 patients (81 percent), the serum amylase level was estimated at the time of diagnosis (Phabedas method, normal range 150 to 300 IU/liter). In 37 patients, amylase levels were also measured in the urine (upper limit of normal, 1,300 IU/liter). In 27 patients (33 percent), the serum amylase level exceeded 1,200 IU/liter, and in an additional 35 (43 percent), it was in the range of 300 to 1,200 IU/liter. The urine amylase level was above 3,000 IU/liter in 17 (46 percent) of the 37 patients in whom it was measured. When all those with a serum amylase level in the equivocal range (300 to 1,200 IU/liter) were included, an abnormally increased amylase level was present in 62 of the 81 patients (76 percent).

TABLE II
Operations, Deaths, and Causes of Pancreatic Pseudocyst

Operation	Total	AA	GS	Other	Deaths
Cystogastrostomy	50*	27	16	4	6
External drainage	11	5	3	3	5
Roux-Y loop drainage	7†	4	4	...	1
Distal resection	8	6	...	2	...
Cystoduodenostomy	3‡	3	...	...	...
Aspiration at laparotomy	4§	4	...	...	...

* Three patients required a second cystogastrostomy.
† One patient had a Roux-Y loop plus cystogastrostomy.
‡ One patient required a cystoduodenostomy and cystogastrostomy.
§ One patient had aspiration followed by cystogastrostomy.
AA = alcohol abuse; GS = gallstones.

Spontaneous regression occurred in 22 of the 100 pseudocysts (22 percent), usually within 6 weeks of diagnosis. The median size of these resolving pseudocysts was 8 cm (range 3 to 10 cm).

Seventy-six patients underwent a total of 80 operations (Table II). Cystogastrostomy was the most frequent operation and was performed in 50 patients, 3 of whom required a second operation because the pseudocyst recurred. In each of these patients, an additional cystogastrostomy was carried out with success. One patient treated by initial aspiration of small pseudocysts in the head of the pancreas at the time of laparotomy required a second operation for a subsequent larger pseudocyst several months later, and a cystogastrostomy was then performed. In three more patients with multiple small pseudocysts in the head of the gland, simple aspiration at laparotomy proved to be an adequate procedure. Two patients had a combination of procedures to drain bilocular pseudocysts in the body and head of the pancreas. One had a cystogastrostomy and a cystoduodenostomy, and the other had a cystogastrostomy and Roux-Y loop drainage of the lesion in the pancreatic head.

Six patients died after cystogastrostomy for a 12 percent mortality rate. The highest mortality rate associated with surgery occurred in those treated with external drainage (45 percent) (Table II). This operation was performed when the pseudocyst wall was immature, usually relatively early after the first clinical suspicion of the diagnosis. Sepsis was not present at the time of operation.

Death occurred in 12 of the 100 patients, all of whom underwent operation. Those in whom gallstones were considered the primary cause had a mortality rate of 22.2 percent, which was four times greater than that in patients with pseudocysts associated with alcohol abuse ($p < 0.05$, chi-square test) (Table III).

Overall, 50 percent of the patients who died from pancreatitis had a gallstone cause. An outline of the major complicating factors, together with age, cause, and operative procedure in the 12 patients who died, is provided in Table IV. The three youngest patients (all less than 40 years of age) had alcohol abuse as the cause, whereas the age range for biliary disease was 52 to 70 years (mean

TABLE III
Causes of Death

Cause	Total	Deaths	%
Gallstones	27	6	22
Alcohol	59	3	5
Unknown	9	2	22
Trauma	4	1	25
Postop	1	...	...

age 59 years). The major cause of death was sepsis (seven patients), with severe hemorrhage occurring in three. Two of the remaining patients also had this complication. The other deaths were associated with a recurrence of pancreatitis in one patient, cardiorespiratory failure in another patient, and total pancreatic necrosis compounded by a possible myocardial infarction in the final patient (Table IV).

Percutaneous aspiration of the pseudocyst was the primary procedure in six patients, but in four of these patients the pseudocyst recurred and surgery was necessary. Therefore, this procedure alone was only successful in two cases.

One of these six patients died, and he was the oldest patient in the group who died. He had long-standing cardiorespiratory disease and, although the initial attempts at aspiration were successful, reaccumulation of fluid occurred so rapidly that surgery was deemed necessary. At operation, a large piece of peripancreatic slough weighing 160 g was removed from the depths of the pseudocyst. This patient also had significant abnormalities in the results of liver function tests, suggesting that gallstones may have been responsible for the pancreatitis. However, family permission for a postmortem examination was refused.

None of the 14 patients with pseudocysts associated with chronic pancreatitis died. Therefore, the mortality rate in patients who had pseudocysts complicating an attack of acute pancreatitis was 14 percent, and the mortality rate was 0 in the smaller group of 14 patients with pseudocysts complicating chronic pancreatitis.

COMMENTS

Problems arise as to what constitutes a pancreatic pseudocyst. For this reason, the definition we used is described in detail in the "Patients and Methods" section. As noted in our introduction, few previous reports have made reference to the proportion of patients in whom the pseudocyst is a consequence of a documented attack of acute pancreatitis, as opposed to those in whom such complications develop in association with chronic pancreatitis. In the present study, it is clear that the former group constituted the majority of our patients. This group had a significantly higher mortality and morbidity rate than the group associated with chronic pancreatitis.

This is an important point, and in future studies of the subject, there should be a clear differentiation between these two groups of patients based on their clinical presentation. Most studies emanating from North America have a preponderance of pseudocysts resulting from alcohol-associated chronic pancreatitis [*1*,*4*–*7*], which biases both treatment and outcome, as has been suggested previously [*4*]. Our results emphasize the importance of the cause of pancreatitis in determining outcome in patients with pancreatic pseudocysts, specifically the mortality rate for those with a gallstone cause that was four times greater than that in patients with alcohol abuse as the cause. Although the age difference between the patients with the two major causes was significant (alcohol group, mean age 39 years and gallstone group, mean age 53 years, $p < 0.05$ by Student's t test), other factors must be taken into account.

TABLE IV
Deaths Associated with Pancreatic Pseudocysts

Age (yr) & Sex	Cause	Operation	Cause of Death
48, F	Trauma	ED	Septic shock
66, M	Gallstone	ED	Septic shock, renal failure
53, F	Gallstone	ED	Duodenal fistula, recurrent AP
57, M	Gallstone	CG	Hemorrhage, AF
39, M	Alcohol	ED	Respiratory failure
52, M	Gallstone	Roux-Y	Sepsis
29, M	Alcohol	CG	Sepsis
57, M	Gallstone	CG	MI
70, M	Gallstone	CG	Sepsis, hemorrhage
35, M	Alcohol	CG	Sepsis, hemorrhage
71, M	Unknown*	ED	Sepsis, hemorrhage
60, M	Unknown	CG	Hemorrhage

* Patient had abnormal results on liver function tests suggesting gallstones, but cause of disease was regarded as unknown.

AF = atrial fibrillation; AP = acute pancreatitis; CG = cystogastrostomy; ED = external drainage; MI = myocardial infarction.

The cause of death in seven patients was overwhelming postoperative sepsis, and this was complicated by gastrointestinal hemorrhage in three. Two additional patients had hemorrhage as the primary cause of death. In both patients, it occurred several weeks after the initial cystogastrostomy.

Sepsis was present in both of the young patients who died with alcohol-associated pseudocysts, whereas four of the six patients with unequivocal evidence of gallstones had septicemia. The disturbing prevalence of death in the gallstone group and the high incidence of sepsis underline the necessity for close clinical supervision. It seems wise, therefore, that patients with a biliary cause of pancreatitis be cared for more diligently.

In view of the major risk of sepsis and hemorrhage complicating pseudocyst drainage, it is sensible to remove all gallstones at the same operation in order to minimize the risk of cholangitis and possible septicemia in the postoperative period. This will lengthen the time of the primary operation for drainage of the pancreatic pseudocyst but may be an important step towards reducing the mortality and morbidity rates of this condition. We also recommend administration of appropriate prophylactic antibiotics in the form of an aminoglycoside, a modern cephalosporin, or a modified penicillin.

Hemorrhage during and after pseudocyst drainage can be an awesome surgical problem [*18*,*19*]. Incorporation of the splenic artery and vein into the posterior wall

of the pseudocyst is the most common source of bleeding, and preoperative angiography can be helpful to forewarn of this problem. At operation, needle aspiration of the pseudocyst to determine the nature of the fluid content was of value before definitive drainage. Of the five patients who died with associated hemorrhage, four bled heavily from the pseudocyst at the time of surgery. In one, bleeding derived from an artery stretched across the internal diameter of the pseudocyst to the point of rupture. In the remaining patients, bleeding was from the wall of the pseudocyst and proved difficult to control.

Arterial embolization might have been utilized in these patients by means of angiographic techniques, but in most, this preoperative procedure was not performed. A patient in whom a stretched artery within the pseudocyst ruptured did survive only to die many days later from sepsis. The hazards of both sepsis and hemorrhage in patients with pancreatic pseudocysts has been highlighted by others [*4,7,18,19*]. To our knowledge, this is the first study that brings into focus the increased risk of sepsis and hemorrhage in patients with a pseudocyst after gallstone-induced pancreatitis.

The need for an accurate clinical definition of a pseudocyst becomes important when assessing the patients in whom the lesion resolves spontaneously. During the prospective phase of our study, regression of pseudocysts was monitored with ultrasonographic scanning in the majority of patients. This was usually associated with both clinical improvement and a return of the blood and urine amylase levels to within normal limits. Our experience concurs with that of Bradley et al [*7*] and Bradley and Clements [*17*] who reported that spontaneous regression 6 weeks after diagnosis is relatively uncommon.

Although many medical textbooks mention the possibility of hyperamylasemia in a patient with a pseudocyst, the frequency with which this is recorded varies considerably (11 to 100 percent) [*2,20*]. Seventy-six percent of patients in our study who had amylase monitoring demonstrated an increase in either the blood or urine amylase level. It is recognized that if recurrent pain develops in a patient with an increased serum amylase level, an increased urinary amylase level, or both (perhaps associated with epigastric fullness and an abdominal mass) after an attack of acute pancreatitis, then there is a high probability that a pseudocyst is present. Further investigations should then be performed and, if necessary, repeated to confirm or refute this diagnosis.

Finally, six patients underwent percutaneous aspiration of a pseudocyst as the first method of treatment. Surgical drainage became necessary in four of them. Our more recent experience with this technique has produced similar results, and we have not found the success rates quoted by other investigators in small studies [*21,22*]. We have only infrequently used repeated aspirations or prolonged catheter drainage for fear of introducing infection.

This predominantly prospective study allowed more careful assessment of the role of cause in the outcome of pancreatic pseudocyst than had previously been achieved. It also enabled further data on the frequency of amylase elevation in blood and urine to be recorded for such patients, adding useful information to the characterization of this complication after an episode of acute pancreatitis.

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CONTROLLED CLINICAL TRIAL OF PERITONEAL LAVAGE FOR THE TREATMENT OF SEVERE ACUTE PANCREATITIS

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Abstract We performed a multicenter, randomized, controlled clinical trial of therapeutic peritoneal lavage (2 liters per hour for three days) in 91 patients with severe acute pancreatitis. Patients were entered into the study if severe pancreatitis was indicated by multiple laboratory criteria or diagnostic peritoneal lavage. All patients received full supportive treatment. The median time between the onset of symptoms and randomization was 38 hours. Forty-six patients were assigned to the control group and 45 to the lavage group. There were 13 deaths (28 per cent) and 16 patients with major complications (35 per cent) in the control group, as compared with 12 deaths (27 per cent) and 17 patients with major complications (38 per cent) in the lavage group. Lavage did not appear to modify the length of survival, the incidence of pancreatic collections (pseudocysts or abscesses), or the plasma amylase concentration. Considering the statistical power of the design, we conclude that the outcome of severe pancreatitis was not greatly, if at all, influenced by the regimen of peritoneal lavage used in this study. (N Engl J Med 1985; 312:399-404.)

DESPITE improvements in intensive medical care, the mortality rate for patients with early signs of acute pancreatitis remains as high as 40 to 60 per cent.[1-4] Experimental studies have suggested that biologically active compounds accumulate in peritoneal fluid and are responsible for the shock-like systemic illness that is characteristic of the acute phase of severe pancreatitis.[5-8] If this hypothesis is correct, it is reasonable to attempt to modify the natural history of the disease by removing the ascitic fluid by means of peritoneal lavage.

Since Wall[9] and Gjessing[10] independently described clinical improvement in a few patients with acute pancreatitis in whom lavage had been used, there have been several enthusiastic anecdotal reports on lavage therapy,[11-16] but only two randomized controlled trials have been described. Stone and Fabian[17] reported a significant reduction in mortality in patients with alcohol-related pancreatitis, but the results are difficult to interpret because many patients were removed from the control group after 24 hours. An interim report on a Swedish study[18] included too few patients for a conclusive result to be expected but showed no evidence of a trend in favor of lavage therapy.

The majority of patients with acute pancreatitis have a benign, self-limiting disease for which a treatment as invasive as peritoneal lavage is both unnecessary and potentially harmful.[3] Furthermore, in a therapeutic trial the effect of such treatment on the more severely ill patients becomes obscured if large numbers of patients with mild attacks are included. It is only the recent emergence of reliable prognostic criteria[1,3,19] that has made a trial of therapeutic lavage feasible. Even if the only patients considered are those with severe attacks, the number of patients required to

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achieve a result within a realistic period precludes a single-center study.

In order to evaluate the clinical application of therapeutic peritoneal lavage, we have carried out a multicenter, prospective, randomized, controlled clinical trial in 91 patients with objective evidence of severe acute pancreatitis.

Methods

Between September 1981 and February 1984, 413 patients with 428 attacks of acute pancreatitis were referred by clinicians in 24 hospitals to a coordinator at one of three centers. All patients were examined by the coordinator as soon as possible after referral and were considered suitable for inclusion in the study if the following criteria were met: the diagnosis of acute pancreatitis had been established on the basis of consistent clinical findings and a plasma amylase level above 1200 IU per liter, or at diagnostic laparotomy (in three patients only); severe pancreatitis was predicted either by the findings of diagnostic peritoneal lavage[19] or by multiple laboratory criteria[20] within 48 hours of admission to the hospital (Table 1); there were no medical contraindications to either of the treatment regimens stipulated by the protocol (e.g., multiple laparotomy scars); and informed consent had been obtained from the patient or relatives and from the attending clinician.

Patients who satisfied these criteria were randomly assigned by sealed envelope to receive either standard conservative treatment (control group) or the same standard treatment plus therapeutic peritoneal lavage (lavage group). The study was approved by the ethics committees of the participating hospitals.

Standard Conservative Treatment

This treatment was continued for at least three days. A nasogastric tube was inserted into the stomach and aspirated hourly. Intravenous crystalloid solutions were given according to clinical requirements and were supplemented by plasma in order to maintain a positive central venous pressure. Oxygen therapy, based on arterial blood gas analysis, was administered by face mask if arterial oxygen tension (PO_2) was less than 9 kPa; assisted ventilation was instituted if oxygen therapy was unsuccessful in maintaining the PO_2. Antibiotics were prescribed only if there was clinical evidence of concurrent infection.

Peritoneal Lavage

Lavage was carried out with a standard peritoneal dialysis cannula (Trocath, McGaw Laboratories, Glendale, Calif.). The same cannula was used for both diagnostic and therapeutic peritoneal lavage. With use of an aseptic technique and local anesthesia with lidocaine (2 per cent) and epinephrine (1:200,000), the cannula was introduced into the pelvis through a 5-mm midline subumbilical incision. After aspiration of any free ascitic fluid, diagnostic lavage was performed with 1 liter of isotonic saline.[19] Therapeutic lavage was instituted with hourly 2-liter cycles of a warmed, balanced, isotonic peritoneal dialysis solution (Dialaflex 61, Boots Ltd., Nottingham, U.K.) to which 4 mmol of potassium chloride and 250 IU of sodium heparin per liter had been added. The hourly volume infused was reduced to 1 liter in two patients with respiratory difficulties. Samples from the lavage effluent were obtained initially and then every 12 hours and were sent for bacteriologic examination. Lavage was continued for 72 hours or for longer if the lavage return fluid remained dark-colored (two patients only). Therapy was closely supervised by the coordinator in order to ensure uniformity of management, and clinical progress was monitored throughout the hospital admission. All patients who survived were followed in the outpatient department for at least six weeks.

Complications were classified as fatal, major, or minor. Pancreatic necrosis, pancreatic or peripancreatic fluid collections, intraabdominal abscess, septicemia, cholangitis, renal failure, gastrointestinal hemorrhage, venous thromboembolism, diabetes requiring insulin therapy, and pulmonary complications associated with hypoxemia (PO_2 above 8 kPa) or with abnormal radiologic signs were defined as major complications. Bacteriologic evidence of a respiratory tract infection without hypoxemia and without abnormal radiologic signs, bacteriuria without systemic signs of sepsis, and a transient psychosis associated with alcohol withdrawal were all defined as minor complications.

Table 1. Prognostic Systems Used to Select Patients for Inclusion in the Trial.

I. Multiple laboratory criteria
Severe pancreatitis was predicted if three or more of the following criteria were met during the first 48 hours of admission:
1. Blood white-cell count $>1500\times10^9$ per liter
2. Plasma glucose >10 mmol per liter and no previous history of diabetes
3. Plasma urea >16 mmol per liter and not falling for six hours
4. Plasma lactate dehydrogenase >600 IU per liter
5. Plasma aspartate aminotransferase >200 IU per liter
6. Plasma uncorrected calcium <2.0 mmol per liter
7. Plasma albumin <32 g per liter
8. Arterial blood PO_2 <8.0 kPa

II. Diagnostic peritoneal lavage
Severe pancreatitis was predicted if one or more of the following criteria were met:
1. More than 20 ml of ascitic fluid
2. Dark-colored ascitic fluid*
3. Peritoneal lavage fluid darker than a pale straw color.*

*A standard color chart was used to assess fluid color.[19]

Because there is no generally accepted definition that distinguishes a pancreatic abscess from an infected pancreatic pseudocyst,[21] the term "pancreatic collection" was used to describe a collection of fluid within the pancreas or peripancreatic tissues (i.e., either a pseudocyst or an abscess). A pancreatic collection was described as infected if bacteria were cultured from samples of fluid within it.

Statistical Analysis

During the design of the study, analysis of the performance of the prognostic systems suggested that about 70 per cent of the patients who were randomly assigned to the control group would have a fatal or major complication.[19,20] Consideration of the Type I and Type II errors[22] indicated that it would be reasonable to analyze the results after 40 patients with severe pancreatitis had been entered into each group. This would give a power of 90 per cent for detecting a 50 per cent reduction in mortality and major morbidity in the lavage group at a two-tailed significance level of $P<0.05$. As a result of this analysis, the trial was concluded after 11 additional patients who had already entered the study had completed the protocol.

The two-tailed normal approximation of Wilcoxon's two-sample rank-sum test (z), corrected for continuity, and the chi-square test, incorporating Yates' correction for continuity, were used to test for statistical significance.

Results

Inclusions, Exclusions, and Withdrawals

Of the 428 attacks of acute pancreatitis in patients referred for assessment, 118 were predicted to be severe by the prognostic criteria. The mortality and morbidity rates associated with these 118 attacks were 26.3 per cent and 34.7 per cent, respectively (31 deaths, 24 nonfatal pancreatic collections, and 17 other major complications), as compared with a 2.9 per cent mortality rate and a 10.0 per cent morbidity rate associated with the 310 attacks that were predicted to be mild (9 deaths, 12 nonfatal pancreatic collections, and 19 other major complications).

Data on 25 of the attacks that were predicted to be severe were excluded from the analysis because

(1) prediction of severe pancreatitis by multiple laboratory criteria was delayed for more than 48 hours after admission (19 attacks with 1 death and 6 major complications); (2) abdominal scars precluded lavage (5 attacks with 1 death and 1 major complication); or (3) peritoneal dialysis was required in order to treat acute renal failure (1 attack with 1 death). In addition, two patients who were initially thought to have severe pancreatitis on the basis of laboratory criteria were withdrawn from the study because the clinical diagnosis was found to be erroneous. One had a thoracoabdominal aortic aneurysm with bilateral renal infarction; the other, who had infected, bile-stained peritoneal fluid, had a perforated gallbladder. Both patients died within 24 hours of admission, and neither had evidence of acute pancreatitis at autopsy. Diagnostic peritoneal lavage revealed an erroneous clinical diagnosis in three other patients who had been referred to the study: two had perforations of the biliary tract, and one had a perforated duodenal ulcer.

Comparability of Groups (Table 2)

Forty-five patients assigned to the lavage group and 46 assigned to the control group were retained in the trial. There was a preponderance of men in the lavage group and of women in the control group (chi-square = 4.20, $P<0.05$), but the two groups were well matched for age, etiologic factors, and clinical and biochemical indexes of severity. There was no significant difference in the duration of symptoms ($z = 0.633$, $P = 0.53$) or in the delay from the diagnosis of pancreatitis to randomization ($z = 0.916$, $P = 0.36$).

Mortality and Morbidity (Table 3)

There were 12 deaths and 17 patients with major complications in the lavage group (27 per cent mortality and 38 per cent morbidity) and 13 deaths and 16 patients with major complications in the control group (28 per cent mortality and 35 per cent morbidity). If the true difference in mortality and major morbidity was 50 per cent, the probability that this result was due to a Type II error (at a two-tailed significance level of $P<0.05$) is 0.11.

The median age of the patients who died was 70 years; only one was under 50. Five of these patients had gallstones and three had alcoholism. The cause of death remains obscure in 17 patients, although autopsies were not performed in 6. Six patients in the lavage group and eight in the control group died within one week of admission from multiorgan failure associated with fulminant pancreatitis, but the timing of death in the two groups was not significantly different ($z = 1.109$, $P = 0.267$). Nine of the 14 early deaths were attributed to pulmonary complications. In addition, one patient in each treatment group died from acute renal failure, and one patient in the lavage group and two in the control group died from cardiovascular failure.

The fatal and major complications are listed in Table 3. The proportion of patients with a complication, the incidence of individual complications, and the time spent in the hospital were similar in the two groups. Thirty patients who survived the first week of the illness acquired a pancreatic collection, which was recognized at a median time of 21 days after admission (range, 4 to 42). Eight of the 14 collections in the lavage group (57 per cent) were infected, as compared with 6 of the 16 in the control group (37 per cent). This difference was not significant (chi-square = 0.50).

The mean plasma amylase concentrations during the first five days after admission in the two groups of patients are shown in Figure 1. Amylase levels did not appear to be influenced by peritoneal lavage.

Table 2. Comparison of Clinical, Biochemical, and Etiologic Factors in Patients Who Were Included in the Trial.*

	Lavage Group (N = 45)	Control Group (N = 46)
Mean age ±S.D.	57±19	59±18
Sex (M/F)	29/16	18/28
Previous pancreatitis	4	3
Ischemic heart disease	3	8
Proved gallstones	16	16
Alcohol abuse	13	11
Hours from onset of symptoms to admission — median (range)	26 (8–108)	28 (4–96)
Hours from admission to randomization — median (range)	12 (1–48)	5 (0–48)
Comatose on admission	4	4
Systolic blood pressure <100 mm Hg	4	3
Abdominal rigidity	39	39
PO_2 <8 kPa	21	15
White-cell count $<1500\times10^9$	28	27
Glucose >10 mmol per liter	18	19
Urea >15 mmol per liter	6	6
Multiple criteria score		
<3	21	19
3–4	18	20
>4	6	7
Predicted "severe" by diagnostic peritoneal lavage	37	31/34 †
Predicted "severe" by both prognostic systems	16	12/34 †

*Figures are numbers of patients except where otherwise indicated.

†Only 34 of the 46 patients in the control group underwent diagnostic peritoneal lavage.

Complications of Lavage

None of the deaths in the lavage group was attributed to peritoneal lavage. However, respiratory difficulties may have been caused by the therapy in two patients, and severe lower abdominal and scrotal swelling occurred in another, presumably because of leakage of fluid into the abdominal wall. One other patient, who had symptoms of alcohol withdrawal, refused further lavage after four cycles. In addition, the lavage cannula was inadvertently introduced into the urinary bladder in one patient. It was repositioned into the peritoneal cavity without untoward sequelae.

The patients in the lavage group lost a median of 44 g of protein per day into the lavage effluent (range, 23 to 160 g per day) and were given significantly more intravenous plasma over the initial three days (median, 2900 ml; range, 0 to 13,800) than were the patients in the control group (median, 400 ml; range 0 to 8100) ($P<0.01$).

With the exception of the patient with a perforated gallbladder (who was withdrawn from the study), none of the study patients had bacteria detected on microscopy of the initial sample of free peritoneal fluid or of subsequent samples of lavage return fluid. In four patients (one in the lavage group and three in the control group) a scanty growth of coliform bacteria was obtained after culture of the free peritoneal fluid. Two of these four patients (both in the control group) died — one from fulminant pancreatitis with early abscess formation, the other as a result of an infected pancreatic collection; in a third patient (in the lavage group) a sterile pancreatic collection developed. Organisms were also cultured from the therapeutic lavage effluent in four patients; one died from pulmonary complications and another had a sterile pancreatic collection, but none of them had intraperitoneal septic complications.

Table 3. Fatal and Major Complications in the 91 Patients with Acute Pancreatitis Who Were Included in the Trial.

Complication	Lavage Group (N = 45)	Control Group (N = 46)
	no. of complications	
Fatal		
Fulminant pancreatitis	6	8
Infected pancreatic collection	3	5
Chest infection	2	0
Renal failure	1	0
Major*		
Pancreatic collection (infected)	11 (5)	11 (1)
Chest infection	12	9
Diabetes	2	2
Renal failure	2	2
Septicemia†	3	0
Gastrointestinal hemorrhage	1	1
Pulmonary embolism	1	0

*There were 12 deaths and 32 major complications in 17 patients in the lavage group and 13 deaths and 25 major complications in 16 patients in the control group.

†Defined as a positive blood culture together with leukocytosis (>1500×10^6 per liter) and pyrexia (temperature >38°C).

Discussion

This study evaluated peritoneal lavage therapy in a selected group of patients with objective signs of severe pancreatitis. The prognostic systems proved reliable for the identification of severe disease: the overall mortality rate for the 91 patients studied was 27.5 per cent, which contrasts with a 2.9 per cent mortality rate for the patients with 310 attacks that were assessed as mild by the prognostic criteria.

Therapeutic lavage did not appear to influence either mortality or morbidity. This finding contrasts with the results of the controlled trial carried out by Stone and Fabian,[17] as well as with favorable reports on lavage in experimental pancreatitis.[23-26] The delay between the onset of pancreatitis and the beginning of lavage therapy may account for the discrepancy between experimental results and the results of this clinical trial. The median time between the onset of symptoms and randomization was 38 hours (range, 4 to 132). Even if therapy had been started as soon as the diagnosis of acute pancreatitis was made, without awaiting evaluation for prognostic criteria, only a minority of patients would have started treatment within 24 hours of the onset of symptoms.

Ranson and Spencer[27] observed that peritoneal lavage appeared to prevent early mortality in patients who met the criteria for severe pancreatitis during the first 48 hours after admission. However, they recorded a high incidence of late septic complications in patients given lavage therapy, and there was no overall improvement in survival in these patients, as compared with historical controls. We were unable to confirm a reduction in early mortality in our lavage group. Indeed, two of the five early deaths occurred within 24 hours of admission, before the results of the multiple laboratory studies used to establish prognostic criteria were available.

Ideally, patients entered into the control group should have received no peritoneal intervention. However, because the efficacy of therapeutic peritoneal lavage may depend on the speed with which it can be instituted[23] and because of delay in obtaining results from the laboratory-based system, diagnostic lavage was used to obtain an early prognosis in 34 of the patients in the control group (9 of whom died). It is possible that diagnostic lavage with a single liter of isotonic saline had a therapeutic effect. An additional advantage of diagnostic lavage was its ability to detect an erroneous clinical diagnosis of acute pancreatitis.

In this study, antibiotics were prescribed only to treat infective complications of acute pancreatitis. There is no evidence that antibiotics influence the outcome of an attack of pancreatitis,[28-30] although published trials have included too few patients to disprove their efficacy.[31] There is a potential risk of contamination of the peritoneal cavity during therapeutic lavage, and peritoneal irrigation with saline may impair the function of peritoneal macrophages.[32] However, bacterial contamination of the lavage fluid occurred in only four patients and was not associated with intraabdominal septic complications. Furthermore, the

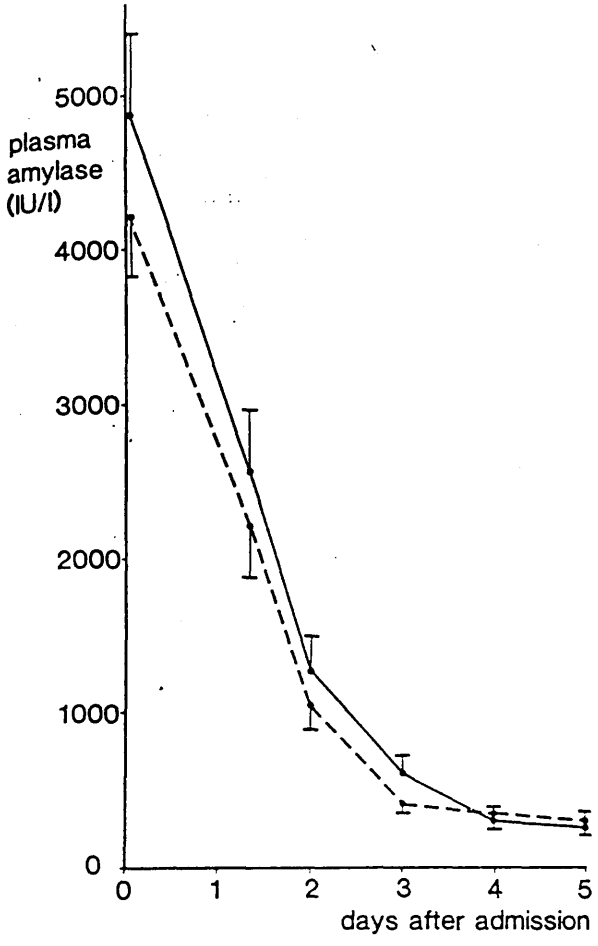

Figure 1. Plasma Amylase Concentrations during the First Five Days after Admission in 45 Patients in the Lavage Group (Broken Line) and 46 Patients in the Control Group (Solid Line).

The initial values in both groups were obtained before randomization. Data points represent mean values; error bars indicate the S.E.M. There were no significant differences in amylase concentrations in the two groups at any time.

incidence of intraabdominal abscess in the lavage group (eight abscesses, three fatal) was similar to that in the control group (seven abscesses, five fatal).

The reasons for using peritoneal lavage therapy in acute pancreatitis are that the peritoneal cavity forms an important reservoir of pancreatic enzymes and their digestion products, and that lavage in the early phase of the disease precludes the systemic absorption of potentially toxic compounds.[7] Our study does not necessarily contradict this reasoning: the delay in delivering treatment may have crucially undermined the effectiveness of the therapy. However, emphasis on the importance of the transperitoneal route for the absorption of pancreatic enzymes and their digestion products into the plasma may be misplaced. A recent study has suggested that the principal route of transfer of enzymes from the pancreas to the plasma in severe pancreatitis is via lymphatics and veins that drain the gland.[33] The observation that therapeutic lavage did not reduce plasma amylase levels is consistent with this theory. Severe pancreatitis is usually associated with local tissue necrosis and hematoma formation. The action of pancreatic enzymes on this avascular retroperitoneal tissue may generate toxic digestion products,[34] which could be absorbed directly into retroperitoneal lymphatics.

The results of this study suggest that a three-day regimen of therapeutic lavage with a conventional peritoneal dialysis solution does not influence the outcome of an attack of severe acute pancreatitis. Prompt recognition of the severe attack and immediate initiation of therapy must be considered priorities for future studies.

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PREDICTION OF SEVERITY IN ACUTE PANCREATITIS: PROSPECTIVE COMPARISON OF THREE PROGNOSTIC INDICES

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Summary The prognostic value of three predictive indices was compared in 436 attacks of acute pancreatitis in 418 patients. The outcome of an attack was graded as uncomplicated (324), complicated (70), or fatal (41); 1 attack was excluded because of puncture of the caecum. The overall mortality rate was 9·4%. Clinical assessment on admission identified only 34% of patients whose attack was severe (ie, complicated or fatal). Multiple laboratory criteria and peritoneal lavage were more sensitive (61% and 53%, respectively) while retaining diagnostic accuracy (79% and 74%). An erroneous diagnosis of pancreatitis was corrected by the findings on lavage in 5 patients. The major advantage of peritoneal lavage over multiple laboratory criteria was the shorter delay between admission to the study and determination of severity (median 4 *v* 24 h), but visceral puncture during insertion of the cannula occurred in 2 of 253 patients (0·8%). When used together, the three indices correctly predicted 82% of the attacks with a severe outcome and identified all patients destined to die within 10 days of admission.

Introduction

THE incidence of acute pancreatitis is increasing.[1] Serious complications supervene in 20–30% of cases, with a fatal outcome in 8–20%.[1-5] Early differentiation of patients with mild and severe disease is important if prompt intensive management is to benefit those with severe disease. This differentiation should be as specific as possible, since the monitoring and treatment of severe pancreatitis are both costly and invasive.

When patients are admitted to hospital with acute pancreatitis, experienced clinicians can identify only about a third of those in whom serious complications will develop.[6] No single biochemical test is completely accurate. Among blood tests, raised fibrinogen[7] and methaemalbumin[8-10] and low calcium levels[4,11] have been suggested as determinants of severity, but they are insensitive. Besides indicating one particular complication of the disease, arterial hypoxaemia may also correlate with a poor overall prognosis.[4,12] The predictive roles of endotoxaemia,[13] changes in complement proteins,[14] and early computed tomography scans[15] require further evaluation. Currently, the most useful guides to prognosis derive from multiple laboratory criteria[16,17] and analysis of the fluid obtained by peritoneal lavage.[4,18,19]

The multiple laboratory criteria introduced by Ranson et al[20] and modified by Imrie et al[3,17] are now generally accepted as providing the best assessment of severity in acute pancreatitis. They are based on the features of shock (fluid loss, falling haemotocrit, serum albumin, acidosis) and widespread tissue injury (hypocalcaemia, raised liver enzymes, uraemia, hypoxia, hyperglycaemia). The drawback of this type of assessment is that it may take 48 h or longer to complete.

The peritoneal exudate in acute pancreatitis was first studied in 1950.[21] The amylase concentration of aspirated fluid was measured but not related to the severity of the attack. The predictive value of peritoneal lavage was described by Pickford et al[18]—the greater the volume and darker the colour of any free peritoneal fluid, the worse the prognosis. If there was no free fluid, one litre of saline was introduced into the abdominal cavity and the colour of the return fluid was assessed. This simple procedure proved more accurate than clinical judgment and much quicker than multiple criteria in the diagnosis of severe acute pancreatitis.[4,6]

We report here the relative success of clinical assessment, multiple laboratory criteria, and analysis of peritoneal fluid in determining the severity of acute pancreatitis at the outset of an attack in a prospective multicentre study of 418 patients.

Patients and Methods

Between September, 1981, and February, 1984, 436 attacks of acute pancreatitis were studied in 418 patients referred by clinicians at twenty-four participating hospitals to the study coordinators at each of three centres, Bristol (A. P. C.), Leeds (A. D. M.), and Glasgow (A. P. D. and M. G. S.). 3 patients were admitted to the study with laparotomy evidence of pancreatic and peripancreatic inflammation. In the other 433 attacks the diagnosis of acute pancreatitis was based on a consistent clinical picture and a plasma amylase level of >1200 IU/l ('Phadebas').[22] Ethical committee approval was given by the relevant health authorities and informed consent was obtained from patients if their clinical condition allowed at the time of hospital admission.

Prognostic Indices

Each patient was seen by the local coordinator as soon as possible after admission and a clinical assessment of the severity of the attack was made. Appropriate blood samples were taken on admission and on the 2 subsequent mornings for determination of eight laboratory criteria of severity:[17] arterial oxygen tension (<8·0 kPa), plasma levels of calcium (<2·0 mmol/l), albumin (<32 g/l), glucose (>10 mmol/l, no previous diabetes), urea (>16 mmol/l with no fall within 6 h), lactate dehydrogenase (>600 IU/l), and aspartate aminotransferase (>200 IU/l) and the leucocyte count ($>15 \times 10^9$/l).

Peritoneal lavage was carried out after urethral catheterisation in 253 attacks. The site chosen was 2 cm below the umbilicus in the midline in 249 attacks. Adjacent scarring precluded this approach in the other 4 attacks, and a point midway between umbilicus and right or left anterior superior iliac spine was chosen. Under aseptic conditions the skin and extraperitoneal tissues were infiltrated with 2% lignocaine and adrenaline 1/200 000. A 5 mm incision was made and a standard peritoneal dialysis catheter ('Trocath', McGaw, Glendale, California, USA) was introduced into the peritoneal cavity. The trocar was withdrawn and the cannula tip advanced into the pelvis. The volume and colour of any aspirated intraperitoneal fluid was noted. A litre of warmed isotonic saline solution was run into the peritoneal cavity, and the patient was rolled gently from side to side. The lavage fluid was then allowed to drain out freely, and its colour was recorded. The intensity of the colour of both free and lavage fluid was determined by comparison with a standard colour chart.[6]

The criteria for prediction of a severe attack were as follows.

Clinical assessment.—The coordinator's initial judgment of the severity of the patient's illness, based on the presence of shock, general peritonitis, and respiratory distress.

Peritoneal lavage.—One or more of >20 ml free intraperitoneal fluid, dark-coloured free intraperitoneal fluid,[6] and lavage fluid darker than a pale straw colour.[6]

Multiple laboratory criteria.—Three or more positive criteria within 48 h of admission to the study.

Patients meeting the criteria for peritoneal lavage or laboratory assessments were entered into a prospective, randomised, controlled trial of therapeutic lavage.[23]

Treatment

Patients considered to have a mild attack received analgesia, intravenous fluid replacement, and initial restriction of oral intake. The standard conservative treatment for predicted severe cases included nasogastric suction, monitoring of urine output and central venous pressure (CVP), with administration of colloid and crystalloid solutions to maintain a positive CVP, and the administration of oxygen via a face mask or assisted ventilation when hypoxaemia was detected.

TABLE I—AETIOLOGICAL ASSOCIATIONS OF ACUTE PANCREATITIS ATTACKS

—	M	F	Total	%
Gallstones	100	134	234	54
Alcohol	78 (12)	9 (2)	87	20
Idiopathic	51	65	116	27
Miscellaneous				4
Pancreatic cancer	3	2	5	
Trauma	1	..	1	
Postoperative	1	2	3	
Post ERCP	1	4 (4)	5	
Hyperparathyroidism	..	1	1	
Drug-induced	2	..	2	

Figures in parentheses = numbers of patients with concomitant gallstones.
ERCP = endoscopic retrograde cholangiopancreatography.

Patients randomised to receive therapeutic peritoneal lavage also received the standard conservative treatment. In addition lavage was carried out through the original dialysis cannula by means of hourly cycles of 2 litres of a warmed dialysate ('Dialaflex 61', Boots Ltd, Nottingham) with added potassium (4 mmol/l) continuing for 72 h. Neither aprotinin ('Trasylol') nor glucagon was given, and antibiotics were reserved for concurrent infections. Intensive biochemical, cardiorespiratory, and renal monitoring was carried out. Survivors were kept under review as outpatients for at least 6 weeks.

Outcome

The clinical outcome was classified as either mild or severe and severe attacks as fatal or complicated (pseudocyst, necrosis and abscess of the pancreas, other intra-abdominal abscess, septicaemia, cholangitis, renal failure, gastrointestinal haemorrhage, venous thromboembolism, development of diabetes requiring insulin, myocardial infarction, and pulmonary complications associated with hypoxaemia and/or radiological signs). Chest infection without respiratory impairment, urinary tract infection, and transient alcohol-withdrawal psychosis were classified as minor complications and did not constitute a severe outcome.

Statistical Analysis

The chi-square test with Yates' correction for continuity and Fisher's exact probability test were used to test statistical significance.

Results

There were 225 attacks in men (52%) and 211 in women. 16 patients had 2 attacks and 1 was admitted 3 times. The median age was 61 years (range, 13–92 years). The main aetiological associations were gallstones (54%) and alcohol (20%); 14 attacks were associated with both gallstones and alcohol. In 116 cases (27%) no obvious aetiological factors could be determined (table I).

Complications of Peritoneal Lavage

3 patients were injured during introduction of the peritoneal dialysis catheter. In 1 a small abdominal wall haematoma developed but did not require active treatment. In another the bladder was inadvertently catheterised suprapubically; the cannula was withdrawn and replaced in the peritoneal cavity after urethral catheterisation (this step had been omitted initially) and there were no subsequent ill-effects. The third patient had a lower midline scar. The catheter was inserted in the right iliac fossa and entered the caecum. This accident was immediately recognised. Laparotomy was carried out and a clean caecal puncture was oversewn. The patient made an uneventful recovery but was

TABLE II—COMPLICATIONS OF ACUTE PANCREATITIS ATTACKS

—	Survived	Died	Total
Severe			
Pancreatic abscess	6	11	17
Pancreatic pseudocyst	31	6	37
Other intra-abdominal abscess	2	7	9
Septicaemia	13	11	24
Cholangitis*	7	3	10
Renal failure	3	13	16
Gastrointestinal haemorrhage	5	7	12
Venous thromboembolism	5	2	7
Diabetes	4	7	11
Myocardial infarction	..	4	4
Severe pulmonary complication	36	29	65
Not severe			
Mild chest infection	7	..	7
Urinary tract infection	30	5	35
Toxic psychosis	12	4	16

*Clinical features developed 2–8 days after admission. Laparotomy or necropsy findings confirmed the combination of cholangitis and oedematous pancreatitis in 6 patients.

excluded from further analysis. The overall visceral puncture rate was 2 in 253 catheter placements (0·8%).

Final Outcome

Of the 435 attacks analysed, 111 (26%) resulted in death (41) or serious complications (70) (table II). More than half the attacks complicated by abdominal abscess, renal failure, gastrointestinal haemorrhage, and acute diabetes were ultimately fatal. The outcome was uncomplicated (mild) in 324 attacks (74%).

Clinical Assessment

70 of the 435 attacks were classed as severe on admission (16%). 19 of these patients died, 19 had a serious complication, and 32 (46%) a benign course. Of the 365 attacks assessed as mild, 292 had a mild outcome, 51 a serious complication, and 12 were fatal. The sensitivity and specificity of clinical assessment, and the other prognostic indices, are shown in fig 1.

Multiple Laboratory Criteria

Only attacks in which the number of criteria measured allowed an unequivocal prognosis were assessed (ie, 3 or more

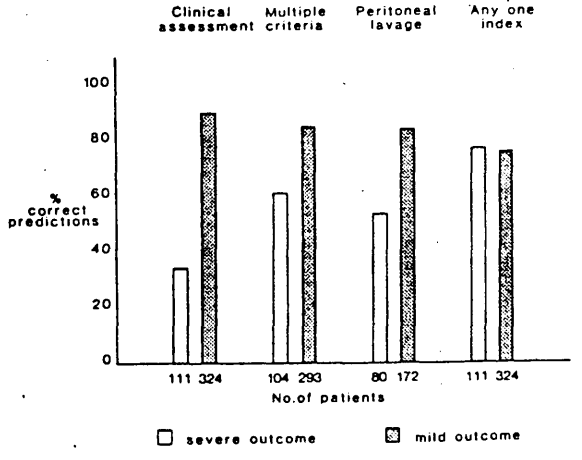

Fig 1—Sensitivity and specificity of prognostic indices in acute pancreatitis.

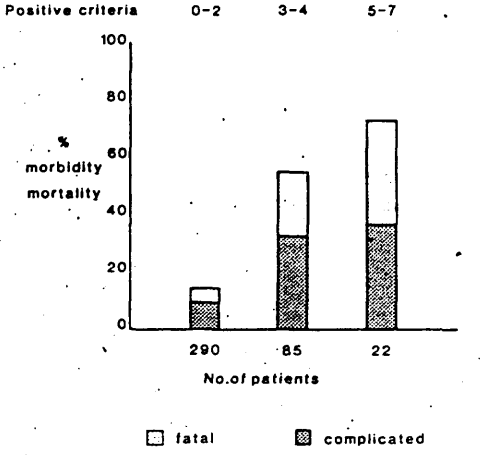

Fig 2—Relation between positive multiple laboratory criteria score and outcome of acute pancreatitis attacks.

criteria positive, all 8 criteria measured, 7 criteria measured and only 1 positive, or 6 criteria measured and 0 positive). In 38 attacks the data were inadequate. Of the 397 attacks assessed 104 were severe, including 39 deaths. 27 of the deaths were included in the 107 attacks graded severe by a multiple criteria score of 3 or more within 48 h of admission. The number of positive criteria in relation to disease outcome is shown in fig 2.

The median delay between the onset of symptoms and a severe prediction by multiple criteria score was 54 h (range, 5–>98). The median delay between diagnosis of acute pancreatitis and severe prediction was 24 h (range 0–>98).

Peritoneal Lavage

155 attacks were not assessed by peritoneal lavage because of the patient's or clinician's reluctance to allow an invasive procedure in an overtly mild attack of acute pancreatitis. Of these 155 attacks 130 confirmed the clinical judgment and pursued a mild course, but 25 (16%) had complications and 8 patients with complications died. 20 other patients were excluded because of extensive abdominal scarring and a further 5 because of dementia, difficulty in catheterisation, gross congestive cardiac failure, and warfarin anticoagulation.

Peritoneal lavage was successfully accomplished in 252 attacks, of which 80 were complicated and 30 were fatal. 21 of the 30 deaths were correctly predicted as severe by this approach.

Of the 69 attacks predicted as severe by lavage, 22 had >20 ml free intraperitoneal fluid which was pale (<number 6 on the colour chart); among this group there were 11 complicated attacks, including 7 deaths. 46 attacks were predicted as severe on the basis of dark intraperitoneal fluid (⩾6 on the colour chart); among this group there were 41 complicated attacks, including 14 deaths. Thus, 68 of the predicted severe attacks were classified on assessment of free fluid (volume or colour). In the one remaining attack, <20 ml of pale free fluid was recovered, but lavage fluid was darker than number 3 on the colour chart; the attack was clinically mild. Among the 183 attacks predicted as mild 27 had some pale free fluid (<20 ml); only 4 of these were complicated and there were no deaths.

The median delay between onset of symptoms and prediction was 26 h (range 5–96), and that between diagnosis and prediction was 4 h (range 0–48).

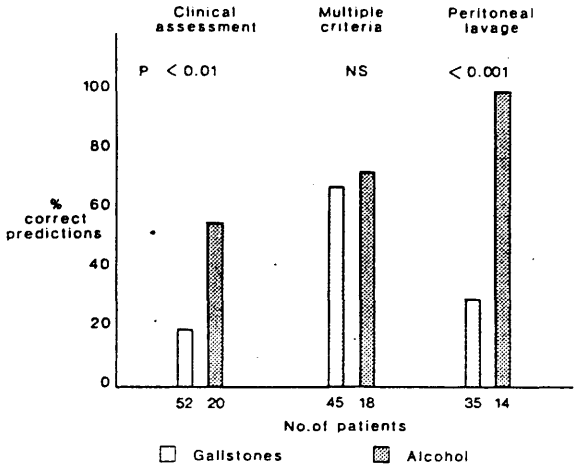

Fig 3—Sensitivity of prognostic indices in gallstone-related and alcohol-related acute pancreatitis.

A further 5 patients were initially admitted to the study, but the findings on peritoneal lavage led to revision of the diagnosis of acute pancreatitis. 2 patients had perforated gallbladder, 1 perforated duodenal ulcer, 1 extensive mesenteric thrombosis, and 1 ruptured thoracoabdominal aortic aneurysm.

Gallstones and Alcoholism

Each of the prognostic indices was more accurate in diagnosing the severity of alcoholic than gallstone pancreatitis (fig 3).

Summation of Prognostic Indices

Among the 271 attacks predicted as mild there were 6 deaths (2·2%, table III) and among the 164 predicted as severe there were 35 deaths (21·3%; $p<0·001$). The sensitivity of each prognostic index for fatal acute pancreatitis is shown in fig 4. Overall 85% of patients who died were predicted to have severe disease by one or more indices, as were all but 1 of the patients (95%) who died within the first 10 days.

For complicated but non-fatal attacks the prognostic indices were less successful; 71% were correctly predicted by one or more method. The overall sensitivity for both fatal and complicated attacks was 77%.

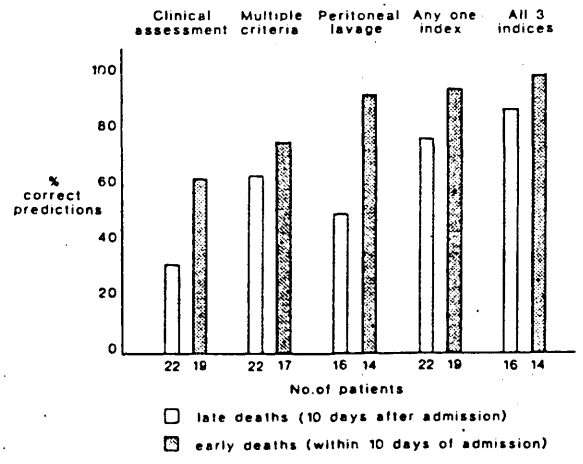

Fig 4—Sensitivity of prognostic indices for late and early deaths in acute pancreatitis.

TABLE III—DETAILS OF FATAL ACUTE PANCREATITIS ATTACKS PREDICTED AS MILD

Case	Sex	Age (yr)	Aetiology	Death	Cause
1	M	57	Idiopathic	Late	Renal failure
2	M	63	Idiopathic	Late	Pseudocyst
3	M	73	Gallstones/alcohol	Late	Myocardial infarction
4	F	70	Gallstones	Late	Septicaemia
5	F	81	Gallstones	Late	Septicaemia
6	F	67	Carcinomatosis	Early	Cardiorespiratory failure

All were predicted as mild by clinical assessment and multiple criteria. Cases 2 and 5 were predicted as mild by peritoneal lavage and case 6 by laparotomy.

In 77 (70%) of the 111 fatal and complicated attacks all three prognostic indices were used. Sensitivity for fatal attacks was 93% (28 of 30), for early deaths 100% (14), and for complicated but non-fatal attacks 74% (35 of 47)—an overall sensitivity of 82%.

Discussion

The good results when all three prognostic indices were used suffer from the inherent drawback of multiple laboratory criteria, a delay of up to 48 h. 2 patients died of fulminating pancreatitis before a multiple criteria score was available. Nevertheless, laboratory criteria were the most sensitive (61%) individual predictor of severe disease. Peritoneal lavage provided an answer much more quickly (mean 4 *v* 24 h) but was less sensitive (53%). Clinical assessment on admission was much less sensitive, but a previous study has suggested that by 48 h after admission clinical assessment may be as good as lavage or laboratory criteria in detecting severe acute pancreatitis.[6]

In previous studies[4,6] peritoneal lavage gave a correct prognosis in 58–72% of severe cases compared with 53% in this study. An additional benefit of lavage, correcting an erroneous diagnosis of pancreatitis, was seen in 5 of 253 cases in this study and 2 of 98 cases in another report.[24] We have previously[4] suggested that dark colouration of the free fluid obtained by peritoneal lavage is more important than its volume in predicting severe disease. Our results support this hypothesis, although differences in sensitivity did not reach statistical significance. Peritoneal lavage is particularly accurate in identifying fulminating acute pancreatitis,[25] but only 8 of the 14 early deaths (57%) were predicted by colour, the remainder by volume.

In over 40% of attacks, patient refusal or clinical reluctance did not permit peritoneal lavage, predominantly because of an overtly mild attack with little or no pain. This reluctance to accept an invasive procedure is understandable and is probably related to current therapeutic options. Is a 0·8% risk of visceral puncture worth the gain of an early diagnosis when no particular treatment schedule has yet been shown to benefit severe cases? Until a specific therapy becomes available, intensive monitoring and resuscitation is all that can be offered for patients with severe disease. Those with fulminating attacks would have most to gain from early prediction, and fortunately in this group lavage provides the most reliable results.

Multiple laboratory criteria scores have been used as prognostic indices in acute pancreatitis for more than 10 years. Our results show similar specificity to previous reports (85% *v* 92%[16,17]) but lower sensitivity for severe cases (61% *v* 96%[16], 100%[17]). Two factors can influence the results—the definition of severity and the aetiological cause of pancreatitis. Fatal attacks are uniformly considered to be

severe, but among survivors severity may be defined as more than 7 days in an intensive-care unit,[16] more than 14 days in hospital, or failure to settle on conservative treatment because of specified complications.[6] We based our definition of severity on the development of local and systemic complications of the disease.

The original sets of laboratory criteria differentiate severe and mild attacks less accurately in gallstone pancreatitis than in alcoholic pancreatitis.[17,26,27] Previous reports[4,6] show a lower proportion of alcohol-related cases in England (3%) than in Scotland (32%)[3] or New York (69%).[16] In this three-centre study we elected to use the criteria applicable to gallstone-related disease.[17] In the event there was no significant difference between alcohol and gallstone disease in the sensitivity of the multiple laboratory criteria. However, peritoneal lavage was more accurate than multiple laboratory criteria in predicting severe alcoholic pancreatitis, presumably because of the early development of haemorrhagic ascites.

The combined results show that it is now possible to identify most patients with severe acute pancreatitis within a few hours of admission, and this ability should be useful in setting up prospective therapeutic trials.[27] A consistently high specificity minimises the waste of resources on mild attacks. Similarly, a high sensitivity allows the maximum number of severe cases to be studied.

Some type of predictive assessment should be possible in any hospital, though local circumstances will dictate which is the most practicable method. If an early answer is desired, peritoneal lavage is the method of choice, despite the small attendant risk of visceral puncture.

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APPENDIX 2

COMPUTER DATA FOR 100 PATIENTS FROM GLASGOW ROYAL INFIRMARY

APPENDIX 2 and **APPENDIX 4** are the print outs of the computer files used for the patients studied in this thesis.

BECAUSE THE DATA HAS BEEN STORED ON COMPUTER AND IS THEREFORE SUBJECT TO THE REGULATIONS OF THE DATA PROTECTION ACT, PATIENT IDENTIFICATION HAS BEEN OBLITERATED FROM THE PRINT OUTS.

All the numerical data presented in the thesis has been cross checked between these files and the separate proformata used to record patient details relating to their pseudocyst.

In this appendix and appendix 4 multiple abbreviations have been used. A glossary is given on the next 2 pages.

ABBREVIATION	MEANING
ABSC	ABSCESS
AET / AETIOL	AETIOLOGY
ALC	ALCOHOL
GS	GALLSTONES
PCA	PANCREATIC CARCINOMA
TRA	TRAUMA
UK	UNKNOWN
AMYL	SERUM AMYLASE
ON AD	ON ADMISSION
ON DIAG	ON DIAGNOSIS OF PSEUDOCYST
ANOR	ANOREXIA
AP	ACUTE PANCREATITIS
AXR	ABDOMINAL X RAY
BM	BARIUM MEAL
CG / CYSTOGAST	CYSTOGASTROSTOMY
CJJ	CYSTOJEJUNOSTOMY
COMP	COMPLICATIONS
CP	CHRONIC PANCREATITIS
CRIT	MULTIPLE CRITERIA ASSESSMENT
CT / CAT	COMPUTERISED TOMOGRAPHY
CYSTODUO	CYSTODUODENOSTOMY
DIST PANC	DISTAL PANCREATECTOMY
ERCP / ERP	ENDOSCOPIC RETROGRADE PANCREATOGRAM
EXTN DRAIN	EXTERNAL DRAINAGE
GB	GALLBLADDER
GI BLEED	GASTROINTESTINAL HAEMORRHAGE
GT SIGN	GREY-TURNER SIGN
HIDA	HIDA SCAN
HLP	HYPERLIPOPROTEINAEMIA
IVC	INTRAVENOUS CHOLANGIOGRAM
JAUN	JAUNDICE
LAP	LAPAROTOMY
LAP ASP	ASPIRATION AT LAPAROTOMY
LAV	DIAGNOSTIC PERITONEAL LAVAGE
N/V	NAUSEA AND/OR VOMITING
OCG	ORAL CHOLECYSTOGRAM
PC	PSEUDOCYST
PE	PULMONARY EMBOLISM
PERCUT ASP / DRAIN	PERCUTANEOUS ASPIRATION
PL EFF	PLEURAL EFFUSION
PYREX	PYREXIA
REN FAIL	RENAL FAILURE
RESP FAIL	RESPIRATORY FAILURE
ROUX / ROUX EN Y	ROUX EN Y CYSTOJEJUNOSTOMY
TIME	TIME FROM AP TO PC DIAGNOSIS
TPN	TOTAL PARENTERAL NUTRITION
SPABS	SUBPHRENIC ABSCESS
US	ULTRASOUND SCAN

HOSPITAL ABBREVIATIONS

BALL	BALLOCHMYLE, AYRSHIRE
BOUR	BOURNEMOUTH GENERAL INFIRMARY
DUND/NINE	NINEWELLS HOSPITAL, DUNDEE
DUNF	VICTORIA INFIRMARY, DUNFERMLINE
FALK	FALKIRK ROYAL INFIRMARY
GRI	GLASGOW ROYAL INFIRMARY
GNK	INVERCLYDE HOSPITAL, GREENOCK
HAIR	HAIRMYRES HOSPITAL, GLASGOW
KILMARNOCK	KILMARNOCK ROYAL INFIRMARY
LAW	LAW HOSPITAL, CARLUKE
NADG	NORTH AYRSHIRE DISTRICT GENERAL HOSPITAL
OBAN	OBAN INFIRMARY
SGH	SOUTHERN GENERAL HOSPITAL GLASGOW
STOB	STOBHILL HOSPITAL, GLASGOW

PSEUDOCYST GRI STUDY: 1

NAME	SEX	AGE	HOSP	DATE OF PC	TIME	AETIOL	SIZE	INVESTIGATIONS	OPERATIONS
ALE	M	43	KIL	05.08.76		ALC	8	US/BM 5.8.76	ROUX EN Y 16.11.76
AND	F	36	DUND	16.03.75	054	GS	16	US:BM	CYSTGAST:GB OUT 19.03.75
ARB	F	50	GRI			GS	20		CYSTGAST
BAL	M	33	GRI	05.08.75	022	ALC	8X8	USX3:OCG:BM	LAP ASP OF CYST 5ml:GASTROENT
BAR	M	29	GRI	11.06.76	005	ALC	8X12	US/BM	CYSTGAST 16.06.76
BEN	M	37	HAIR			ALC	12	US:BM:OPN	CYSTGAST 14.12.77
BLA	M	52	FALK			GS	SMALL		ROUX EN Y
BLA	M	25	GRI	16.05.72		ALC TR	15	BM	CYSTGAST 6.6.72:CYSTGAST 28.8.72
BON	M	26	GRI	20.12.68	059	ALC		BM 20.12.68	CYSTGAST 3.2.69
BRA	M	70	GRI	24.05.77	028	GS	12	US/BM	CYSTGAST: 27.05.77
BRO	M	25	STOB	10.09.83	232	ALC	5X6	USX2: ERCP	DISTAL PANC 06.12.83
CAM	M	46	GRI	27.04.79	017	GS	LARGE	US	CYSTGAST 12.05.79
CHA	M	31	GRI	10.12.78	229	ALC	7	US/OCG	EXT DRAIN 29.12.78
CHR	F	44	PERT	15.11.76	152	GS	5	US/BM/OPN	ROUX EN Y 24.11.76
CLE	M	57	GRI	14.05.73	015	GS	10x5	US:BM	CYSTGAST 21.8.73:1200ml
CLO	M	84	GRI	06.09.78	014	ALC	LARGE	US/OCG	
CRI	F	43	GRI	25.08.80	006	UK	5.2	US	
CUT	F	48	LAW	06.07.81		GS	7.5	US	CYSTGAST 06.07.82
DEV	F	69	GRI	22.08.82	018	GS	10X6.	USX3:BM	CYSTGAST: GB OUT 1.12.82
DOU	M	33	GRI	03.08.82		ALC	8.2X1	BM: USX9:ERCP 5	PERCUT DRAIN 9.2.83:350ML
DUF	M	23	GRI	17.10.77	004	ALC	10	US	
DUN	F	38	GRI	05.03.70	215	GS+ALC		BM 20.04.70	CYSTGAST 29.05.70: 1000ml
DUN	M	66	BALL	25.04.67	009	GS			EXTN DRAIN & GE 25.04.67
ERS	F	50	GRI	16.12.78		ALC	4.8	US/CT	LAP ASP TDS 09.03.83
EVA	F	21	GRI	07.02.79	011	ALC	15x12	US 10.08.78:7.2	CYSTGAST 13.03.79: 2500ml
FER	M	25	SGH	24.05.75		ALC	SMALL	US/BM	DIST PANC 24.05.75
FIT	M	54	GRI	14.02.84	004	ALC	7.5X2	USX5	
FIT	F	33	GRI	30.08.78	150	ALC	7	US/BM/OCG	CYSTDUOD 21.11.78
FRE	F	74	GRI	14.11.62		GS		LAP	CYSTGAST 1.12.62
FRE	M	43	GRI	16.02.81	022	ALC	8x6	US	
GAR	M	48	GRI	10.04.74	031	ALC	20	LAP	CYSTJEJUN 30.04.74
GIL	M	35	GRI	27.10.76	375	ALC	10	US/BM	CYSTGAST 02.11.76
HAL	M	27	GRI	12.02.80	204	ALC	20	US	CYSTGAST ROUX EN Y 20.02.80
HEN	F		GRI			ALC			
HER	M	36	GRI	27.06.77		ALC	12	US	CYSTGAST 11.07.77
HIG	M	19	GRI	19.09.74	027	TRAUMA	18x20	BM 16.9.74/ US	CYSTGAST X2 17.10/29.10
HOD	M	36	GRI	05.06.79	107	GS/ALC	LARGE	US/OPN	CYSTGAST 06.06.79:GB OUT EXPLOR CBD V&P
HOO	M	34	NADG	29.06.84	100	ALC	5	US	
HUG	M		GRI			ALC			CYSTGAST
KEL	M	45	GRI	24.12.73	109	GS	8.5	US/BM	
KEL	M	77	GRI	16.03.82	008	GS	9X11	CAT:USX4:HIDA:I	PERCUT DRAIN:
KEN	M	69	LAW	11.04.78	038	UK	LARGE	US/LAP	DIST PANC 11.04.78
KES	M	31	GNK	29.01.81	082	ALC	7X3	ERCP/US	CYSTDUOD 30.01.81
KIN	M	37	GRI	08.03.85	479	ALC	11X14	US:OCG:BM	CYSTGAST 11.03.85
LAI	M	34	GRI	03.12.79	400	ALC	4.5	CT:ERP:US	
LAN	M	33	GRI	02.06.73		ALC	9		CYSTGAST 27.06.73
LAU	M	55	LAW	26.10.79	250	ALC	LARGE	AXR DISTORT STO	CYSTGAST 26.10.79
MAG	F	30	HAIR			TRAUMA	16		CYSTGAST
MAR	F	46	GRI	12.06.79	019	GS	7	US	
MCC	M	74	GRI	23.10.73	024	GS		US/BM	

PSEUDOCYST GRI STUDY: 1

NAME	SEX	AGE	HOSP	DATE OF PC	TIME	AETIOL	SIZE	INVESTIGATIONS	OPERATIONS
MCC	M	54	KILM	01.04.78		ALC	14	US	CYSTGAST 02.05.78
MCD	M	37	GRI	20.10.75	069	GS+ALC	6	US	ROUX/DIST PANC/GB OUT 18.11.75
MCD	F		GRI			UK			
MCE	M	31	KILM	28.02.80	021	ALC	15	BM/US	CYSTGAST 28.02.80
MCG	M		GRI			GS			CYSTGAST
MCG	M	31	SGH	30.10.78		ALC	9	US/AXR	CYSTGAST 29.11.78
MCK	F	53	BALL			GS			CYSTGAST
MCK	M	55	GRI	2.2.68	029	GS		LAP	DRAIN ABSC 12.1.68:CG 02.02.68
MCK	M	36	GRI	14.06.77	005	ALC	5	US	
MCL	M	35	DUNF	02.10.81	030	ALC	5X6	US/CT	CYSTGAST 04.12.81
MCM	M	56	GRI	20.03.73	021	ALC		BM/BE (LP DIAGN	EXTN DRAIN 20.03.73 300ML
MCN	F	56	BALL			ALC	5		EXTN DRAIN
MCP	M	49	HAIR	18.02.75	015	ALC	8x10	US:OPN	ROUX EN Y 26.02.75
MCR	M	38	GRI	15.09.83		ALC		ERCP	DIST PANC:SPLEN 07.10.83
MEE	F	60	GRI	15.12.80	034	GS	3X7	US:CAT	CYSTGAST 10.04.81:GB OUT
MIL	M	45	GRI	11.04.78		ALC	4		CYSTGAST 18.04.78
MIL	M	44	GRI	08.09.78	009	ALC	SMALL	US	
MOR	F	30	GRI	24.7.82		ALC HE	8X5	US:HYP DUODG	CG 30.8.82:TDS ROUX LOOP 2.9.83:WHIPPLES
MOR	F	30	GRI	25.02.81	022	GS	8X5.5	CAT: USX3	
NEI	M		GRI			TRAUMA			EXTN DRAIN
PAT	M	47	NINE	25.04.78		UK	SMALL	ERCP	DIST PANC ROUX EN Y25.04.78:
PRE	M	60	GRI	21.05.84	012	UK	12X7	US:BM:CAT	CYSTGAST 01.06.84
RAD	M	30	GRI	05.12.79	7	ALC	10	US	CYSTGAST 09.09.79
RAE	F	54	GRI	7.9.66	090	GS		LAP	EXTN DRAIN 7.9.66:GB OUT
RAM	M	62	BOUR	24.04.80	012	UK	7	US	
RAY	M		GRI			ALC			
REI	M	38	GRI	14.11.75	055	ALC	5	US/BM +	
REI	M	36	GRI	05.11.72	114	GS	10	OPN:GASTG MASS	EXTN DRAIN
REI	M	38	GRI			ALC			LAP ASP
ROB	F	73	GRI	15.01.74	016	UK	10	US	
ROS	M	50	GRI	10.09.72		ALC	17	BM 10.09.72: EX	CYSTGAST 20.09.72:1500ml BILE DUCT DECOM
SEL	F	56	LAW	17.01.78	100	ALC	8	US:ERCP	CYSTGAST 23.01.78:
SEM	F	58	GRI	01.05.84	028	ALC	5	USX3: IVC	CYSTDUOD/CYSTGAST 04.05.84
SHA	M	54	GRI	06.09.77	067	ALC	9	US	CYSTGAST 11.11.77
SIM	F	49	GRI	04.05.83	018	GS/ERC	5	USX4:BM	
SME	M	45	OBAN	1.3.84	046	ALC	10	US	CYSTGAST 6.3.84
SMI	M	21	GRI	13.03.74	074	ALC	LARGE	US	CYSTGAST 14.08.74
SMI	F	24	GRI	29.07.77	100	ALC	10	US	LAP ASP 31.3.78:CYSTGAST 31.10.78
STE	M	62	STOB	12.04.77	041	ALC	8	USX2:IVC	EXT DRAIN 26.04.77
STE	M	71	BALL			UK	12	US/OGG	EXTN DRAIN
STI	F	78	GRI	15.12.81	008	POST O	8X9	USX4	ASP NEED X2 23/12:30/12: CG 12.1.82
SUL	F	30	GRI	01.07.82	109	GS	8	US	PERCUT ASP:CG 15.08.82:CG 16.01.85
SWE	M	58	GRI	19.07.78	414	ALC	9	US	
TEM	F	49	GRI	17.03.78		ALC	SMALL	US	DIST PANC 28.3.78
WAL	M	52	GRI	25.02.82		ALC		LAP/ERCP	DIST PANCT
WAT	M	37	GRI	03.08.78	024	UK	SMALL	US/BM	
WEI	M	57	GRI	20.04.77	023	GS	LARGE	US/BM	CYSTGAST 13.05.77
WIG	M	54	GRI	22.7.70	010	GS		LAP	CYSTGAST/GB OUT
WIL	M	39	HAIR			ALC			EXTN DRAIN 29.07.74
WIL	F	48	GRI	14.01.65	019	TRAUMA	LARGE	LAP	EXTN DRAIN 14.01.65

PSEUDOCYST GRI STUDY: 2 CLINICAL DATA

NAME	AMYL ON DIAG	WBC	PYREX	PAIN	TEND	MASS	N/V	ANOR	DIST	ILEUS	JAUND	CHEST	DEATH/PM	COMPLICATIONS
ALE	510:U 500	6.8				Y								
AND	310	7		Y		Y		Y						PL EFF
ARB														
BAL	710:U 4200	5.3		Y	Y		Y	Y						
BAR	150	6.4		Y	Y	Y	Y	Y					Y	
BEN	700	10.7		Y		Y	Y	Y	Y					
BLA													Y	
BLA	2950:U 7400	5.2		Y	Y	Y								
BON	400W	13.8	Y	Y		Y	Y					Y		
BRA	4600:U 22200	5.5		Y	Y					Y	Y	Y	Y	PL EFF/JAUND/GI BLEED/DIAB/DVT
BRO	1250	11		Y	Y									
CAM	121:U 185													
CHA	2930	17.4		Y	Y	Y		Y				Y		ABS:GT SIGN:CYST RUPT:CP
CHR	215	9.7												
CLE	4500:U 2300	15.1		Y	Y	Y	Y	Y	Y				Y	GI BLEED
CLO	435	9					Y							
CRI	192	20	Y	Y	Y							Y		PL EFF
CUT	190:U 2950	7.4		Y		Y								
DEV	1942	6.4	Y	Y	Y	Y						Y		
DOU	350:U 3470	11.2		Y	Y	Y	Y		Y					
DUF	380:U 8000	7.4		Y										
DUN	10W	7.2		Y		Y	Y	Y			Y			
DUN			Y	Y	Y	Y	Y						Y	REN FAIL/JAUND/SEPTIC/PE
ERS	2180:U 21050	6.8		Y	Y									
EVA	781	7.5		Y	Y	Y								
FER	1075	7.5		Y	Y									FISTULA:WOUND INF:RECURR ABSCE
FIT	300	4.7	Y	Y	Y				Y					UTI
FIT	2390:U 29700	7.7		Y	Y	Y	Y	Y						
FRE				Y		Y								
FRE	850:U 3600	12.9							Y					
GAR	710:U 2550	37.6		Y	Y	Y		Y				Y		GI BLEED: CHEST
GIL	4800	10.6	Y	Y	Y	Y	Y	Y	Y					
HAL	519:U 2125	6.8		Y	Y		Y							
HEN														
HER	620:U 3750													
HIG	5000	10.2		Y	Y	Y	Y	Y	Y					
HOD	900	6		Y	Y	Y		Y			Y			
HOO	1290	7.8		Y	Y		Y	Y						GAST OUT OB
HUG														
KEL	260:U 327	5.9		Y	Y									
KEL	1240	12	Y	Y		Y						Y		
KEN	160	10.7		Y	Y	Y	Y	Y						
KES	900:U 4225	13.9		Y	Y		Y		Y					
KIN	1515	10.2		Y	Y	Y	Y	Y						
LAI	1120:U 22050			Y	Y									
LAN	610:U 7900													
LAU	550	10.4		Y	Y									CHEST/WOUND DEHIS
MAG														
MAR	1620:U 560	5.6		Y	Y	Y	Y							
MCC	389	18.9		Y	Y		Y		Y	Y	Y			

PSEUDOCYST GRI STUDY: 2 CLINICAL DATA

NAME	AMYL ON DIAG	WBC	PYREX	PAIN	TEND	MASS	N/V	ANOR	DIST	ILEUS	JAUND	CHEST	DEATH/PM	COMPLICATIONS
MCC	145	10.2		Y		Y		Y			Y			SB FIST/WOUND INFN
MCD	2000:U 6000	10.5		Y	Y									
MCD														
MCE	740	11.1	Y	Y	Y		Y	Y	Y					DOU OBST:INF CVP
MCG														
MCG	1840:U 18960			Y	Y	Y								
MCK														
MCK	33W	23	Y	Y	Y	Y	Y	Y			Y	Y		WOUND DEHIS:DVT
MCK	250:U 1550	22.1		Y										
MCL	557	9		Y	Y	Y		Y	Y		Y	Y	Y	PL EFF/JAUND
MCM	250:U 450	15.3	Y	Y	Y	Y			Y			Y		CHEST/AX V THROMB
MCN														
MCP	3000:U 12790	7.2		Y		Y	Y	Y						
MCR		5.1												UTI
MEE	1609:U 10420	9.9		Y	Y			Y						PL EFF:?GT
MIL	240:U 2050	12.9												
MIL	420	7.4	Y	Y				Y						ASCITES
MOR	720:U 3500	5.3		Y	Y	Y								
MOR	2700	20.1	Y	Y	Y				Y	Y		Y		PL EFF
NEI														
PAT	330:U 1661	4.9		Y										
PRE	1890	8.6		Y	Y	Y	Y	Y			Y		Y	
RAD	15800	6	Y	Y	Y							Y		
RAE				Y			Y						Y	DOUD OBSTN
RAM	1420:U 5130	6.5		Y	Y	Y					Y			JAUND
RAY														
REI	1150:U 900	12.1		Y	Y				Y					PL EFF
REI	140		Y	Y	Y	Y								BLEED
REI														
ROB	290	10.6				Y						Y		CHEST:ANAEMIA
ROS	410:U 700	9.2		Y		Y	Y				Y			WOUND DEHIS: RECURR CYST
SEL	6200	10		Y	Y	Y	Y	Y						
SEM	6100	21.5	Y	Y	Y	Y			Y					ASCITES/SKIN NODULES
SHA	910													
SIM	350	9.4			Y									PL EFF
SME	3000	6.4				Y			Y					
SMI	140:U 1680	7.6		Y	Y	Y	Y	Y		Y		Y		
SMI	266:U 1070	8.1		Y	Y	Y		Y	Y					
STE	690	5.6		Y	Y	Y	Y	Y						
STE													Y	
STI	5000	17.8		Y			Y							SKIN NODULES
SUL	5000	7.4		Y	Y	Y	Y							
SWE	175:U 500	8.2		Y	Y	Y								
TEM	660:U 2325													
WAL														DIABETES
WAT	1445	10.2	Y	Y	Y		Y		Y		Y	Y		UTI
WEI	1480	13.2		Y	Y	Y		Y					Y	CARDIAC ARREST
WIG	5W	16		Y	Y	Y						Y		SPABS
WIL				Y	Y								Y	RESP FAIL/UTI
WIL	13.2W	24.9	Y	Y		Y							Y	DVT/SEPSIS

PSEUDOCYST GRI STUDY: 3

NAME	COMMENT	FOLLOW UP
ALE	CP:RECURR AP 1968 ON:PANC CALC:EXO INSUFF	WELL LS 24.07.79
AND	REF NINE AP'74-'75 RECURR PAIN, WGT LOSS, VOMIT:RE	WELL
ARB		
BAL	AP'71:AP 10.7.75 READM 30.7 PAIN,VOMIT,WGT LOSS PC	US CYST GONE: DISCH 02.06.76
BAR	COLLECTION ? 24.12.75 US	AP 1974 LAP:DISCH 4.11.76: READM THEN DIED SEPSIS
BEN	MANY APS OVER 18M:REF GRI	RECURR PAIN 5.78 & 7.79
BLA	DIED SEPSIS	
BLA	RECURR CYST:TRAUMA 41 DAYS PRIOR	WELL3.73
BON	DISCH WITH PYR/TACHY: 3LT FLUID IN CYST	
BRA	GI BLEED/OPN /VESSEL STRETCHED/ STONE IN GB	GI BLEED AGAIN:SEPSIS:DIED
BRO	RESOLV: REFILL-DATA	VERY WELL
CAM		
CHA	HLP:CYST BLEED:ABSC POST OP:DRAINED 14.1.79:FAEC F	DEV CP:DIABETIC 4.3.81:CDJJ FOR JAUND 15.6.83
CHR	REF PERTH ABSC DRAINED 6.7.76:DEV FISTULA:PC PROB	BILOCULAR CYST: WELL ON FU
CLE	4.7.73 GB OUT MASS IN HEAD:READM PAIN VOMIT WGT L	RECURR CYST DIED GI BLEED 8 DAYS POST CG
CLO	RESOLVED/US	US 6.12 RESOLV/FU 23.3.79:READM 19.10.78 ?OBST
CRI	CULLENS:RESOLVED	OCG ONLY DISH 09.07.81
CUT	CP:AP1980:RECURR PC:DIAG 1980:PAIN1982	ENDO & EXO INSUFF: WELL
DEV	AMYL 1942 PREOP 218 POST	READM 31.12 VOMIT BIOCHEM UPSET US ?NECROSIS: FU 2
DOU	REF TO MOPD WITH PAIN BM PC:AP DATE UNKNOWN	WELL DISCH 14.03.84
DUF	RESOLVED NO US	NO US BUT DISCH 4.1.79
DUN	AP '68-'69:GB OUT 1.12.69:MASS 3.70:ICTERIC CG	WELL: '73 CIRRHOSIS
DUN	OPN AT BALLO:PC DIAG AT OPN:DIED SEPSIS	E COLI GROWN FROM WOUND DRAIN:PM GRAVEL IN GB:PREV
ERS	AP PC 1978:REC PC BY US/CT TO 83	PROB CP:NO FU 83:3 PC ?2 RESOLVED
EVA	3cm CYST: RECURR 29.12.78	GB OUT 12.09.78:PANC HEAD HARD: CYST REFORM:FU AT
FER	CYST AT NECK OF PANC:SMALL	ABSC x3 9.75-4.77
FIT	RESOLVED	US 3.3 4X7.5: US 6.4 2.8: 13.3.85 WELL DISCH
FIT	CD 65ml FLUID:	READM 8.9.79 PAIN VOM:ALCOHOLIC GE CLIN TO 10.86 N
FRE	NO AP NOTE:REF CLINIC MASS:CYST ANAST TO ANT WALL	COLON CA 1963:POOR DATA
FRE	PC FOUND AT CLINIC:US SHOW RESOLVE	US RESOLVED:WELL 15.04.81
GAR	PAIN/MASS/W LOSS: 5LT IN PC: GI BLEED	READMX2 6.1.76 PAIN US/BM SWELL PANC: 24.12.75 PAI
GIL	ABSC 23.10.76:READM X5 PAIN & ?PC:PC PROB FROM BLO	2.12.76 DISCH
HAL	1000ml IN CYST	RECURR PAIN:CP TOTAL PANC
HEN	RESOLVED	
HER	CP	
HIG	TAILBOARD TO ABDN: LAP TEAR ON PANC PC NOTED LATER	WELL 11.3.75
HOD	READM BLEED DU FOUND TO HAVE PC 800ml	READMx3 TO 1981 NO ^ SA:RECURR DU OPN'84
HOO	AP80-PC-CG:GAST OB-GB OUT 4.6.84	WELL
HUG		
KEL	RESOLVED 28.02.74	
KEL	PYREXIA AND ^AMYL POST DRAINAGE	HB FELL:GB OUT 10.06.82:NO CYST:NO FU
KEN	REF LAW INVEST PC NOT FOUND UNTIL LAP	WELL 9.1.80
KES	CP RECURR PAIN	NO CYST ERCP 1986
KIN	PC CLINICALLY & ON AXR	6.85 WELL: RECURR CYST 11.86 CG
LAI	RESOLVED	2ND CYST 31.1.80 2CMS
LAN		
LAU		
MAG		
MAR	RESOLVED PC AFTER AP:GB OUT:PC AGAIN RESOLV:GT SIG	GB OUT 12.07.79: MASS IN HEAD
MCC	DUBIOUS PC RESOLVED ON US	TO 11.9.74 WELL SURGERY DEFERRED

PSEUDOCYST GRI STUDY: 3

NAME	COMMENT	FOLLOW UP
MCC	REF KILM 18MNTH H/O PAIN PC ON US: 700ML: GB RUPTU	WELL TO 5.7.78
MCD	AP HAIR X4 73-74 EXT DRAIN PC 7.74 REF GRI BETTER	HAIRM
MCD	RESOLVED	
MCE	LAP DIAG: PAIN/VOMIT/PYREX DOU OBST	BUGS IN PC
MCG		
MCG	CP/ APX5 76-78 PANC CALC	WELL TO 15.08.79
MCK		
MCK	AP 19.12.67 READM 4.1.68: ABSC & GB OUT: PC AFTER	DIAB 1981
MCK	RESOLVED:READM 3.8.77 SA 3900 US PC 3CM:US PC NOT	US CONFIRM RESOLVED:READM 18.6.84 DIED 21.6.84 SEV
MCL	ABSC/REN RESP FAIL/SEPTIC POST OP/7 OPNS OPEN WOUN	BROUGHT FOR PC DRAIN:BLEED:SEPSIS
MCM	PROB CP: DIED 10.74	READM 17.06.74 SP ABSC DRAINED X2 REN FAIL DIED 24
MCN	?ABSC/?BLEED FROM SPLENIC	
MCP	V&GE DUOD OBST 12.74:^ SA HAIRM REF FOR INVEST:MUL	LONG FU WELL
MCR	CP:AP 1975 X6:PC FOUND BY ERCP	AP 7.84/ 3.86: DISCH 1,87
MEE	RECURR PC 80-87:NO GS ON PATH	86 STILL PAIN SMALL CYST
MIL		
MIL	RESOLVED:US DIAG ??:US 22.20.78 RESOLV	AP'75:'78:2.84:ERCP 4.86 PD ABN CP
MOR	CP:ANNULAR PANC: RECURR PAIN	RECURR PAIN FURTHER SURG:CP:LAST SEEN 9.11.84
MOR	RESOLVED:CULLENS	USX2 PC STILL THERE: GB OUT 12.03.84: NO COMMENT O
NEI		
PAT	CP:AP 9.74&8.76 PC CG:REC PAIN:ERCP SHOWED SMALL C	WELL
PRE	2 CYST DRAINED: DUOD OBST: FALLING HB	DIED GI HAEM ? SPLENIC ARTERY
RAD	2PC:CG THEN EXT D 7.12 7CM	WELL
RAE	DIED: AT OPN CYST IN P HEAD UNEXPECTED	READM + 27 VOMIT OPN DUOD FISTULA DIE 15.11.66
RAM	RESOLVED:TRANS BOURNM:IMPROVED AFTER DISCH BUT PC	US AND SA RESOLVED: BETTER BEFORE RESOLV
RAY	RESOLVED	
REI	RESOLVED ON US:DEVEL CP	?CYST 23.02.77 ERP FAILED: 1981 PANC CALC NO PC GE
REI	READM WITH BLEED INTO PC	ANAEMIC:GB OUT17.06.73
REI		
ROB	RESOLVED CLINICAL ONLY	NO US:OCG 24.9.74 NORMAL:WELL
ROS	REF CLINIC NO AP NOTED	
SEL	REF LAW APX2 :BILOCULAR	1981 UNWELL:? MALAB:ERCP PD FILL TO NECK ONLY:??CP
SEM	ASCITES: SKIN NODULES	READ 8.6.84 1 DAY: WELL FU X1
SHA	LAP 19.07.77 GB OUT ?NO CYST	CP:CYST RECURRED
SIM	GT SIGN:POST SPHINCT: US PC RESOLVED	ERCP 7.7.83 STONE: 29.11.84 2ND SPHINCTPLAST
SME	RECURR AP 1980-84	WELL 14.11.84
SMI	CYST WENT AND REFILLED:BILOC 1LT FLUID:	FU DIAB PANC INSUFF:FU DIAB GE CLIN TO 11.85
SMI	RECURR CYST 1ST 7.77:WENT 2ND 3.78:LAP ASP:3RD 9.7	DIED OD:NO RECURR CYST:SA WAS HIGH WITH CYST.
STE	PREV AP ABSC 1972:ALCOHOL	WELL 13.6.77
STE	REACUM AFTER PCUT DRAIN:DIED SEPSIS & BLEED	
STI	CYST REFILL: AMY FELL POST OP: SKIN NODULES	NIL
SUL	PERCUT ASP 6.82:500ml:RECURR PAIN: CG 8.82:RECURR	22.10.84 PERCUT DRAIN:OPN 16.01.85
SWE	CP:MANY AP:PC 19.7.78 AND 10.07.79:RESOLVED:ANAEMI	WELL: OCC PAIN: DEV TIA
TEM	? TRUE CYST	WELL
WAL	CP:AP 1979: PAIN 1981: ERCP 1982 DIST PANC 1.3.82	AP DATA NOT RECORDED
WAT	US DIAG:PROLONGED N/V:RESOLVED DUBIOUS	NO US:OCGX3 N:IVC N: LAST 18.3.82
WEI	DIED DAY 1 POST ELECT OPN ?MI	LESSER SAC PC GREEN FLUID
WIG	500ML IN CYST:NECR PANC	
WIL	DEID 4D POST OP:PM BP/UTI/AP/CIRRH/RESID PC 4CM	
WIL	NO SA PRE OP/13.2 POST/DRAIN FLUID BECAME INFECTED	E COLI EVENTU/NO GROWTH IN CYST FLUID/CLINIC UPS &

APPENDIX 3

LIST OF PARTICIPATING CONSULTANTS AND HOSPITALS FOR LEEDS, BRISTOL AND GLASGOW STUDY

APPENDIX 3

LIST OF PARTICIPATING CONSULTANTS AND HOSPITALS.

HOSPITAL	CONSULTANT
Bradford Royal Infirmary & St Luke's Hospital, Bradford	B Gadsby Peet JJ Price M Whittaker
Bristol Royal Infirmary	RN Baird MJ Cooper WK Eltringham HJ Espiner DJ Leaper M Horrocks JH Peacock AJ Webb RCN Williamson
Dewsbury General Hospital & Staincliffe General Hospital	PJ Lyndon
Frenchay Hospital, Bristol	LR Celestin CM Davidson RE May
Glasgow Royal Infirmary	DC Carter DG Gilmour JSF Hutchison CW Imrie CS Mcardle T Menzies JK Todd
Hairmyres Hospital, Glasgow	JR Goldring JR Richards WO Thomson
Halifax Royal Infirmary	VK Modgill D London KW Wilson
Huddersfield Royal Infirmary	GA Bunch NG Graham WG Harris
Leeds General Infirmary & Chapel Allerton Hospital, Leeds	EA Benson RL Doig D Johnston MJ Mcmahon JH Shoesmith FG Smiddy NS Williams

Princess Margaret Hospital, Swindon	PH Powley
Royal United Hospital, Bath	DC Britton K Lloyd-Williams WFW Southwood AR Turnbull
St Martin's Hospital, Bath	RB Smith
Scarborough Hospital	AV Pollock GMR Smith
Southern General Hospital, Glasgow	JC Ferguson A Litton GC McBain HI Tankel
Southmead Hospital, Bristol	BD Pentlow MH Thompson HJO White
Stobhill Hospital, Glasgow	MH Calvert FT Crossling R Dalling JA Garrett
Taunton and Somerset Hospital	CD Collins GN Lumb PJ O'boyle
Victoria Infirmary, Glasgow	AJ Mack IS Smith
Weston Super Mare General Hospital	TJ Flew A Hinchliffe
Wharfedale General Hospital	DJ Adams
York District Hospital	JL Craven R Hall DS Hopton TS Matheson

APPENDIX 4

COMPUTER DATA FOR 29 PATIENTS FROM LEEDS, BRISTOL AND GLASGOW

PSEUDOCYST DATA: PROSPECTIVE STUDY (3 CITY) 1

NAME	SEX	AGE	TYPE	AET	LAV	CRIT	DIAG	DAY	OPN	TYPE	DIED	COMP	COMPLICATIONS
ADA	F	76	PC	GS	S	5S	US	21	1	CG		2	UTI/PL EFF
AUS	F	70	PC	GS	S	3S	US	6			25	5	CHEST PL EFF:DIAB:MI:REN FAIL:
BIR	F	34	PC	GS	M	3S	CAT	22		GB OUT		1	CHEST
BRA	M	45	PC	GS	M	1M	US	4	1	GB OUT		0	
CAM	F	61	PC	GS	S	6S	US	12	1	CJJ:GB		2	CHEST: DIAB
COO	M	43	PC	UK	S	3S	CAT	13	1	CJJ		2	PL EFF:PSM COLITIS
DEV	F	69	PC	GS		4S	US	18	1	CG		2	CHEST: PSYCHOSIS
FLU	M	21	PC	ALC	S	1M	US	28	1	SB OBST		3	CHEST:GI BLEED:SB OBST
GOO	M	52	PC	GS	M	2M	US	23				4	CHEST: GI BLEED:UTI: PSYCH
GOO	F	30	PC	UK	S	2M	US	10				1	UTI
HIR	M	32	PC	ALC	S	2M	US	49	1	BYPASS		2	CHEST: DIAB
LAR	F	63	PC	UK	S	2M	US	10				1	UTI
LEW	F	78	PC	UK	M	0M	US	19	1	CG		0	
LYT	F	58	PC	GS		3S	US	3		GB OUT		0	
MCC	M	29	PC	ALC		3S	US	18	1	CG		1	CHEST
MIT	F	62	PC	GS	M	2M	US	8		GB OUT		2	PL EFF: UTI
MUD	F	71	PC	GS	M	1M	US	22	1	CG		0	
O'L	M	38	PC	ALC	-	0M	US	-					
PAT	M	56	PC	CAR	S	2M	US	33	1	EXT DRA		3	CHEST:REN FAIL:FISTULA
PHI	M	60	PC	GS	M	4S	US	20		GB OUT		0	
PHI	M	63	PC	UK	M	2M	US	16	1	LAP	36	3	CHEST PL EFF:GI BLEED:CVS
RAN	M	42	PC	ALC	S	0M	CAT	21				0	
SMI	M	56	PC	GS	S	1M	US	22	1	CG:GB 0		1	WOUND INF
STA	F	57	PC	UK	M	2M	US	33				2	PE:PSYCH
TAT	M	77	PC	GS	S	2M	US	28				1	PSYCH
VEN	F	61	PC	UK		2M	US	15	1	CJJ		0	
WAL	M	74	PC	ALC	S	2M	US	12				0	
WAR	M	44	PC	ALC	M	1M	US	24				2	CHEST:DIAB
WIC	F	50	PC	GS	M	3S	US	23	1	GB OUT		0	

PSEUDOCYST DATA: PROSPECTIVE STUDY (3 CITY) 2

			OPERATION			POST MORTEM			XRAY	CYST	AT DIAGNOSIS			Rx	
NAME	STAY	LAV(T)	OP DAY	TYPE	FINDINGS	PM	PM	FINDINGS	US CT	SIZE	TEMP	WBC	AMYL	ANTIBS	TPN
ADA	39	Y	28	CG	PC:500ml				Y+	5	^	22	95	CEPH/F	
AUS	25	N				Y		NECROTIC PANC:CYSTIC	Y+	LARGE	^	14.	88	GENT/A	Y7
BIR	16	N	139	GB O	PANC HEAD SWOLL				Y+ Y+	3.5	N	5.5	166	TETRA	
BRA	13	N	23	GB O	NO PC				Y+	NO SIZ	N	10	413		
CAM	95	N	266	CJJ:	PSEUDO				Y+ N	NO SIZ	^	12.	2146	Y	Y
COO	28	Y	43	CJJ	PC 200ml				Y+ Y+	NO SIZ	^	28.	400	AMP:FL	
DEV	28	N	117	CG	PC 800MLS: GB OUT CG				Y+	9X5.5		9.9	1110	CEPH/A	
FLU	39	N	11	SB O	SB OBST				Y+ N	LARGE	^		1900	AMP/GE	
GOO	25	N							Y+	6	^	10	253	GENT/C	Y3
GOO	61	N							Y+ N	4	^	11	748	SEPT	Y37
HIR	13	Y	59	BYPA	DUO OBST				Y+ N	LARGE	^	^	^	YES	Y44
LAR	24	N							Y+ N	5X7.5	^	16.	1015	MOX/AM	N
LEW	25	N	67	CG	10CM PC				Y+ N	10	N	20	360	Y	Y7
LYT	15	N	120	GB O	PANC SWELL: NO PC				Y+ Y+	6x4	N	17.	573		
MCC	23	N	62	CG	PC 1200ml				Y3 N	9	^	16.	1362	NET	Y.E
MIT	68	N	131	GB O	PANC HARD				Y4 Y+	4x9	^	18	100	Y	Y6
MUD	63	N	41	CG	PC 60ml:NEC PANC				Y+ Y+	8	^	14	1782	CEPH	Y30
O'L	8	N							Y+ N	3.5	N	7.3	4900		
PAT	12	Y	39	EXT	RUPTURED CYST GI BLE				Y+ N	6	^	13	1350	AMP	Y
PHI	20	N	83	GB O	CYST L SAC & HEAD				Y5 N	4.5	^	17.	135		
PHI	36	N	21	LAP	2 CAVITIES WASHED OU	N			Y+	NO SIZ	N	13	1670	SEPT:	Y
RAN	37	Y							N Y+	5	^	6.9	132	GENT	Y8
SMI	7	N	48	CG:G	PC 600ml:GS				Y+	8	^	15.	3097		Y
STA	39	N							Y4 N	NO SIZ	^	17.	1120	SEPT:	
TAT	35	N							Y2 N	8		11.	2170	Y	
VEN	12	N	56	CJJ	LESS SAC 60ml DUCT C				Y+ N	8x10	N	12.	1333	MULT	
WAL	27	Y							Y+ N	LARGE	N	10.	490		
WAR	16	N							Y+ Y+	LARGE	^	5.6	1298	CEPH	Y
WIC	27	N	57	GB O	MUC OF GB MASS INV D				Y+ N	5	^	5.5	113		

PSEUDOCYST DATA: PROSPECTIVE STUDY (3 CITY) 3

NAME	CONFIRM	COMMENT	FOLLOW UP
ADA	US:OPN	HYPOCALC: GB NOT OUT:	DEVELOPED DYSPHAGIA:CAND OESPH
AUS	US:PM	PC NOTED US6,11,18: NECR PANC	
BIR	CAT:OPN	SEVERAL CYSTS IN PANCREAS: 3.5 MAX IN NECK	GB OUT 23.8.82
BRA	US:CLIN	SPONT RES OF CYST: NO SIZE	GB OUT 9.2.83: NO PC
CAM	US:OPN	CULLENS ITU: READM X3	3RD ADM PC 25.08.83:REF UCL
COO	CAT:BM:US:	READM 10.12:PC 200ml AT OPN	
DEV	US:OPN	PC SEEN DAY 18: DISCH DAY28: READM +66:PC 4.5X7.5:	AFTER CYST DRAINED READM WITH VOMITING SETTLED
FLU	US:CLIN	LAP DAY 15 FOR ADHESIONS TO FAT NECR:PANC NEC NO P	READM AFTER 1 WEEK SETTLED: DISCH AFTER 6 MONTHS
GOO	US:CLIN	NOTED TO HAVE CA IN R KIDNEY	NEPHRECT:PC 1.5.86 PERCUT ASP
GOD	US:CLIN	PC DAY 10:PAIN DAY 15 PC 4CM ^TEMP AND AMYL	PC RESOLVED: DISCH AFTER 6 MONTHS
HIR	US:OPN	READM +23:PC ON US DUOD OBSTRC BYPASS GJJ 10.8:DIS	
LAR	US:CLIN	?PC DAY 4:TEMP WBC UP:US DIA6	NO CLINIC FU
LEW	US:OPN	PROLONG ILEUS:MASS:USPC:READM +40:DRAIN 67	VENTRAL HERNIA REP 4.82 DIED
LYT	US:CAT	GB OUT 2ND ADM	PANC OED NO PC AT OPN
MCC	US:OPN	READM +29: COMP BY SPABS ST AUR	
MIT	US:CLIN	PC RESOLVED DAY 45 ON US	GB OUT
MUD	US:CAT:OPN	? GS IN FAECES	ERCP/SPHINC NO CBD GS:PD OBSTN: WELL 1.86
O'L	US	US PC PRIOR TO ADM	SMALL PC 15.09.83 DISCH
PAT	US:OPN	READM +17:EXT DRAIN:DISCH 84	CA AMPULLA: CDJJ: DIED 7.10.84
PHI	US:OPN	CT OP CYST STILL THERE	DISCH 12.11.84
PHI	US:OPN	SUDDEN COLLAPSE ?RUPT CYST:LAVAGE ONLY	DIED CARDIAC ARREST:CHEST
RAN	CT	CAT RESOLVED	LAST SEEN 6.2.86
SMI	US:OPN	READM 17.07.83 PAIN PC	WELL
STA	US:CLIN	US PC RESOLVED 1 MONTH	OC6/IVC NE6 RESOLVED
TAT	US	US NOT SPECIFIC PROBABLE	
VEN	US:CT:OPN	CAEC PERF:READM +14 WITH PC	FU CYST ^ READM 7.6: PAIN AFTER OP
WAL	US:CLIN		US PC STILL THERE: REFUSE OPN
WAR	US:CT	READM +3: CT PC	EZ 8.11.85 & 3.1.86 PAIN:DIST PANCT 15.10.86
WIC	US:CLIN:OP	CYST RESOLVED ON US 16.07	

PSEUDOCYST DATA: PROSPECTIVE STUDY (3 CITY) 4

NAME	PYREX	PAIN	TEND	MASS	N/V	ANOR	DIST	ILEUS	JAUN	CHEST
ADA	Y	Y	Y	N	Y		Y			Y
AUS	Y	Y	Y	Y					Y	Y
BIR	N	Y	Y	N			Y			Y
BRA	N	Y	Y	N						
CAM	Y	Y	Y	Y	Y			Y		Y
COO	Y	Y	Y	Y			Y			Y
DEV	N	Y	Y	Y			Y			Y
FLU	Y	Y	Y		Y				Y	Y
GOO	Y	Y	Y							Y
GOO	Y	Y	Y		Y					
HIR	Y	Y	Y							
LAR	Y	Y	Y		Y				Y	
LEW	N	Y	Y	Y	Y		Y	Y		
LYT	N	Y								
MCC	Y	Y	Y	Y			Y			Y
MIT	Y	Y	Y	Y						Y
MUD	N	Y				Y				
O'L	N	Y	Y	N	Y				N	
PAT	Y	Y	Y	Y	Y		Y			Y
PHI	Y	Y	Y	Y						
PHI	N	Y	Y	Y			Y		Y	Y
RAN	Y	Y	Y							Y
SMI	Y	Y	Y	Y	N		N		N	
STA	Y	Y	Y	Y						Y
TAT	N	Y	Y						Y	
VEN	N	Y	Y	Y			Y			
WAL	N	Y	Y	Y						
WAR	Y	Y	Y							Y
WIC	Y	Y	Y	Y						

APPENDIX 5

COPY OF TRIAL PROFORMA

TRIAL OF PERITONEAL LAVAGE IN SEVERE ACUTE PANCREATITIS

INSTRUCTIONS
Write numerate answers in the boxes provided

e.g. for pulse rate of 72 — pulse rate 0 7 2

Where alternative answers are given, ring the correct answer to the question

e.g. for male patient — sex (male (1) / female 2)

Patient's name

Address

Trial number (from coordinator) 0 1 | 1 2 3 4 5 6

sex (male 1 / female 2) 7

Date of birth (day month year) 8 9 10 11 12 13

Age 14 15

Hospital — Do not write in these boxes 16 17

Hospital number 18 19 20 21 22 23

Date of admission to hospital (day month year) 24 25 26 27 28 29

Consultant — Do not write in these boxes 30 31

Presenting symptoms

abdominal pain	yes / no	1 / 2	32
vomiting/retching	yes / no	1 / 2	33
collapse/coma	yes / no	1 / 2	34
back pain	yes / no	1 / 2	35

Write in other significant symptoms — 36

Do not write in these boxes — 37 38

Previous History

Episodes of similar pain (None / (Undiagnosed pain / (Proven pancreatitis — 1 / 2 / 3 — 39

Number of episodes 40 41

Months since first episode 42 43 44

Alcohol intake

Pints of beer per week 45 46

Glasses of wine per week 47 48

Measures of spirits per week 49 50

Previous

Jaundice	yes / no	1 / 2	51
Dyspepsia	yes / no	1 / 2	52
Proven gall stones	yes / no	1 / 2	53
Ischaemic heart or vascular disease	yes / no	1 / 2	54
Diabetes	yes / no	1 / 2	55
Previous surgery — Cholecystectomy	yes / no	1 / 2	56
Common bile duct exploration	yes / no	1 / 2	57
Sphincterotomy/ sphincteroplasty	yes / no	1 / 2	58
Peptic ulcer operation	yes / no	1 / 2	59

Write in other relevant operations — 60

Do not write in these boxes — 61 62

2

Trial Number 1 2 3 4 5 6 — 0 2 — Serum amylase IU/L 7 8 9 10 11

Physical Examination

Height in cms	12 13 14	
Weight in kg	15 16 17	
Body mass index	18 19 20	
Temperature °C	21 22 23	
Pulse rate	24 25 26	
Systolic BP mmHg	27 28 29	
Abdominal pain	absent / mild / moderate / severe	1 / 2 / 3 / 4 — 30
Peritonism	absent / localised / generalised	1 / 2 / 3 — 31
Clinical assessment of severity	mild / severe	1 / 2 — 32

Diagnostic Lavage

	performed satisfactorily / failed attempt / not done	1 / 2 / 3 — 33
Volume of free fluid(ml)	34 35 36	
Colour of free fluid	pale fluid / dark fluid	1 / 2 — 37
Free fluid colour number (from colour chart)		38
Colour of lavage return fluid	pale straw colour / darker than pale straw	1 / 2 — 39
Return fluid colour number		40
Response to lavage	pain improved / no change	1 / 2 — 41

Multiple Criteria

pO_2 < 8.0KPa(600mmHg)	yes / no	1 / 2 — 42
WBC > 15,000	yes / no	1 / 2 — 43
Glucose > 10mmol/L	yes / no	1 / 2 — 44
Urea > 16mmol/L and no fall after 6 hr	yes / no	1 / 2 — 45
LDH > 600 IU/L	yes / no	1 / 2 — 46
GOT > 200 IU/L	yes / no	1 / 2 — 47
Ca^{++} < 2.00mmol/L	yes / no	1 / 2 — 48
Albumin < 32g/L	yes / no	1 / 2 — 49
Multiple Criteria score		50
Assessment of severity by trial criteria	mild / severe	1 / 2 — 51
laparotomy(necrosis or haemorrhagic pancreatitis)	diagnostic lavage / hypoxia alone / multiple criteria / clinical assessment alone	1 / 2 / 3 / 4 / 5 — 52
Hours from onset of symptoms to diagnosis of severe pancreatitis		53 54
Hours from diagnosis of pancreatitis to diagnosis of severe pancreatitis		55 56
Supplementary oxygen	yes / no	1 / 2 — 57
Amylase content of free fluid IU/L		58 59 60 61 62
Comments on diagnostic difficulties	Do not write in these boxes	63 64 65 66 / 67 68 69 70

3

Trial Number	1	2	3	4	5	6			Randomised for	lavage	1	2	7
					0	3				no lavage			

Therapy				
Therapeutic lavage performed	yes	1	2	8
	no			
Duration of lavage (days)			9	10

ADDITIONAL TREATMENT			DAY + COMMENTS	leave blank	
Antibiotics	yes	1			
	no	2			
		11		12	13
Antispasmodics	yes	1			
	no	2			
		14		15	16
Dextran	yes	1			
	no	2			
		17		18	19
Diuretics	yes	1			
	no	2			
		20		21	22
Fresh frozen plasma	yes	1			
	no	2			
		23		24	25
Glucagon	yes	1			
	no	2			
		26		27	28
Mechanical ventilation	yes	1			
	no	2			
		29		30	31
Parenteral nutrition	yes	1			
	no	2			
		32		33	34
Pressor agents	yes	1			
	no	2			
		35		36	37
Steroids	yes	1			
	no	2			
		38		39	40
Trasylol	yes	1			
	no	2			
		41		42	43

Write other relevant treatment (see separate sheet for operations)		
	44	45
	46	47
Do not write in these boxes	48	49
	50	51

Progress		
Uncomplicated recovery	1	
Complication but survived	2	
Died	3	
	52	
Day of discharge from acute bed or death	53	54
Oxygen required until day :	55	56
Temperature normal from day:	57	58
Flatus first passed on day:	59	60
Parenteral analgesia required until day	61	62

Any other comments on progress:

63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80

4

Trial Number	1	2	3	4	5	0	6	4	Number of operations following acute admission	7

Operation findings (or autopsy findings) Day of (first) operation 8

Peritoneal fluid	none		1
	straw coloured		2
	dark coloured		3
	cloudy		4
	bile stained		5
	frank blood		6
			9
Fat necrosis	absent		1
	localised		2
	generalised		3
			10
Bruising	absent		1
	localised to pancreas		2
	more remote		3
			11
Pancreatitis	oedematous		1
	haemorrhagic	focal	2
		extensive	3
			12
Pancreatic	necrosis	yes	1
		no	2
			13
	pseudocyst	yes	1
		no	2
			14
	abscess	yes	1
		no	2
			15
Other intra abdominal abscess		yes	1
		no	2
			16
Liver	normal	yes	1
		no	2
			17
	cirrhosis	yes	1
		no	2
			18
Gall bladder	normal	yes	1
		no	2
			19
	dilated	yes	1
		no	2
			20
	stones	yes	1
		no	2
			21
	inflamed	yes	1
		no	2
			22

Operative cholangiogram		yes	1
		no	2
			23
Pancreatic duct filling on OTC		yes	1
		no	2
			24
Common bile duct	normal	yes	1
		no	2
			25
	dilated	yes	1
		no	2
			26
	stones	yes	1
		probably	2
		possibly	3
		no	4
			27
	cholangitis	yes	1
		no	2
			28
Procedure	no procedure	yes	1
		no	2
			29
Pancreas	drainage	yes	1
		no	2
			30
	debridement	yes	1
		no	2
			31
	pancreatectomy	yes	1
		no	2
			32
Cholecystectomy		yes	1
		no	2
			33
Exploration CBD (supraduodenal)		yes	1
		no	2
			34
Sphincterotomy/plasty		yes	1
		no	2
			35

Comments and other procedures leave blank

	36
	37
	38
	39

5

Trial number					0	5	
	1	2	3	4	5	6	

Aetiology

Gall stones	yes	1	7
	no	2	
Alcohol	yes	1	8
	no	2	
Ca. pancreas	yes	1	9
	no	2	
Trauma	yes	1	10
	no	2	
Post-operative	yes	1	11
	no	2	
Post-ERCP	yes	1	12
	no	2	
Hyperparathyroid	yes	1	13
	no	2	
Drug induced (specify)	yes	1	14
	no	2	
Viral (specify)	yes	1	15
	no	2	
Other (specify)	yes	1	16
	no	2	
Unknown	yes	1	17
	no	2	

Write in drugs prior to admission

leave blank	
18	19
20	21
22	23
24	25
26	27
28	29

Investigations

Proven gall stones	yes	1	30			
	no	2				
Abdominal x-ray	yes	1	31	Gall stones shown	yes	1	32
	no	2			no	2	
Oral cholecystogram	yes	1	33	Gall stones shown	yes	1	34
	no	2			no	2	
I.V. cholangiogram	yes	1	35	Gall stones shown	yes	1	36
	no	2			no	2	
P.T. cholangiogram	yes	1	37	Gall stones shown	yes	1	38
	no	2			no	2	
U.S. scan	yes	1	39	Gall stones shown	yes	1	40
	no	2			no	2	
C.T. scan	yes	1	41	Gall stones shown	yes	1	42
	no	2			no	2	
Laparotomy	yes	1	43	Gall stones shown	yes	1	44
	no	2			no	2	

Autopsy Report and Cause of Death

leave blank	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	

6

Trial number					0	6
	1	2	3	4	5	6

Bacteriology (write organisms and date)	leave blank	
Sputum	7	8
Urine	9	10
Blood	11	12
Bile	13	14
Pancreatic abscess	15	16
Other intraabdominal abscess	17	18
Diagnostic lavage fluid/peritoneal fluid	19	20
Therapeutic lavage fluid	21	22
Other	23	24

Complications of lavage (state)		
	25	26
	27	28
	29	30
	31	32
	33	34
	35	36

Complications					
Chest	yes / no	37	day	38	39
Cholangitis	yes / no	40	day	41	42
DVT/PE	yes / no	43	day	44	45
Diabetes	yes / no	46	day	47	48
G.I. bleed	yes / no	49	day	50	51
Myocardial infarct	yes / no	52	day	53	54
Pancreatic abscess (or fistula)	yes / no	55	day	56	57
Other intra abdominal abscess	yes / no	58	day	59	60
Pseudocyst	yes / no	61	day	62	63
Renal failure	yes / no	64	day	65	66
Septicaemia	yes / no	67	day	68	69
Toxic psychosis	yes / no	70	day	71	72
Urinary tract infection	yes / no	73	day	74	75

Write other complications		
	76	77
	78	79
		80

PERITONEAL LAVAGE TRIAL HOSPITAL PATIENT'S NAME UNIT NO.

Blood → Arterial Plasma or Serum →

WEEK	DAY	DATE	WBC (10^9/L)	PCV (%)	Platelets (10^9/L)	PO_2 (KPa)	Na+ (mmol/L)	K+ (mmol/L)	Urea (mmol/L)	Creat. (μmol/L)	Alk. Phos. (IU/L)	GOT (IU/L)	Bilirubin (μmol/L)	Total protein (g/L)	Albumin (g/L)	Ca++ (mmol/L)	PO_4^{--} (mmol/L)	LDH (IU/L)	Glucose (mmol/L)	Amylase (IU/L)	Fluid Balance +/-	Fluid Balance Volume (ml)
Trial No	1 2 3 4 5 6	0																				
Week	Day	Date																				
	0																				+ / -	1 / 2

Trial No	1 2 3 4 5 6	1	WBC	PCV	Plates	PO_2	Na+	K+	Urea	Creat	AP	GOT	Bili	Prot	Alb	Ca++	PO_4^{--}	LDH	Gluc	Amylase	+ / -	Fluid balance 1 / 2
Week	Day	Date																				
	1																					

Trial No	1 2 3 4 5 6	2	WBC	PCV	Plates	PO_2	Na+	K+	Urea	Creat	AP	GOT	Bili	Prot	Alb	Ca++	PO_4^{--}	LDH	Gluc	Amylase	+ / -	Fluid balance 1 / 2
Week	Day	Date																				
	2																					

Trial No	1 2 3 4 5 6	3	WBC	PCV	Plates	PO_2	Na+	K+	Urea	Creat	AP	GOT	Bili	Prot	Alb	Ca++	PO_4^{--}	LDH	Gluc	Amylase	+ / -	Fluid balance 1 / 2
Week	Day	Date																				
	3																					

Trial No	1 2 3 4 5 6	4	WBC	PCV	Plates	PO_2	Na+	K+	Urea	Creat	AP	GOT	Bili	Prot	Alb	Ca++	PO_4^{--}	LDH	Gluc	Amylase	+ / -	Fluid balance 1 / 2
Week	Day	Date																				
	4																					

Trial No	1 2 3 4 5 6	5	WBC	PCV	Plates	PO_2	Na+	K+	Urea	Creat	AP	GOT	Bili	Prot	Alb	Ca++	PO_4^{--}	LDH	Gluc	Amylase	+ / -	Fluid balance 1 / 2
Week	Day	Date																				
	5																					

Trial No	1 2 3 4 5 6	6	WBC	PCV	Plates	PO_2	Na+	K+	Urea	Creat	AP	GOT	Bili	Prot	Alb	Ca++	PO_4^{--}	LDH	Gluc	Amylase	+ / -	Fluid balance 1 / 2
Week	Day	Date																				
	6																					

7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62