CLINICAL STUDIES COMPARING LAPAROSCOPIC AND MINILAPAROTOMY CHOLECYSTECTOMY

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CONTENTS

CONTENTS (continued)

CONTENTS (continued)

LIST OF TABLES

List of Tables (continued

LIST OF FIGURES

List of Figures (continued)

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List of Work Published and Presented

Original Articles:

McMahon AJ, O'Dwyer PJ, Russell IT, Baxter JN.
Laparoscopic versus open cholecystectomy and the need for a randomised trial: a survey of surgeons and ethical committees in the British Isles.
Journal of Laparoendoscopic Surgery 1992; **2** (6): 277-80.

McMahon AJ, O'Dwyer PJ, Cruikshank AM, McMillan DC, O'Reilly DStJ, Lowe GDO, Rumley A, Logan RW, Baxter JN.
Comparison of metabolic responses to laparocopic and minilaparotomy cholecystectomy.
British Journal of Surgery 1993; **80** (10): 1255-8.

McMahon AJ, Baxter JN, Russell IT, Anderson JR, Ramsay G, Galloway D, Sunderland G, O'Dwyer PJ.
Laparoscopic versus minilaparotomy cholecystectomy: a randomised trial comparing postoperative pain and pulmonary function.
Surgery In press.

McMahon AJ, Baxter JN, Kenny G, O'Dwyer PJ
Ventilatory and blood gas changes during laparoscopic and open cholecystectomy.
British Journal of Surgery 1993; **80** (10): 1252-4.

McMahon AJ, Ross S, Baxter JN, Russell IT, Anderson JR, Moran C, Ramsay G, Galloway D, Sunderland G, O'Dwyer PJ.
Laparoscopic versus minilaparotomy cholecystectomy: a randomised trial.
Lancet In Press.

McMahon AJ, Baxter JN, Murray W, Imrie C, Kenny G, O'Dwyer PJ.
Helium pneumoperitoneum for laparoscopic cholecystectomy: ventilatory and blood gas changes.
British Journal of Surgery In Press

Review Articles

McMahon AJ, O'Dwyer PJ, Baxter JN.
Laparoscopic versus open cholecystectomy: an examination of the evidence.
Journal of the Irish Colleges of Physicians and Surgeons 1993; **22** (3): 186-190.

McMahon AJ Baxter JN, O'Dwyer PJ.
Preventing complications of laparoscopy.
British Journal of Surgery 1993; **80** (12): In press.

Letters

McMahon AJ, Baxter JN, Russell IT, O'Dwyer PJ.
Laparoscopic cholecystectomy.
Lancet 1991; **338**: 1333.

McMahon AJ, Baxter JN, O'Dwyer PJ.
The open technique for laparoscopy.
Annals of the Royal College of Surgeons of England 1992; **74**: 439.

McMahon AJ, Baxter JN, Russell IT, O'Dwyer PJ.
Laparoscopic versus mini-cholecystectomy.
Lancet 1993; **341**: 249.

McMahon AJ, Baxter JN, O'Dwyer PJ.
Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy.
British Journal of Anaesthesia 1993; **70**: 493-4.

McMahon AJ, Baxter JN, O'Dwyer PJ.
Physiological and metabolic responses to open and laparoscopic cholecystectomy.
British Journal of Surgery 1993; **80**: 402.

McMahon AJ, Baxter JN, O'Dwyer PJ.
Pathogenesis and management of gallstones.
New England Journal of Medicine 1993; 328: 1854.

Book Chapters

O'Dwyer, PJ, McMahon, AJ. Mini Cholecystectomy. In: Grace P. ed.
Techniques in the Management of Gallstone Disease. Oxford: Blackwell Scientific, 1993 In press.

Presentations (with published abstracts):

McMahon AJ, Baxter JN, Anderson JR, Ramsay G, Galloway D, Russell IT, O'Dwyer PJ.
Assessment of pain after laparoscopic and minilaparotomy cholecystectomy: a randomised trial.
Surgical Research Society, Edinburgh, July 1992
British Journal of Surgery 1992; **79** (11): 1224.

McMahon AJ, Baxter JN, Anderson JR, Ramsay G, Galloway D, Russell IT, O'Dwyer PJ.
Pulmonary function after laparoscopic and minilaparotomy cholecystectomy: a randomised trial.
Patey Prize Session of the *Surgical Research Society,* Edinburgh, July 1992
British Journal Surgery 1992; **79** (11): 1226.

Presentations (continued)

McMahon AJ, O'Dwyer PJ, McMillan D, Cruikshank A, Lowe G, Rumley A, O'Reilly D, Logan R, Baxter JN.
Does the laparoscopic method result in a reduced metabolic response to surgery?
Combined Meeting of the *Association of Surgeons of Great Britain and Ireland and Trinity College Dublin (Quarter Centenary)*, Dublin Sept 1992
Irish Journal of Medical Science 1992; **161** (suppl 11): 39.

McMahon AJ, O'Dwyer PJ, Russell IT, Baxter JN.
Controlled clinical trials and laparoscopic cholecystectomy: a surgeon's viewpoint.
Combined Meeting of the *Association of Surgeons of Breat Britain and Ireland and Trinity College Dublin (Quarter Centenary)*, Dublin Sept 1992
Irish Journal of Medical Science 1992; **161**(suppl 11): 23.

McMahon AJ, Baxter JN, Anderson JR, Ramsay G, Galloway D, Sunderland G, Russell IT, O'Dwyer PJ.
Postoperative pain and pulmonary function after laparoscopic and minilaparotomy cholecystectomy: a prospective randomised trial.
Caledonian Society of Gastroenterology, Newcastle, November 1992.

McMahon AJ, Lesley H, G Fullarton, Bell G.
An audit of 1500 laparoscopic cholecystectomies in the West of Scotland.
Audit Symposium, The Royal College of Surgeons of Glasgow, November, 1992.

McMahon AJ, Baxter JN, Anderson JR, Ramsay G, Galloway D, Sunderland G, Russell IT, O'Dwyer PJ.
Postoperative pain and analgesia requirement after laparoscopic and minilaparotomy cholecystectomy: a prospective randomised trial.
British Society of Gastroenterology September, 1992
Gut 1992; **33** (2): S63.

McMahon AJ, O'Dwyer PJ, Cruikshank A, McMillan D, Lowe G, Rumley A, O'Reilly D, Baxter JN.
Metabolic changes after laparoscopic and minilaparotomy cholecystectomy: a randomised trial.
Patey Prize Session of the *Surgical Research Society*, London January 1993.
British Journal of Surgery 1993; **80** (5): 641.

McMahon AJ, Baxter JN, Kenny G, O'Dwyer PJ.
Ventilatory changes during laparoscopic and open cholecystectomy: a randomised trial.
Patey Prize Session of the *Surgical Research Society*, London, January 1993
British Journal of Surgery 1993; **80** (5):647.

Presentations (continued)

McMahon AJ, Baxter JN, Anderson JR, Ramsay G, Galloway D, Sunderland G, Russell IT, O'Dwyer PJ.
Postoperative pain and pulmonary function after laparoscopic and mini-cholecystectomy: a randomised trial.
Annual Registrar's Research Prize Evening, Royal College of Physicians and Surgeons of Glasgow, March 1993 - **awarded prize for best clinical paper.**

McMahon AJ, O'Dwyer PJ, Cruikshank A, McMillan D, Lowe G, Rumley A, O'Reilly D, Baxter JN.
Metabolic Changes after laparoscopic and minilaparotomy cholecystectomy: a randomised trial
Scottish Society of Experimental Medicine, Glasgow, December 1992.
Scottish Medical Journal 1993; **38** (3): 93.

McMahon AJ, Baxter JN, Kenny G, O'Dwyer PJ.
Ventilatory changes after laparoscopic and minilaparotomy cholecystectomy: a randomised trial.
Association of Surgeons of Grt Britain and Ireland, Birmingham April 1993.

McMahon AJ, Ross S, Russell IT, Baxter JN, Anderson JR, Ramsay G, Galloway D, Sunderland G, O'Dwyer PJ.
Return to normal activity after laparoscopic and mini-cholecystectomy: a randomised trial.
American Gastroenterological Association, Boston, USA, May 1993.
Gastroenterology 1993; **104**(4): A370.

McMahon AJ, Baxter JN, Anderson JR, Ramsay G, Galloway D, Sunderland G, Russell IT, O'Dwyer PJ.
Postoperative pain and pulmonary function after laparoscopic and mini-cholecystectomy: a prospective randomised trial.
American Gastroenterological Association, Boston, USA, May 1993.
Gastroenterology 1993; **104**(4): A370.

McMahon AJ, Ross S, Russell IT, Baxter JN, Anderson JR, Ramsay G, Galloway D, Sunderland G, O'Dwyer PJ.
Return to normal activity after laparoscopic and mini-cholecystectomy.
British Society of Gastroenterology, Manchester, March 1993.
Gut 1993; **34** (Suppl 1): S68.

McMahon AJ, Baxter JN, Russell IT, O'Dwyer PJ.
Comparison of the cost of laparoscopic and mini-cholecystectomy.
British Society of Gastroenterology, Manchester, March 1993.
Gut 1993 ; **34** (Suppl 1): S68.

Laparoscopic versus small incision cholecystectomy.
"Making the Right Choices in the Management of Gallstone Disease": A National/International Seminar for the Providers and Purchasers of Services, Sheffield, November, 1992

Presentations (continued)

Comparison of the cost of laparoscopic and minilaparotomy cholecystectomy. *Minimal Access Surgery Working Group* (reporting to Prof. K. Calman, Chief Medical Officer of the NHS) - The Scottish Office, Edinburgh, December 1992.

McMahon AJ, Baxter JN, Murray WR, Imrie CW, Kenny G, O'Dwyer PJ.
Helium pneumoperitoneum for laparoscopic cholecystectomy: ventilatory changes.
Surgical Research Society, London, January 1994.
British Journal of Surgery 1994; 81: In press

McMahon AJ, Baxter JN, Russell IT, Ross S, Anderson JR, Morran C, Sunderland G, Galloway D, Ramsay G, O'Dwyer PJ.
A randomised trial comparing patient outcome after laparoscopic and mini-cholecystectomy.
Tripartite Meeting of the Society of University Surgeons, Surgical Research Society, European Society for Surgical Research, Japanese Surgical Society and Surgical Research Society of Australasia.
Jackson, Mississippi, February 1994.

McMahon AJ, Baxter JN, Murray WR, Imrie CW, Kenny G, O'Dwyer PJ.
Helium pneumoperitoneum for laparoscopic cholecystectomy: ventilatory changes.
Tripartite Meeting of the Society of University Surgeons, Surgical Research Society, European Society for Surgical Research, Japanese Surgical Society and Surgical Research Society of Australasia.
Jackson, Mississippi, February 1994.

LIST OF ABBREVIATIONS USED

χ^2	chi-square
CBD	common bile duct
CI	confidence interval
CO_2	carbon dioxide
CRP	C reactive protein
ERCP	endoscopic retrograde cholangiopancreatography
ES	endoscopic sphincterotomy
FDPs	fibrin degradation products
FEV1	forced expiratory volume in one second
F_IO2	inspired oxygen concentration
FVC	forced vital capacity
$[H^+]$	hydrogen ion concentration
$[HCO_3^-]$	bicarbonate concentration
H_2O	water
HADS	hospital anxiety and depression score
IL-6	interleukin-6
IQR	interquartile range
IVC	intravenous cholangiogram
kPa	kilopascals
O_2	oxygen
N_20	nitrous oxide
Pa_{O2}	arterial oxygen tension
PA_{O2}	alveolar oxygen partial pressure
P_{aCO2}	arterial carbon dioxide tension
$(Pa_{CO2} - P_{E'CO2})$	arterial to end-tidal carbon dioxide partial pressure difference
$(PA_{O2}-Pa_{O2})$	alveolar arterial oxygen gradient
P_B	barometric pressure minus water vapour pressure saturated at body temperature
$P_{E'CO2}$	end-tidal carbon dioxide partial pressure
PEFR	peak expiratory flow rate
PMN elastase	polymorphonuclear elastase

List of Abbreviations (continued)

R	respiratory quotient
RCT	randomised controlled trial
SD	standard deviation
SF-36	the short form 36 question health survey questionnaire

SUMMARY

Summary

Laparoscopic cholecystectomy was first performed by Mouret in France in 1987. Although laparoscopic cholecystectomy has rapidly been introduced into routine practice, there has been no rigorous evaluation comparing it with open cholecystectomy. Use of a small transverse subcostal incision ("minilaparotomy") for open cholecystectomy has been shown to result in a more rapid postoperative recovery than standard incisions [1-7]. Therefore a trial was undertaken in which some 300 patients were randomised to laparoscopic (151) or minilaparotomy (148) cholecystectomy over an eighteen months period.

Over the first year of the trial, postoperative pain, opiate analgesia consumption, oxygen saturation and pulmonary function (forced vital capacity (FVC), forced expiratory volume in one second(FEV1), and peak expiratory flow rate (PEFR)) were assessed after laparoscopic (n=67) and minilaparotomy (n=65) cholecystectomy. Laparoscopic cholecystectomy was associated with lower linear analogue pain scores (median 40 v 59 mm, $p<0.001$), lower patient-controlled morphine consumption (median 22 versus 40 mg, $p<0.001$), a smaller reduction in postoperative pulmonary function (mean PEFR 64% of pre-operative value versus 49%, $p<0.001$) and better oxygen saturation (mean 92.9% versus 91.2%, $p=0.008$) than minilaparotomy cholecystectomy.

In the randomised trial as a whole, recovery after surgery was assessed by length of hospital stay, outpatient review at ten days and four weeks, and a modified version of of the SF-36 health survey questionnaire one, four and twelve weeks after surgery. The median operation time was 20 minutes shorter for minilaparotomy (50 versus 70 minutes, $p<0.001$), while the median postoperative hospital stay was shorter after laparoscopic cholecystectomy (2

versus 4 days, $p<0.001$). The mean hospital cost was £396 greater for the laparoscopic procedure (£1486 versus £1090, $p<0.001$). There was a similar incidence of complications after both procedures (minilaparotomy group 20%, laparoscopic group 17%).

Laparoscopic patients returned to work in the home more rapidly (median 10 versus 15 days, $p<0.001$). At one week, laparoscopic patients had significantly better physical and social functioning, less role limitation due to physical problems, less pain, and lower depression scores. At four weeks, only the physical functioning and depression scores were better in the laparoscopic group, and by three months, there were no significant differences. Laparoscopic patients were more satisfied with the overall outcome of their operation, and the appearance of their scars. Compared with minilaparotomy cholecystectomy, laparoscopic cholecystectomy results in moderate benefits in length of hospital stay, post-operative dysfunction, and time to return to normal activity, but an increased cost to the National Health Service.

The stress of surgery evokes a wide variety of biochemical and physiological changes, known as the metabolic response to injury. The magnitude of the metabolic response to injury has been shown to be proportional to the degree of the surgical trauma [8-11]. As part of the randomised trial, the metabolic response to laparoscopic (n=10) and minilaparotomy cholecystectomy (n=10) was assessed. Venous blood samples were taken at 0, 3, 6, 9, 12, 18, 24, 48, 72 and 168 hours after incision and analysed for C reactive protein, interleukin-6, cortisol, albumin, transferrin, iron, fibrinogen, fibrin degradation products, polymorphonuclear elastase, neutrophil, and lymphocyte count. 24h urine samples were analysed for urea, creatinine, 3-methylhistidine and catecholamines. The magnitude of the metabolic changes from base-line levels was quantified by calculating areas under each individual curve. A significant

metabolic response with a similar time course and magnitude of changes occurred after laparoscopic and minilaparotomy cholecystectomy but with wide inter-individual variation in the magnitude of the response. The laparoscopic technique did not reduce the metabolic response when compared with open surgery using a small incision.

Some recent studies have suggested that during laparoscopic cholecystectomy carbon dioxide absorption from the pneumoperitoneum may result in hypercarbia and respiratory acidosis [12-14]. In order to clarify these previous findings, ventilatory and arterial blood gas changes were assessed during laparoscopic (n=30) and minilaparotomy (n=30) cholecystectomy as part of the randomised trial. Measurements were made during anaesthesia before commencing surgery, and at the time of removal of the gallbladder. Despite an increase in minute ventilation from a mean (SD) of 5.7 (1.4) litres to 6.1 (1.2) litres (*95% CI of the difference 0.01-0.9*), arterial carbon dioxide tension (P_{aCO2}) rose from 5.3 (0.6) to 6.0 (0.9) kPa (*95% CI of the difference 0.3-0.9*) during laparoscopic cholecystectomy. Peak airway pressure increased from 17 (4) to 23 (4) cm H_20 (*95% CI of the difference 5-7*). By comparison, no clinically significant changes in ventilation or blood gas values occurred during minilaparotomy cholecystectomy. Laparoscopic cholecystectomy using a CO_2 pneumoperitoneum is associated with a significant increase in carbon dioxide output, requiring a significant but variable increase in minute ventilation to prevent hypercarbia.

End-tidal CO_2 partial pressure ($P_{E'CO2}$) monitoring is increasingly used during anaesthesia as an indirect measure of arterial CO_2 tension (P_{aCO2}). Therefore the relationship between these two variables was assessed. $P_{E'CO2}$ had poor precision in predicting P_{aCO2} (95% limits of agreement -0.61 to +1.93 kPa). The mean (P_{aCO2} - $P_{E'CO2}$) did not change significantly during surgery,

although there was significant within-patient variation. During laparoscopic cholecystectomy, minute ventilation should be be increased to maintain $P_{E'CO2}$ towards the lower end of the normal range (4-5 kPa) in order to avoid inadvertent hypercarbia.

In some patients with severe cardiac or respiratory disease undergoing laparoscopic cholecystectomy, it may be impossible to eliminate the increased CO_2 burden by hyperventilation [13,15]. Therefore, a study was carried out to assess helium as an alternative to carbon dioxide for creating the pneumoperitoneum. Ventilation requirements, Pa_{CO2} and $P_{E'CO2}$ were assessed before creating the pneumoperitoneum and at the time of gallbladder removal during laparoscopic cholecystectomy using a helium pneumoperitoneum (n=30). Helium pneumoperitoneum did not result in any significant changes in minute ventilation requirement, although like CO_2 pneumoperitoneum, it was associated with a mean rise in peak airway pressure of 7 cm H_2O ($p<0.001$, paired t test). There was a 3.2 kPa rise in the alveolar-arterial oxygen gradient ($p=0.006$). Four patients had surgical emphysema persisting for five days. Helium may be a suitable alternative for patients with severe cardiorespiratory disease undergoing laparoscopic procedures in whom carbon dioxide insufflation results in excessive hypercarbia and acidosis.

Chapter 1

INTRODUCTION - REVIEW OF THE LITERATURE

1.1 History of Cholecystectomy

The first cholecystectomy was performed in Germany by Carl Langenbuch on July 15th, 1882 [16-18]. In spite of the fact that the operation was successful, he engendered much criticism among his peers [19]. Nevertheless, before the turn of the century, cholecystectomy had become a common operation [20]. Cholecystectomy has now been the gold standard treatment for gallstone disease for over 100 years, despite the development of a whole range of different treatment options. It is currently the most frequently performed elective major operation in the western world. Over 600,000 cholecystectomies are performed each year in the USA [21] and up to 50,000 in the UK and Ireland [22].

1.2 Gallstones, Symptoms, and Indications for Treatment

Cholelithiasis is common, but the majority of subjects with stones are and remain asymptomatic. In a cross-sectional screening study in Denmark involving a sample of 4,807 subjects, the prevalence of gallstones in 30 year old females was 5% increasing to 22% in 60 year olds, whereas in males the incidence was 2% and 13% respectively [23]. However, of those subjects with gallstones, only a third had had right upper quadrant pain and less than 10% had had right upper quadrant pain radiating to the shoulder [24].

There is general agreement on what constitutes symptomatic gallstone disease, namely the occurrence of biliary pain, acute cholecystitis, biliary obstruction or pancreatitis [25]. Upper abdominal pain not clearly due to another cause in the presence of gallstones is often ascribed to gallstones. Nevertheless, even patients with apparently typical biliary pain may not be relieved of their symptoms by cholecystectomy [25-28], suggesting a significant degree of diagnostic inaccuracy. With the reduced morbidity and patient discomfort with the new methods of cholecystectomy, has come a reduced symptom

threshold for cholecystectomy, if not in this country, certainly in the United States [29,30] and Germany [31,32]. In the University of Cologne group's first 400 laparoscopic cholecystectomies, 14 per cent were asymptomatic and 56 per cent had only mild and very occasional symptoms not requiring analgesia, whereas before the introduction of laparoscopic cholecystectomy, these two categories together comprised only 10 per cent of their cholecystectomy patients [32]. Words of caution have been made against the non-discriminating application of laparoscopic cholecystectomy to patients with vague complaints. Spiro satirically referred to such operations as "*diagnostic* laparoscopic cholecystectomies" - "lap-choly will not cure the pains of life" [33].

1.3 Sequelae of Cholecystectomy

Biliary symptoms may be replaced after cholecystectomy by new symptoms in part due to gallbladder removal. Loss of the reservoir function of the gallbladder results in disturbance of bile changes from intermittent, meal-related to continuous, and its composition also changes, becoming more damaging to gastric and oesophageal mucosa. This leads to increased duodenogastric reflux [34], which is aggravated further by the impaired function of the antropyloric motor unit that appears to result from a direct effect of bile on the duodenum [35]. Subsequent symptoms have been related to the increased incidence of gastritis (described in up to 50 per cent of patients), to alkaline duodenogastric reflux [34], and to the qualitative change in bile composition [36]. Gastro-oesophageal reflux and the incidence of oesophagitis also increases after cholecystectomy [37,38]. The bile salt pool is reduced by 50 per cent, which may result in subclinical fat malabsorption and post-cholecystectomy diarrhoea which may be attributed to bile catharsis [39]. Finally, some authors have claimed that cholecystectomy results in an increased risk of colorectal cancer [40]. Although there is a definite association

between gallstones and colorectal cancer [41], it remains unclear whether cholecystectomy per se is an independent risk factor.

It is because cholecystectomy has several adverse longterm sequelae, that some have advocated using treatments that preserved the gallbladder in patients in whom it is still functioning [22].

1.4 Gallbladder preserving treatments for gallstones

Oral dissolution therapy

Oral dissolution therapy, which was first used in 1970 [42], has considerable limitations. Less than 20% of patients are suitable for treatment (criteria are non-pigment, radiolucent stones less than 1cm in diameter in a fuctioning gallbladder in a non-obese patient) [43]. With treatment taking up to 2 years for complete stone dissolution, treatment is expensive [44]. Even in selected patients, it will completely dissolve stones in only 40-60% of patients [44], with recurrence at 5 years of 50% [45].

Extracorporeal shockwave lithotripsy

This treatment method was first applied to gallstones in humans in 1986 [46]. Absolute inclusion criterion for this treatment is a functioning gallbladder. Additional inclusion criteria laid down in the Munich study [47], are radiolucent stones which are less than 3 cm in diameter, and not more than three, which leaves only 15% of patients suitable for lithotripsy [48]. Using these entry criteria, 90% of patients treated by lithotripsy (with adjuvant litholytic therapy) are gallstone free after 12-18 months. However, a recent randomised trial found that compared to open cholecystectomy, lithotripsy was only cost-effective for patients with a stone bulk less than 4 cubic centimetres [49].

Percutaneous cholecystolithotomy

Percutaneous cholecystolithotomy, is a minimally invasive technique allowing surgical removal of stones while preserving the gallbladder [50,51]. The only exclusion criterion is a contracted thickwalled gallbladder. It is performed under general anaethesia or local anaesthesia with intravenous sedation and takes 25-90 minutes. At the end of the procedure, a Foley catheter is left in the gallbladder which is removed after 10 days. The procedure is successful in 90% of cases. Patients are discharged 24-48 h after the procedure, returning for removal of a Foley catheter. However, open cholecystolithotomy is associated with an 83% symptomatic stone recurrence rate at 15 years [52], and therefore it is likely that this technique will only be suitable for elderly patients unfit for cholecystectomy.

Since gallbladder preserving treatments for cholelithiasis are only applicable to a small percentage of patients, for the foreseeable future cholecystectomy is likely to remain the treatment of choice for symptomatic gallstones in the majority of patients. Langenbuch's assertion that "the gallbladder needs to be removed not because it contains stones but because it forms them" is a pertinent today as it was over 100 years ago [16-18].

1.5 Methods of performing cholecystectomy

The first cholecystectomy was performed through a T-shaped laparotomy incision [16-18]. The horizontal limb of the incision was parallel to the liver edge and the longitudinal limb ran along the lateral border of the rectus muscle. Nowadays, the most commonly used incisions are right paramedian, midline, oblique subcostal (Kocher's), and transverse subcostal incision. The transverse or oblique subcostal incisions are preferred by most surgeons because they result in less postoperative pain and less reduction in postoperative pulmonary function than midline incisions [53,54]. The Kocher's

incision extends from the tip of the ziphoid caudally and laterally 5-6 cm below the costal margin into the flank [55]. Such an incision varies in length between 15 and 30 cm depending upon the size of the patient, and is recommended for adequate exposure with minimal retraction.

1.6 Minilaparotomy cholecystectomy

It is likely that many surgeons over the years have used small incisions for performing open cholecystectomy. However the first published report of minilaparotomy cholecystectomy was by Dubois in 1982 [1]. He used a transverse incision 3 to 6 cm long in a series of 1500 cholecystectomies out of a total of 1800 cholecystectomies over a 10 year period. Further reports over the last decade were made by Goco [2,56], Morton [57], Merrill [3], O'Dwyer [5], O'Kelly [6], and Moss [58,59]. In essence, the technique is simply an open cholecystectomy limited to an incision of 4-6 cm, but the surgeons's hand does not enter the abdomen at any stage. A number of aids to the procedure have been described. The use of a headlight may be helpful to provide additional lighting through the incision which resembles a well [5]. Russell and Shankar recommended the use of a stabilized ring retractor with a variety of fixed and malleable blades to provide accurate, fixed retraction [60]. In elderly patients, the rectus muscle may be split along its fibres [5] or retracted medially [61], although in younger patients this does not usually provide adequate exposure. A fundus first dissection technique is often easier in minilaparotomy cholecystectomy. The minilaparotomy cholecystectomy technique is undoubtedly technically demanding, and many surgeons find the restricted access difficult. Obesity, which is common in this patient group, makes the procedure even more difficult, and often the incision requires to be extended [5].

1.7 Laparoscopic cholecystectomy

Diagnostic laparoscopy was first performed in a dog by Kelling using a cystoscope in 1901[62], and in humans by Jacobeus in 1911 [63]. In the 1930s, a spring-loaded needle designed by Veress for therapeutic pneumothorax, was modified for the safe introduction of gas into the abdomen. Gynaecologists in Europe began to use laparoscopy regularly for diagnosis and tubal diathermy in the 1960s. Semm developed instruments and techniques for gynaecological procedures and in 1983 performed the first laparoscopic appendicectomy [64].

Laparoscopic cholecystectomy was first performed in March 1987 by Philipe Mouret, a French surgeon, with experience in gynaecological laparoscopic procedures [65]. After hearing about the method, Dubois began performing the technique in May 1988, reporting the results of his first 36 procedures a year later [66,67]. Perissat was also a key figure in the early development of the technique in France [68-70]. Word of the technique spread rapidly. Reddick and Olsen introduced the technique to the United States, performing their first case in September 1988 [71], and comparing its outcome with minilaparotomy [72]. The technical development which allowed the procedure to become widespread was the small video camera, allowing the operation to be viewed on a televison screen. By 1990, it was estimated that over 2500 procedures had been performed world-wide [73], and by September 1991, there had been more than 14 reported series totalling 3225 operations [74].

The rapid development and introduction of laparoscopic cholecystectomy into routine practice as the preferred technique of cholecystectomy is unprecedented in the history of surgical procedures. Laparoscopic cholecystectomy was introduced into routine practice before full evaluation, and certainly before any controlled data were available. The rush to adopt the technique was driven firstly by equipment manufacturers and health care

providers through advertisements and promotions, and secondly by consumers who had been convinced, by media coverage, that the method had significant proven advantages [75]. The enthusiasm for the laparoscopic technique has spread to encompass the whole of surgical gastroenterology, with many surgeons attempting virtually every conceivable abdominal operation by the laparoscopic technique.

1.8 Comparison of laparoscopic and open cholecystectomy

Many of the reported series on laparoscopic cholecystectomy are difficult to compare to those on open cholecystectomy because patients in laparoscopic series are a selected subgroup of patients. They are younger, have less severe biliary disease than those requiring emergency surgery, and patients with possible common bile duct stones are often excluded. Operations are usually performed by surgeons performing large numbers of cases [32,76,77] unlike open cholecystectomy, in which many operations are performed by surgeons performing fewer cases or surgeons in training [78-80]. In addition, the accuracy of the data from large, multi-centre reports 77,81 has been questioned [82-84]. Also, it is a well recognised fact that publication bias occurs in the reporting of a new procedure with serious complications and bad results less likely to be reported [85].

1.9 Bile duct injury

Bile duct injury during cholecystectomy is undoubtedly a catastrophic event that can lead to significant long-term morbidity (recurrent stricture, cholangitis, reoperation, cirrhosis, and premature death) [86]. It is difficult to calculate accurately the incidence of bile duct injuries after open or laparoscopic cholecystectomy for three reasons: firstly because it is an uncommon problem, secondly beacuse of under-reporting and thirdly, because of variations in the precise definition of what constitutes a bile duct injury. A small longitudinal

tear, which is immediately repaired by primary suture or insertion of a T tube has a quite different prognosis from complete division of the bile ducts above the bifurcation, which goes unrecognised, and is repaired at a delayed interval.

The incidence of bile duct injury in reported series of open cholecystectomy is shown in Table 1.1 [78,79,87-97]. The average incidence was only 0.2%. The series reported by Roslyn *et al.* [94] was a retrospective audit using information from computerized discharge data from all hospitals in California and Maryland in 1989. The 91 patients in this series with possible bile duct injury (0.21%) included patients with laceration of the gastrointestinal tract or a biliary fistula, and the authors therefore concluded that this was likely to be an overestimate of the true bile duct injury rate. Only one of the eight other bile duct injuries reported in the series shown in Table 1.1 required biliary reconstruction; the remaining seven were managed by T tube insertion (two), peritoneal drainage (three), suture of the laceration (one), and stricture dilatation (one). Although, intuitively, it might be thought that minilaparotomy cholecystectomy might result in more bile duct injuries because of the restricted access, in the published results for over 2500 cases [1-7,57,60,86,98-100] there have been only two bile duct injuries, one requiring hepaticojejunostomy [98], and the other, a 2mm longitudinal laceration of the common bile duct, requiring only T tube insertion [6].

Several early reports [32,101], some some of which were anecdotal [102-105], found that laparoscopic cholecystectomy was associated with an increased bile duct injury rate compared to open cholecystectomy. In a series of 400 operations [32], Troidl *et al.* reported 4 bile duct injuries (1%), one of which resulted in death. Traverso reported 17 common bile duct injuries (2.8%) in a series of 597 operations [104]. In a series of 264 laparoscopic cholecystectomies performed in 10 hospitals in the south-east of England,

Author of series (ref.)	Period (years)	Number of patients	Bile Duct Injuries n	(%)
Vanderpool [87]	1976-85	360	0	0.00
Ganey [88]	1978-83	1,035	0	0.00
Warwick [89]	1982-90	384	0	0.00
Clavien [90]	1984-89	1,088	0	0.00
Davies [91]	1985-90	630	0	0.00
Saltzstein [92]	1988-90	500	0	0.00
Herzog [93]	1984-90	1,357	1	0.07
Morgensten [78]	1982-88	980	2	0.20
Cox [94]	1985-89	457	1	0.21
Roslyn [95]	1989	42,474	91	0.21
Raute [96]	1972-91	7057	16	0.22
Harte [97]	1973-78	390	1	0.26
Gilliland [79]	1982-87	671	3	0.45
TOTAL		**57,383**	**115**	**0.20**

TABLE 1.1 Bile duct injury rate in reported series of open cholecystectomy.

there were 5 bile duct injuries (1.9%), 4 of which required hepaticojejunostomy [103].

Lord Smith of Marlow reported his findings from interviewing biliary surgeons attending the American College of Surgeons in 1991 [102]. All surgeons interviewed reported that bile duct injuries from laparoscopic cholecystectomy were occurring out of all proportion to that encountered at open cholecystectomy. From the first 4 surgeons interviewed, Lord Smith "gleaned" more than 30 bile duct injuries. He went on to comment that for the non-specialist occasional cholecystectomist "laparoscopic cholecystectomy was a recipe for disaster - a keyhole scar and catastrophy within". These increased risks of laparoscopic cholcystectomy have received coveraged in the national press [106]. Specialist hepatobiliary units on both sides of the Atlantic have reported a dramatic increase in the number of referrals for the management of bile duct injuries [103,107-112].

Most single centre series of more than 300 laparoscopic cholecystectomies have reported a bile duct injury rate less than 0.4%, with an average of 0.26% [96,113-128], although two series reported a incidence of 1% or more [32,129] (Table 1.2). By contrast, nine out of sixteen multicentre audit series found a bile duct injury rate greater than 0.4%, with an average of 0.5% [29,76,77,81,130-137] (Table 1.3). Two factors may explain this apparent discrepancy. Firstly, it is a well recognised fact that publication bias occurs in the reporting of a new procedure with serious complications and bad results less likely to be reported [85]. Secondly, the single centre series are reported by surgeons who have performed large numbers of procedures, and are therefore far up the "learning curve", whereas the majority of surgeons in audit series are probably still on the "learning curve".

Author (ref. no.)	n	Bile duct injuries	
		n	%
Ko [113]	300	0	0.00
Nottle [164]	308	0	0.00
Fitzgibbons [165]	350	0	0.00
Wilson [117]	350	0	0.00
Wolfe [118]	381	0	0.00
Taniguchi [128]	600	0	0.00
Lane [123]	641	0	0.00
Baird [125]	800	0	0.00
Graffis [126]	900	0	0.00
Raute [96]	1,022	0	0.00
Barkun [166]	1,300	5	0.38
Soper [124]	647	1	0.15
Clair [121]	514	1	0.19
Brown [120]	474	1	0.21
Berci [119]	418	1	0.24
Davis [122]	622	2	0.32
McGee [127]	950	3	0.32
Graves [114]	304	1	0.33
Perissat [167]	700	3	0.43
Troidl [32]	400	4	1.00
Kozarek [129]	597	11	1.84
TOTAL	**12,578**	**33**	**0.26**

TABLE 1.2 Bile duct injury rate in reported series of laparoscopic cholecystectomy with more than 300 patients.

Author	Place	Number of patients	Bile Duct Injury n	%
Litwin [130]	Canada	2,201	3	0.14
Airan [131]	USA	2,671	5	0.19
Larson [76]	USA	1,983	5	0.25
Deveny [132]	Oregon state	9,597	27	0.28
Dunn [133]	England	2,131	6	0.28
Orlando [29]	Connecticut State	4,640	15	0.32
Cuschieri [77]	Europe	1,236	4	0.32
Ref. [133]	Switzerland	1,091	5	0.46
Meyer [81]	USA	1,518	7	0.46
Deziel [134]	USA	77,604	365	0.47
Gigot [136]	Belgium	3,244	16	0.49
Fullarton [135]	Scotland	1,655	11	0.66
Suc [136]	France	3,606	25	0.69
Go [137]	Netherlands	6,076	52	0.86
Ref. [133]	Japan	2,888	26	0.90
Ref. [133]	Singapore	1,100	10	0.91
TOTAL		**123,241**	**582**	**0.47**

TABLE 1.3 Bile duct injury rate in multicentre audit series of laparoscopic cholecystectomy with more than 1,000 patients.

There is substantial evidence to suggest that the learning curve has contributed to the high rates of bile duct injury. In the Southern Surgeons Club series, the bile duct injury rate in the first 13 patients operated on by each surgical group was 2.2%, as compared with 0.1% for subsequent patients [81]. In the national survey of United States hospitals [134], the average bile duct injury rate was 0.65% in hospitals with less than 100 laparoscopic cholecystectomies performed compared with 0.42% at hospitals with more than 100 performed. Similarly, in the Connecticut state audit [29], half of the bile duct injuries had occurred in the surgeon's first 10 cases, a third in the surgeon's 11th to 50th case, and only an eighth of injuries occurred after the 50th case. Of 17 biliary injuries or leaks reported by Kozarek [129], 13 occurred within the first 20 procedures performed by the surgeon.

Learning curve aside, it is still generally acknowledged that the common bile duct is more at risk during laparoscopic cholecystectomy than open cholecystectomy [107-110]. This is because cephalad traction on the fundus compresses Calot's triangle while lateral traction on Hartmann's pouch tents up the common bile duct, which is then mistaken for the cystic duct, especially when the cystic duct is very short. The classic pattern of laparoscopic injury is resection of a portion of the common and hepatic ducts, and an associated right hepatic artery injury [107-109]. The injuries at laparoscopic cholecystectomy [107-109] tend to be more extensive and higher in the duct system involving the bifurcation (Bismuth Grade 3 and 4) than open cholecystectomy, thus reducing the chance of a successful outcome to reconstruction [86].

1.10 Bile leak

Bile leak after cholecystectomy may result in an intrabdominal collection, a biliary fistula, or biliary peritonitis, which is a life threatening complication. It may may arise from three sources: the cystic duct, a subvesical bile duct (duct of Luschka [128,138]), or a bile duct injury (the latter usually being considered separately in classsification of complications). The subvesical duct of Luschka is a slender duct 1-2 mm in diameter passing from the right lobe of the liver in the gallbladder fossa to join the right hepatic or common hepatic duct [138-141]. Because of its position and small size, it is particularly vulnerable during cholecystectomy [138]. Anatomical studies using resin casting, dye injection, and histology of cadaver livers have shown that a subvesical duct is present in about 30-50% of patients, although using endoscopic retrograde or operative cholangiography it can only be detected in 1.3% of patients [128].

The incidence of bile leaks after open cholecystectomy varies considerably amongst reports. In several recent large audit series of open cholecystectomy, there were no reports of bile leak [79,87,89,92,93,97,142]. Clavien reported four (0.3%) bile leaks requiring re-operation in a series of 1,252 open cholecystectomies. Morgenstern reported 6 (0.5%) bile leaks resulting in fistulae in a series of 1,200 cholecystectomies, but all six resolved spontaneously. In a series of 196 cholecystectomies in which routine drainage of the gallbladder bed was used for an average postoperative of six days, bile was noted in the drain fluid in 19 (10%) cases, but only one (0.5%) required a second procedure [138]. The source of bile leak after open cholecystectomy is often not positively identified but cystic duct leak is thought to be extremely rare.

Bile leak is reported with greater frequency after laparoscopic cholecystectomy [32,121,129,137,143]. Wolf *et al.* [118] reported 5 (1.3%)

clinically significant postoperative bile leaks in a series of 381 laparoscopic cholecystectomies; 4 were from the cystic duct, of which 3 required operation. Peck [105] reported 9 (1.9%) bile leaks in a series of 482 laparoscopic cholecystectomies, 6 of which were from the gallbladder bed. Walker reported 7 (2.7%) bile leaks in a series of 264 procedures [143].

There are a number of reasons why laparoscopic cholecystectomy may be associated with a greater risk of a bile leak. Clips rather than ties are used for the cystic duct. Cystic duct leak may occur because a clip becomes dislodged [144], because a clip does not completely traverse the duct, or because electrocautery injury results in delayed tissue necrosis of the cystic duct. In laparoscopic cholecystectomy, the gallbladder is usually dissected from the liver bed by the use of diathermy, whereas in open cholecystectomy, it is usually done by blunt or sharp dissection. It is possible, therefore, that the subvesical duct is at greater risk of accidental damage during laparoscopic cholecystectomy because of the depth of thermal injury caused by the use of electrocautery dissection.

1.11 Per- and Postoperative Haemorrhage

Significant haemorrhage may occur during or after a difficult open cholecystectomy [78,94,95], although in several large series there were no reports of major bleeding [79,88,91,142]. Significant haemorrhage has been reported more frequently with laparoscopic cholecystectomy [32,76,94,115,120,122]. In Cuschieri's initial series of 60 procedures, two patients required postoperative transfusion [145], and in Troidl's series of 400 patients, four had major haemorrhage [32]. Haemorrhage during laparoscopic cholecystectomy is more difficult to control, as direct compression is not possible, suction removes the pneumoperitoneum, and spurting blood may obscure the telescope lens. "Blind" diathermy or clipping in an attempt to

stop bleeding is said to be one of the causes of the increased incidence of bile duct injury during laparoscopic cholecystectomy [107,108]. In addition to bleeding from the cystic artery, hepatic artery or liver bed, bleeding may also occur from inadvertent injury to the epigastric artery, major vessels, solid organs, mesentery or omentum.

1.12 Problems related to laparoscopy

Laparoscopic cholecystectomy carries additional risks over open cholecystectomy which are intrinsic to the technique of laparoscopy. The most catastrophic and most feared complication of laparoscopy is injury to the major retroperitoneal vessels. In gynaecological series, the incidence of this is between 3-10 per 10,000 closed laparoscopies [146-148]. While the development of disposable trocars with spring-loaded safety shields and improvements in technique may have reduced the risk of this potentially fatal complication, reports on laparoscopic cholecystectomy indicate that they do not prevent it [121,134,149,150]. One reason for this is that the external safety shield of the trocar is often held back by a loose layer of peritoneum after it has entered the abdomen, leaving the sharp trocar exposed [149]. In a survey throughout the United States, 36 major retroperitoneal vessel injuries (three of which resulted in death) were reported in a series of 77,604 laparoscopic cholecystectomies, an incidence of 5 per 10,000 [134]. These injuries were attributed mainly to trocar insertion. On the other hand, the 35 injuries to other intra-abdominal vessels (incidence 5 per 10,000) were atttributed mainly to Verres needle insertion. Vascular injury at the time of insertion of additional trocars should never occur, as these can be inserted under direct laparoscopic vision. Major vascular injury can be completely eliminated by routine use of open laparoscopy. Penfield reported no vascular injuries in almost 11,000 open laparoscopies performed by eighteen gynaecologists in the United States [151].

Another serious complication of closed laparoscopy is hollow viscus perforation [148]. Perforation of the small bowel, colon, stomach, bladder, uterus, and ureter have all been reported. In the American survey of laparoscopic cholecystectomy previously alluded to, 109 bowel injuries (five of which were fatal) were reported, an incidence of 0.14% [134], which is similar to the incidence found in gynaecological experience [152]. These injuries, which are typically unrecognised at the time of operation, often present late with peritonitis, intra-abdominal abscess, or enterocutaneous fisula [134], and may result in death [118]. While bowel laceration can occur with open laparoscopy (six in 11,000 [151]), the major advantage this method has is that accidental perforation is usually recognised and can be repaired at the time of laparoscopy (four out of six [151]).

An exceedingly rare but potentially life-threatening complication of laparoscopy is gas embolus, which occurs in less than 1 in 10,000 procedures [153-155]. It is usually secondary to accidental intravascular injection of carbon dioxide during insufflation through a misplaced Veress needle, but has also been reported as a result of accidental placement of an air-cooled laser tip into a vessel [156]. Another rare complication resulting from peritoneal insufflation is a tension pneumothorax, which is usually due to a congenital defect of the diaphragm (a patent pleuroperitoneal canal) [157] although accidental perforation of the diaphragm by the gallbladder-retracting forceps is another cause [158].

Another avoidable complication of either open or closed laparoscopy is herniation of omentum [125] or bowel [76,137,159-161] through the laparoscopic trocar site, which may result in small bowel obstruction [76,159-161]. This is more likely to happen when the trocar site is enlarged to remove, for example, the gallbladder at laparoscopic cholecystectomy, and should always be accompanied by suture closure of the fascial defect.

1.13 Operative mortality

Open cholecystectomy has an excellent safety record. In a detailed analysis of mortality after all elective cholecystectomies performed in Denmark from 1977 to 1981 (13,854 patients), the mortality for elective cholecystectomy in patients under 50 years was 0.02%, in patients 50-70 years old it was 0.47%, and in patients over 70 it was 2% [162]. In an audit of all open cholecystectomies (42,474) performed in the two States in America in 1989, the mortality rate in those under 65 years of age was 0.03%, while in those over 65 years of age it was 0.5% [95]. Six recent large reports with a total of 3,630 patients, reported no deaths [79,87,90,92,94,97]. In five other recent reports with a total of nearly 5,000 patients [78,88,89,91,93], there were no deaths thought to be due to technical complications (such as common bile duct injury, bile leak, haemorrhage, or bowel injury) . Deaths after cholecystectomy are usually related to the severity of the biliary disease (e.g. biliary peritonitis, severe pancreatitis, jaundice with cholangitis), concomitant medical problems (cardiovascular and respiratory disease, cirrhosis, and diabetes), and advanced age [78,80,88,89,91,93,162,163].

The mortality rate in most series of laparoscopic cholecystectomy is very low. In the multi-centre audit reports [29,76,77,81,130-132,134-137], totalling over 100,000 patients, the overall mortality rate was less than 0.1% (Table 1.4). A statewide report from Connecticut found that the overall mortality rate associated with cholecystectomy fell in 1991 after the introduction of laparoscopic cholecystectomy [29]. This was partly due to a 29% increase in the frequency of cholecystectomy with the advent of the laparoscopic procedure. Nevertheless, the overall number of deaths from cholecystectomy did not increase after the introduction of the laparoscopic procedure. However, the worrying finding is the reporting of a significant number of deaths as a result of technical complications: haemorrhage [29,134,137],

Author	Place	Total No. of Patients	Deaths		Iatrogenic Deaths	
		n	n	%	n	%
Cuschieri [77]	Europe	1,236	0	0	0	0.00
Litwin [130]	Canada	2,201	0	0	0	0.00
Deveny [132]	Oregon state	9,597	4	0.04	2	0.02
Deziel [134]	USA	77,604	33	0.04	18	0.02
Meyer [81]	USA	1,518	1	0.07	0	0.00
Larson [76]	USA	1,983	2	0.10	0	0.00
Airan [131]	USA	2,671	3	0.11	1	0.04
Go [137]	Netherlands	6,076	7	0.12	5	0.08
Orlando [29]	Connecticut State	4,640	6	0.13	3	0.06
Suc [136]	France	3,606	6	0.17	0	0.00
Fullarton [135]	Scotland	1,655	8	0.48	2	0.12
TOTAL		**106,711**	**63**	**0.06**	**26**	**0.02**

TABLE 1.4 Mortality in audit series of laparoscopic cholecystectomy.

bile duct injury [29,32,132,134,137], bile leak [32,137], and bowel injury [131,134,160]. In Deziel's national survey of laparospic cholecystectomy at American hospitals, 18 of the 33 postoperative deaths were related to iatrogenic operative injury [134] and in the other multi-centre audit series there were a further eight deaths related to technical complications (Table 1.4).

In summary, open cholecystectomy has a very good safety record, with deaths being related complications of cholelithiasis, concomitant medical problems and advanced age. While the overall mortality rate from laparoscopic cholecystectomy is very low, the deaths resulting from iatrogenic complications gives cause for concern. It remains to be seen whether the incidence of iatrogenic deaths will diminish as the the experience of surgeons with the laparoscopic technique increases.

1.14 Common Bile Duct Stones

Patients with common bile duct (CBD) stones may be divided into two groups according to presentation: firstly, patients who present primarily with signs or symptoms (jaundice, cholangitis or pancreatitis) believed to be caused by stones in the CBD; secondly, patients who present with symptoms related to stones in the gallbladder but have CBD stones detected by preoperative or operative cholangiography. Criteria requiring that pre-operative or per-operative cholangiography be performed are a history of recent jaundice, raised liver enzyme levels or dilatation of the CBD on ultrasonography [166,168].

Ductal stones found by cholangiography during open cholecystectomy can be easily dealt with by CBD exploration. Operative cholangiography is technically more difficult during laparoscopic cholecystectomy than during open operation, and although success rates of 90% have been achieved

[145,169,170], most authors report rates below 50% with technical failure rates of 10-25% [81,114,171], and more than half of surgeons in the UK never perform operative cholangiography during laparoscopic cholecystectomy [172]. Therefore, laparoscopic cholecystectomy patients with suspected CBD stones (abnormal liver function tests and/or dilated CBD on ultrasound) should be screened pre-operatively by intravenous cholangiogram (IVC) [128,173] or endoscopic retrograde cholangiography (ERCP) [128,166,168,174].

Although laparoscopic common bile duct (CBD) exploration by the trans-cystic duct [175,176] or choledochotomy route [175,177] have been described, these methods still require to be fully evaluated. Most centres now choose to treat patients with CBD stones by pre-operative ERCP, endoscopic sphincterotomy (ES) and duct clearance before proceeding to laparoscopic cholecystectomy [166,168,178,179]. The mortality rate of ERCP, ES and duct clearance is around 1% [180-183]. Exploring the bile duct during open cholecystectomy seems to add little to the risk of death in patients aged under 60 (mortality 0.3%), but it is associated with an increase mortality in patients aged over 60 (mortality 4%) [162]. Though the overall mortality (1%), morbidity (8%), and duct clearance rate (90%) associated with endoscopic treatment of CBD stones is comparable with that associated with open exploration of the bile duct, the endoscopic complications are largely independent of age [180-183]. Thus patients at low risk from open surgery (aged under 60) who undergo laparoscopic cholecystectomy and endoscopic treatment of common duct stones may suffer greater morbidity and mortality than they would if they underwent open operation [184].

1.15 Postoperative Pain and Pulmonary Function

Open cholecystectomy without the use of postoperative regional anaesthesia results in significant postoperative pain [53,54,185-188]. This results in an altered pattern of breathing to minimize wound discomfort: coughing and diaphragmatic breathing is inhibited [189], abdominal and lower intercostal muscles undergo reflex spasm [190], and breathing becomes shallow and rapid, with loss of sighing [191]. This abnormal breathing pattern results in a substantial reduction in pulmonary function [53,54], and closure of small airways, which causes intrapulmonary shunting and hypoxaemia [192]. Anaesthetic agents and opiates may also induce prolonged hypoventilation [193] or episodes of obstructive sleep apnoea [194] resulting in oxygen desaturation in the postoperative period.

An oblique [54] or transverse [53] subcostal incision has been shown to result in less postoperative pain, and better pulmonary function than a midline incision for cholecystectomy. Furthermore, a small randomised trial has demonstrated that a 5-8 cm minilaparotomy incision results in less reduction in postoperative pulmonary function than a 15-20 cm subcostal incision [195].

A number of small studies have compared postoperative pain and/or pulmonary function after laparoscopic and standard open cholecystectomy [195-203], but all except one [195] of these studies were non-randomised, and several used historical controls [196,197,201,203]. Laparoscopic cholecystectomy resulted in better pulmonary function [195,199-202], lower pain scores [197,202], and lower opiate analgesic requirement [196,201-203] than standard cholecystectomy. However, since these studies were not randomised, the results could have been subject to selection bias. Furthermore, as analgesics were given on nurses' assessment of pain, rather than a patient controlled device, there was a danger of observer bias.

Three small randomised trials have compared postoperative pain and/or pulmonary function after minilaparotomy and laparoscopic cholecystectomy [98,99,195]. Laparoscopic cholecystectomy resulted in better postoperative pulmonary function [98,195], lower analgesia requirement [99], and lower pain scores [98] than minilaparotomy cholecystectomy. Although one study found no statistically significant difference in pain scores between the groups [99] and another found no difference in analgesia requirements [98], these may have been false negative findings due to the small numbers in these studies. Intuitively, the laparoscopic technique might therefore be associated with a lower risk of pulmonary complications. However, in recent published series of open cholecystectomy the incidence of significant pulmonary complications was less than 1% [78,79,88,142].

Wound pain, postoperative pulmonary function, arterial oxygen tensions, and the incidence of pulmonary complications after open cholecystectomy can all be substantially improved by either intercostal [194] interpleural [186,187] or thoracic epidural [185,188] bupivacaine. However, intercostal and interpleural blocks carry a small but significant risk of pneumothorax, and all three methods carry a significant cost due to increased time in the theatre. Hence, they are not widely used after cholecystectomy.

1.16 Recovery after Cholecystectomy

The principal advantage of laparoscopic over open cholecystectomy is said to be reduced hospital stay, and recovery period. Hospital stay after cholecystectomy is dependent on the severity and duration of postoperative pain and the time to resume oral fluids and diet. Additional factors are patients' social circumstances, and pre-conceived expectations of the "normal" duration of convalescence. Hospital stay for open cholecystectomy has been falling over the past decade and now averages six days in the British Isles [197,204]

while in the United States it is four days [95,203]. Several American studies have reported even shorter average postoperative hospital stays of 3.2 days [205], 2.8 days [92], 2.5 days [206], 1.5 days [207], and 24 hours [58,59]. Factors claimed to help reduce the length of hospitalization after open cholecystectomy are wound infiltration with bupivacaine, avoidance of the use of drains, early resumption of oral intake of fluids and diet, and early mobilization [59]. The time to return to normal activity after standard cholecystectomy has not been well documented but is commonly believed to be about five [203] to six [205] weeks.

Several authors have reported that minilaparotomy cholecystectomy results in a shorter hospital stay and postoperative recovery period than standard cholecystectomy [1-5,57-60,208]. In many minilaparotomy series [3,5,60,72,99], the hospital stay was three to four days, and the time to return to normal activities three to four weeks. Ledet reported a series of 200 consecutive minilaparotomy cholecystectomies performed as day case procedure, with the time to return to work being four to five days for those in sedentary jobs, and 21 days for those in heavy manual work (sometimes sooner for those allowed a light duty status by their employer) [4]. Goco and Chambers reported an average hospital stay of 1.2 days in a series of 450 consecutive minilaparotomy cholecystectomies [2] with average time to return to work of 18 days [56].

The average postoperative hospital stay reported after laparoscopic cholecystectomy ranges from 1 to 4.8 days [29,32,77,81,130,135-137,197,203,205,209]. In many single centre series from the United States, the postoperative average stay was one day with some patients discharged on the day of operation [114,119,120,124,125,165,203]. By contrast, the average postoperative stay in a state wide audit was 3.1 days, and in four large audit

series from Europe it was 3 [77], 3.5 [137], 4 [135], and 4.8 [136] days. The median time taken to return to work or normal activity ranges from 5 to 14 days with an average of about 10 days [32,77,104,108,115,117,120,124,203]. While these results are substantially better than most surgeons experienced with open cholecystectomy, they are similar to the results mentioned above after minilaparotomy cholecystectomy. Both hospital stay and return to work are heavily influenced by social circumstances, cultural normals and the surgeon's and patient's pre-conceived expectation about a "normal" duration of convalescence: they are very subjective and variable indicators. In a report comparing recovery after laparoscopic cholecystectomy in America to that in France, patients in sedentiary occupations returned to work after 10 days in America, compared to 28 days in France [210].

1.17 Cost

Cholecystectomy is one of the most common elective surgical operations, with approximately 50,000 performed per year in the UK, and 600,000 per year in the United States. Therefore, the costs of the different methods of cholecystectomy have major implications for health economics. As a cause of hospitalization, gallstones are the most common and most costly digestive disease, with an annual estimated overal cost of more than $5 billion in the United States [21].

The two main factors determining the cost of a hospital admission for cholecystectomy are the theatre time and hospital stay [211]. Laparoscopic cholecystectomy is associated with extra costs due to equipment, disposable instruments, and longer operating time than open cholecystectomy [99,203] but result in savings from reduced hospital stay. The estimated cost of laparoscopic cholecystectomy varies greatly depending on the operative time, whether disposable trocars and instruments are used, and whether

emergency/urgent procedures are included whereas variations in the estimated cost of open cholecystectomy depend on the hospital stay.

Until recently, before resource management units have been introduced throughout the National Health Service, comparison of the costs of different treatments was almost impossible. As a result some have applied a simplistic approach of dividing all hospital costs by the total number of patient bed stay days, to derive a cost per patient per day. Using such a simplistic approach, Grace *et al.* [209] suggested that the laparoscopic method more than halved the cost of cholecystectomy (Ir£895 versus Ir£2210) , while Attwood *et al.* [197] suggested it reduced costs by about 30% (£1450 versus £1030). Two British studies using more detailed resource management information have compared the cost of laparoscopic and open cholecystectomy, although both were non non-randomised [212,213], and one used historical data for open cholecystectomy with a mean hospital stay of 10 days [213]. In the first of these studies, in which open cholecystectomy hospital stay was 6.5 days [212], laparoscopic cholecystectomy was found to be marginally more expensive when disposable instruments were used, while the second study, laparoscopic cholecystectomy was marginally cheaper, even allowing for the extra cost of disposable instruments [213].

A statewide analysis in Connecticut [29] and a reported from a large private practice-based health maintenance organization in America [30] both found that the introduction of laparoscopic cholecystectomy had reduced the average cost of cholecystectomy by 25%. The average hospital stay for open cholecystectomy in these studies was nine [29] and six [30] days. By contrast, two American studies, in which average hospital stay for open cholecystectomy was less than three and a half days, found that the cost for laparoscopic cholecystectomy (surgeons' fees and hospital charges) was

about 25-33% more than standard open cholecystectomy [205,214]. Surgeons in the United States have increased professional fees for cholecystectomy by the laparoscopic method [215], but an additional cost to the American surgeon performing laparoscopic cholecystectomy is the higher malpractice insurance premium [215], reflecting the high incidence of technical complications. The increased used of endoscopic retrograde cholangiography both pre- and post-operatively [128,179,216,217] represents a hidden cost from the introduction of laparoscopic cholecystectomy .

As alluded to in section 1.2, the introduction of laparoscopic cholecystectomy has resulted in a lowering of the symptom threshold for cholecystectomy, with many surgeons perfoming cholecystectomy on asymptomatic patients with cholelithiasis [31,32]. Hence, even if the average cost of cholecystectomy is reduced by the laparoscopic method, total costs for health care organisations and the health service resulting from cholecystectomy are likely to be higher because of an increase in the number of cholecystectomies performed. The report from a private practice-based health maintenance organization in America found a 60% increase in the cholecystectomy rate after the introduction of laparoscopic cholecystectomy. Hence, although the unit cost of cholecystectomy fell by 25%, the total expenditure on gallbladder disease increased by 11%. The statewide analysis in Connecticut found that from 1989 to 1991, the cholecystectomy rate increased by 30%, and total expenditure on cholecystectomies increased from $60 million to $90 million.

The increased used of endoscopic retrograde cholangiography [128,179,216-218] both pre- and post-operatively to screen for common bile duct stones represents another hidden cost from the introduction of laparoscopic cholecystectomy.

1.18 Randomised Trials in Surgery

It is vital that the efficacy of all new medical interventions be judged on the highest quality of evidence, and that they be compared with the currently accepted method(s), in order to save current and future patients from the therapeutic passions of clinicians developing new treatments. The greater the scale of intervention, the more irreversible the consequences of such invasions, then the greater is the entitlement of the public to unequivocal evidence. There is a hierarchy in the cogency of evidence that may be adduced in defence of medical interventions [219]. Of lowest order is the anecdotal case report. Higher than this would rank case series without controls or series with controls from published papers. Higher still might be comparisons with computer data bases or case-controlled observational studies; and the summit of the pyramid is the randomised controlled clinical trial.

Randomisation avoids bias in treatment allocation - prognostic factors, whether known or unknown, tend to be balanced between treatment groups. Thus, randomisation guarantees the validity of statistical tests of significance. In nonrandomised studies, on the other hand, chance or bias can result in the selection of patients for innovative treatment who are either the least diseased or the most severely affected. Depending on the case mix, a treatment that has no effect can appear to be effective or toxic when historical controls are used. With improvement in diagnostic accuracy and the understanding of disease that has occurred with the passage of time, today's patients are identified earlier in the natural history of their disease. Recently selected case series therefore often have patients who are less ill and an outcome that is considerably better than that of past case series, even without changes in treatment.

The first randomised controlled trial, inspired by Bradford Hill and conducted by the Medical Research council was reported in 1948 and evaluated streptomycin in the treatment of pulmonary tuberculosis [220]. The first randomised controlled trial in surgery, which compared vagotomy with gastroenterostomy or antrectomy versus subtotal gastrectomy in the elective treatment of duodenal ulcer, was reported by Goligher in 1964 [221]. This report spurred surgeons all over the world to conduct randomized controlled trials but it is still true that most clinical reseach in surgery relies on comparisons with historical or contemporary non-random controls [222].

Randomised controlled trials are ideally suited to the testing of new drugs because the trial can usually be double-blind and placebo controlled. Objective testing of this rigour is is an absolute necessity before any new pharmaceutical product is released by the Committee of Safety of Medicines (CSM) in the UK and the Food and Drug Administration (FDA) in the USA. By contrast, "blinding" of the surgeon can never be achieved, and can only sometimes be achieved for the assessor and the patients. Recruitment for surgical trials is usually slower than for many drug trials and financial support is frequently more difficult to raise, so that it is more difficult to mount trials of sufficient size to produces clear results.

Historically, the introduction of new surgical procedures result from the initiative of individual surgeons, and the new technique was usually tested by comparing the results with historical controls. The history of surgery is littered with examples of surgical practice where less rigorously evaluated procedures have been found to be ineffective. Examples are the Halsted radical mastectomy [223], gastric freezing for peptic ulceration, carotid body denervation for bronchial asthma, prophylactic porto-caval shunt in patients with oesophageal varices, and periarterial sympathectomy [224].

Nevertheless, randomised controlled trials are used less frequently in the evaluation of surgical procedures for several, at least partly valid, reasons. One of the principal determinants of surgical outcome is the skill and experience of the surgeon. This factor has been highlighted in two major studies of outcome of surgery for large bowel cancer [225,226]. Surgical experience, a strong variable determining outcome, is inevitably going to be greater for the standard method and therefore not directly comparable with that for the new technique, particularly during any learning curve. Further bias accrues in that new surgical techniques are usually introduced by enthusiastic and skilled surgeons whereas the standard technique is practised by all surgeons in that specialty. There is no statutory control over the development and introduction of new operative techniques. As a result, new surgical techniques are introduced to clinical care much earlier than is the case for new drugs. Difficulty then arises in deciding when a randomised trial should be commenced. Chalmers has argued strongly for randomisation of the first patient [227]. This seems impractical [228]. Since there is a learning curve for each new operation, randomisation of 'the first patient' to a new procedure would introduce selective bias against it. The investigator must be allowed to exercise judgement about the earliest possible point at which a randomised controlled trial can begin. An example of starting a trial too early in the development of an operation was the Veterans Administration trial of coronary artery bypass surgery, which was criticized because the poor early operative results did not reflect current experience [229].

One of the theoretical prerequisites for the conduct of a randomised controlled trial is that a state of "clinical equipoise" exists [230]. That is to say, that on the available data, neither treatment arm of a study should be established as preferable to the other [231]. The principal objection to a randomised controlled trial of laparoscopic cholecystectomy, has been that surgeons' early

experiences of laparoscopic cholecystectomy have been so favourable in terms of less postoperative pain, rapid hospital discharge, and rapid return to normal activity that they felt the benefits of the procedure were obvious. Maybe partly as a result of the the glamour of the new technology (miniature video cameras, lasers etc.), the media has taken considerable interest in the new technique of laparoscopic cholecystectomy, and portrayed the keyhole procedure as having huge advantages over the "old-fashioned" standard procedure. This has meant that patients have come demanding the new operation. It is not surprising, therefore, that there has been no randomised trials comparing laparoscopic and standard open cholecystectomy.

1.19 Results of Randomised Trials of Laparoscopic versus Minilaparotomy Cholecystectomy

Two small randomised trials comparing laparoscopic and minilaparotomy cholecystectomy were published in 1992, one from Germany [98], and one from Canada [99].

German Study

A randomised trial of laparoscopic versus minilaparotomy cholecystectomy has been recently reported in the German literature [98]. In this study, only 77 patients out of a total of 325 cholecystectomies performed during the one year study period were randomised. Pain scores were significantly lower in the laparoscopic group on the first three postoperative days. Forced vital capacity was significantly better in the laparoscopic group on the first two postoperative days, but by the third day pulmonary function in the two groups was similar. However, the difference in analgesia rquirement between the groups was not significant. This was probably due to the small size of the study and the method of assessment: two analgesics were used and analgesia requirement was not patient-controlled. Even though all patients were kept in

hospital a minimum of 3 days as part of the postoperative assessment, hospital stay was significantly shorter in the laparoscopic group (3.5 versus 5.8 days). One major complication occurred in each group. One patient in the laparoscopic group developed postoperative haemorrhage, which required subhepatic drainage, but did not require transfusion. The bile duct was injured in one patient in the minilaparotomy group, requiring hepaticojejunostomy. The mean duration of surgery was 101 minutes in both groups.

Canadian Study

There is only one randomised trial of laparoscopic versus minilaparotomy cholecystectomy reported in the English literature [99]. In this study, with 62 evaluated patients, median postoperative hospital stay was 2 days for laparoscopic cholecystectomy and 3 days for minilaparotomy cholecystectomy while the median time to return to normal activity was 9 and 14 days respectively. Analgesia requirement was also lower after laparoscopic cholecystectomy.

However, the study has been strongly criticised and several factors limit its value [232,233]. Firstly, only 70 patients were recruited by 8 surgeons in 5 University hospitals over a one year period, and therefore the patients were highly selected. The withdrawal from the study after randomisation by seven patients in the minilaparotomy group but only one in the laparoscopic group (Fisher's exact test, p=0.013) raises questions about the patients' perceptions of the relative advantages of the two procedures.

Secondly, the trial was stopped early, after 70 rather than the predetermined 100 patients had been recruited "because significant differences in primary endpoints had been reached". It is well known that trials that were stopped

because p-values became significant are too small and difficult to interpret [234]. In this case, the important p-values relating to the stated primary endpoint were only just less than 0.05 (shorter mean duration of convalescence, $p<0.04$; and return to normal activities, $p=0.03$) and it is likely that any appropriate analysis taking into account the fact that there could have been more than one assessment (e.g. Bonferroni correction) would yield non-significant results. Even with 100 patients, the power of this study would have been extremely low. Based on preliminary studies (before the trial) and reasonable estimates of convalescence outcome, Barkun *et al.* calculated that 50 patients in each group should enable the detection of a difference in duration of convalescence of 18 days, with $\alpha=0.05$ and statistical power of 0.8.

Thirdly, the three outcome measures (opioid analgesia use, hospital stay, and duration of convalescence) which showed significant intergroup differences in favour of laparoscopic cholecystectomy were all dependent on judgments by unblinded carers, and therefore open to observer bias. On the other hand, postoperative pain (measured by McGill questionnaire and not dependent on observer judgment) did not differ significantly between the groups. Also, fewer patients in the minilaparotomy group complained of right shoulder pain (5% versus 33%).

Fourthly, health gains after cholecystectomy were assessed using three different instruments to measure quality of life. Contrary to the recommendations of the developers of the Nottingham Health Profile Questionnaire [235], the answers were given equal weights and combined into a single index. Furthermore, no intergroup statistical comparison of quality-of-life scores were reported. Instead, by reporting within-group statistical comparison of postoperative versus pre-operative values, it is implied that quality of life scores improved faster in the laparoscopic group.

Finally, the incision size used in the minilaparotomy cholecystectomy patients is not stated. Also, one surgeon used a midline incision, which is associated with greater postoperative pain and depression of pulmonary function than a transverse incision [53,54].

1.20 Metabolic response to cholecystectomy

The stress of surgery evokes a wide variety of biochemical and physiological changes including production of cytokines [9,11,236,237] and acute phase proteins [238], increase in the levels of "stress hormones [10,239,240], loss of muscle protein [241], increased vacular permeability [242], and changes in white cell count subsets [243-245]. Although some of these responses are considered to be a homeostatic defence mechanism, some of the consequences such as the catabolic state, are thought to be deleterious [241].

It has been shown that the magnitude of the metabolic response to injury is proportional to the degree of the surgical trauma [8-11]. It has been postulated, therefore, that the reduction of "access trauma" by the laparoscopic technique might diminish the metabolic response [145]. However, diagnostic laparoscopy alone is associated with a substantial hormonal and glycaemic response, which may be evoked by the stimulus of peritoneal distension [246]. Furthermore, the magnitude of the metabolic response has been shown to correlate with the duration of surgery [9,237], which for laparoscopic cholecystectomy, is longer than open cholecystectomy [81,99,203].

Three recent studies have compared selected aspects of the metabolic response to laparoscopic and standard cholecystectomy using historical [201] and non-randomised [198,202] controls. A greater rise in serum levels of interleukin-6 [201], and C reactive protein [201,202] and the erythrocyte sedimentation rate [202] occurred after standard cholecystectomy compared to

laparoscopic cholecystectomy, but there was a similar cortisol response after both procedures [198,201]. One of the studies reported a trend towards lower plasma levels of adrenaline after laparoscopic cholecystectomy [201], while another of these three studies found higher urinary catecholamine breakdown products (vanillylmandelic acid) after laparoscopic cholecystectomy [202].

The metabolic response to minilaparotomy cholecystectomy has not been previously described.

1.21 Ventilatory and blood gas changes during laparoscopic cholecystectomy

Until the advent of extended therapeutic laparoscopic procedures such as laparoscopic cholecystectomy, most laparoscopies were brief and performed in young, otherwise healthy, gynaecological patients. Ventilatory changes in these patients have been extensively studied [247-250]. Carbon dioxide (CO_2) absorption during laparoscopy performed under local anaesthesia results in an increased respiratory drive, with minute ventilation increasing by a mean of one l/min and thus maintaining arterial CO_2 tension (Pa_{CO2}) within the normal range [251]. On the other hand, during laparoscopy under relaxant general anaesthesia with fixed minute ventilation volume, mean Pa_{CO2} is reported to rise by 0.6 - 1.4 kPa [247,250,252-254].

With the increasing popularity of minimally invasive general surgery, many laparoscopic procedures now require long periods of peritoneal insufflation, and are often performed on patients who are older and have respiratory disease. Two recent studies have suggested that greater ventilatory changes occur in these patients [13,14]. Wittgen *et al* compared the changes in 20 normal patients to that in 10 patients with cardiorespiratory disease [13]. During laparoscopic cholecystectomy, Pa_{CO2} rose by 0.8kPa in the normal patients (without increasing ventilation), while in patients with

cardiopulmonary disease Pa_{CO2} rose by 2.0 kPa despite an increase in minute ventilation of 1.2 litres. The corresponding changes in end-tidal CO_2 tension ($P_{E'CO2}$) were much less and did not fully reflect the changes in Pa_{CO2}: in normal patients $P_{E'CO2}$ increased only by 0.3 kPa, while in the patients with cardiorespiratory disease, it increased only by 0.6 kPa. In contrast, in a study of gynaecological laparoscopy [252], mean (Pa_{CO2} - $P_{E'CO2}$) did not change significantly with CO_2 pneumoperitoneum. Wittgen *et al* concluded that end-tidal measurement of P_{CO2} was a poor indicator of changes in Pa_{CO2}. Marked within-patient variability in (Pa_{CO2} - $P_{E'CO2}$) during anaesthesia has also been shown in a study of patients undergoing major surgery [255]. Indeed, within-patient variations in (Pa_{CO2} - $P_{E'CO2}$) were comparable to or greater than the inter-patient differences.

In the second study of blood gas and ventilatory changes during laparoscopic cholecystectomy, Liu *et al* [14] found that $P_{E'CO2}$ and Pa_{CO2} both increased by a mean of 1.4 kPa during laparoscopic cholecystectomy, with 13 out of 16 patients requiring an increase in minute ventilation to maintain $P_{E'CO2}$ below 6 kPa. They claimed that there was good agreement between paired $P_{E'CO2}$ and Pa_{CO2} measurements, but their data do not support this statement. On analysing their results, it is apparent that 95% of patients had a Pa_{CO2} between 0.42 kPa lower to 1.08 kPa higher than paired $P_{E'CO2}$ measurements.

In a pig model of laparoscopic cholecystectomy, Pa_{CO2} increased by 1.9 kPa and carbon dioxide output by 30% of baseline values [12]. In a canine model of prolonged laparoscopy (2 hours), the effects of CO_2 and helium pneumoperitoneum were compared [256]. Even with a 57% increase in minute ventilation to maintain a constant $P_{E'CO2}$, CO_2 pneumoperitonum was associated with a significant rise in Pa_{CO2} and (Pa_{CO2} - $P_{E'CO2}$). The rise in minute ventilation requirement, Pa_{CO2}, and (Pa_{CO2} - $P_{E'CO2}$) was greater in

dogs with papain-induced pulmonary emphysema, supporting the previously mentioned findings of Wittgen *et al* in patients with pulmonary disease undergoing laparoscopic cholecystectomy [13]. Intra-operative blood gas monitoring may be advisable in patients with severe respiratory disease, as they may have larger differences between Pa_{CO2} and $P_{E'CO2}$ and a greater tendency to retain CO_2 [13].

1.22 Helium pneumoperitoneum

The adverse effects of a CO_2 pneumoperitoneum, particularly in patients with respiratory disease, have prompted a search for an alternative gas to carbon dioxide for insufflation of the abdomen. The ideal pneumoperitoneum gas requires a number of properties. Firstly, it should be chemically, physiologically, and pharmacologically inert. Secondly, it should not support combustion. Intestinal gas contains substantial amounts of hydrogen and methane [257], and since hydrogen is one of the most diffusible gases known, it can diffuse across the bowel wall into the abdominal cavity. The explosion threshold of hydrogen in a gas supporting combustion is only 5.5% by volume [258], with the activation energy required to initiate explosion with these gases being a fraction of that produced by an electrocautery device [259]. Therefore, it is paramount that the gas used during therapeutic laparoscopy, must not support combustion. Thirdly, it should also be highly water soluble, so that if an air embolism occurs, it will rapidly dissolve in the blood stream, rather than forming an "airtrap" in the right ventricle.

The two gases most widely used nowadays for laparoscopy are CO_2 and N_2O, although air and O_2 have also been used in the past. CO_2 has been shown to result in a greater pain stimulus than N_2O, due to CO_2 dissolving on the peritoneal surface to form carbonic acid [260-262]. CO_2 also has the disadvantage, demostrated in this and other studies [12-14], that its absorption

from the peritoneal cavity results in an increased ventilatory requirement. The principal advantage of CO_2 over other gases is that it is highly water soluble. This gives it a much higher safety margin than any other gas in the rare event of gas embolism. Also, CO_2 that is inadvertently insufflated into the abdominal wall is rapidly absorbed. N_2O pneumoperitoneum does not result in any changes in arterial blood gases. However, because it supports combustion, N_2O can only be used in laparoscopic procedures not requiring diathermy [263].

Helium has recently been suggested as an alternative insufflation gas to CO_2 in patients with severe respiratory disease [256,264]. Helium is an inert gas, which is chemically, physiologically and pharmacologically inert, and does not support combustion. Its physical property of low airflow resistance is utilized in patients with narrowed airways [265], and also to operate intra-aortic balloon pumps. It is thus readily available in hospitals. Two animal model studies have confirmed the suitability of helium for insufflating the abdomen during laparoscopy, and showed that it does not alter ventilation requirements [256,266] or cause hypercarbia and acidosis. In the first human study of helium pneumoperitoneum, Leighton *et al.* compared ventilatory changes.
The only drawback of helium is that it is relatively insoluble. In order to reduce the risk of insoluble gas vascular embolism with helium pneumoperitoneum, the open technique of laparoscopy might be used [151], which avoids the risk of insufflation through a misplaced Veress needle. Alternatively, the initial pneumoperitoneum could be created using CO_2, and once the pneumoperitoneum is safely established, CO_2 could be exchanged for helium as the maintenance gas.

Chapter 2

LAPAROSCOPIC VERSUS OPEN CHOLECYSTECTOMY AND THE NEED FOR A RANDOMIZED TRIAL: A SURVEY OF SURGEONS AND ETHICAL COMMITTEES IN THE BRITISH ISLES

2.1 INTRODUCTION

Laparoscopic cholecystectomy was first performed in 1988. By the end of 1991, over a half of the general surgeons in the British Isles had begun performing laparoscopic cholecystectomies, and a further third of the surgeons intended to introduce the laparoscopic technique [172]. The assessment of laparoscopic cholecystectomy up to 1992 was based largely on case series without controls [76,77,81], and on a few small case studies with historical [203,209] or non-randomised [72] controls. Randomised controlled trials (RCTs) are the optimum method for assessing any new intervention and the investigatory tool which can best avoid selection and observation bias [267]. However, the response of patients, the media, and surgeons to laparoscopic cholecystectomy has been so favourable that some surgeons have argued that it would be impossible to recruit patients to a RCT comparing laparoscopic and open cholecystectomy [268,269]. Some even have gone as far as stating that a RCT would be ethical [268].

Therefore, a survey was carried out in April 1992 to ascertain the views of general surgeons and ethical committees in the the British Isles on the necessity and ethics of a RCT comparing laparoscopic and open cholecystectomy.

2.2 METHODS

From a computer database of all consultant general surgeons in the British Isles (obtained from Ethicon, Edinburgh, UK), two hundred names were randomly selected. These surgeons were sent a brief one page questionnaire in April 1992 (Appendix 1). The questions related to surgeons' views on the safety of laparoscopic cholecystectomy, the need for a RCT, the practicality and ethics of a RCT, their interest in participating in a trial, and their choice of operation if they were to require cholecystectomy. Answers were in the form of a 4 or 5 point response scale. The effect of surgeon seniority and laparoscopic cholecystectomy experience on the answers was assessed using Spearman rank order correlations.

In addition, forty hospitals (20 teaching and 20 district general hospitals) were selected at random from a list of all hospitals in the UK. Ethical committee chairmen were identified by telephone enquiry and sent a hypothetical application for ethical approval to carry out a RCT comparing standard cholecystectomy and laparoscopic cholecystectomy.

2.3 RESULTS

A reply was obtained from 117 (59%) surgeons of which 5 were excluded (3 retired, 2 not general surgeons). 56% were district general hospital surgeons, 35% teaching hospital surgeons, and 9% were academic surgeons. A representative spread of surgeon seniority was found among responders (median number of years appointed 12, range 1-30). A third of surgeons had not performed any laparoscopic cholecystectomies, a third had performed up to 20, and a third more than 20 (Figure 2.1).

42% thought a RCT comparing laparoscopic cholecystectomy with standard cholecystectomy was necessary, while 51% thought a RCT comparing laparoscopic cholecystectomy with minilaparotomy cholecystectomy was necessary (Table 2.1). A total of 58% thought either one or both of these trials was necessary. 31% of surgeons thought an RCT would be unethical. In contrast, 24 ethical committees gave approval to the concept of a RCT comparing laparoscopic cholecystectomy and standard cholecystectomy, while only 3 considered that a RCT was unethical (13 refused to comment on a hypothetical application). A suprisingly high percentage of surgeons (45%) expressed interest in participating in an RCT.

63% of surgeons were satisfied with the safety of laparoscopic cholecystectomy, while 28% were unsure of the safety of laparoscopic cholecystectomy, and 10% concerned about the safety of laparoscopic cholecystectomy. Surgeons with greater experience in laparoscopic cholecystectomy tended to be more satisfied with the safety of the procedure ($r=0.56$, $p<0.001$), less convinced of the need for a RCT comparing laparoscopic cholecystectomy with standard cholecystectomy ($r=0.36$, $p<0.001$, see Figure 2.2) or minilaparotomy cholecystectomy ($r=0.41$, $p<0.001$), less interested in participating in a RCT ($r=0.28$, $p=0.003$), and

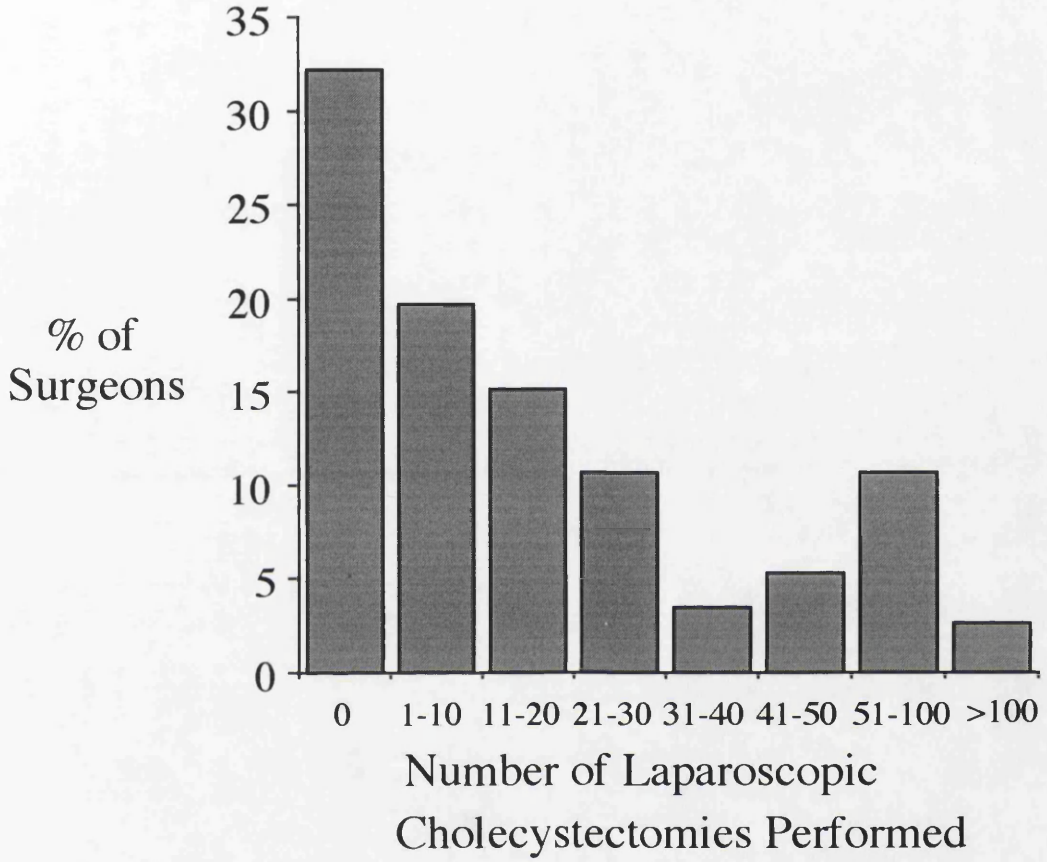

FIGURE 2.1 Number of laparoscopic cholecystectomies performed by surgeons responding to questionnaire

	Minilaparotomy Cholecystectomy	Standard Cholecystectomy
Very necessary	22%	21%
Probably necessary	30%	19%
Unsure	12%	12%
Probably unnecessary	24%	30%
Totally unnecessary	13%	18%

TABLE 2.1 Response to the Question: "Do you think there is a necessity for a randomised controlled trial comparing laparoscopic cholecystectomy with open cholecystectomy (minilaparotomy or standard)?:

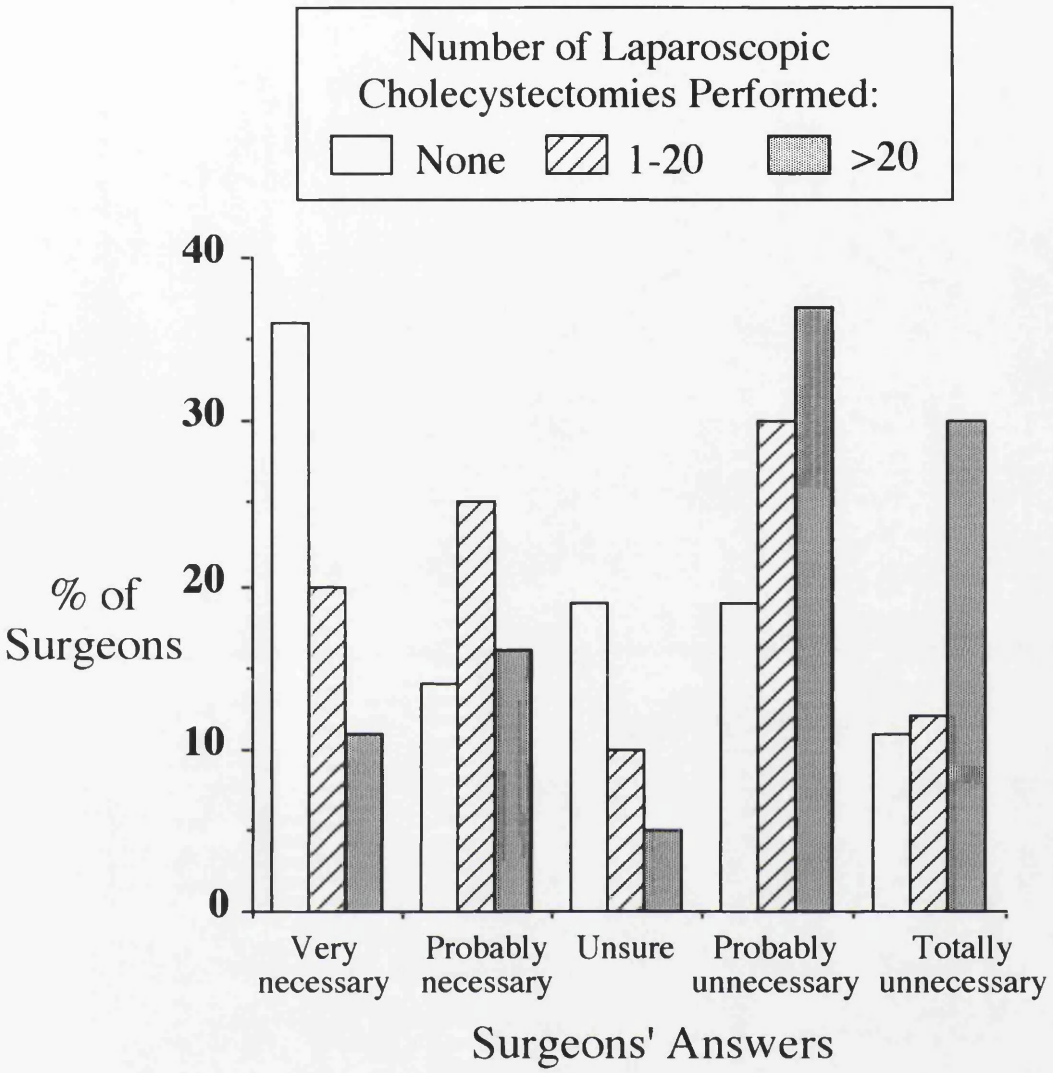

FIGURE 2.2 Effect of laparoscopic cholecystectomy experience on response of surgeons to the question "Do you think there is a necessity for a randomised controlled trial comparing laparoscopic cholecystectomy with standard cholecystectomy?"

tended to chose laparoscopic cholecystectomy as their preferred choice of operation (r=0.30, p=0.001). Junior consultants tended to have performed more laparoscopic cholecystectomies (r=0.29, p=0.002), but surgeon seniority and type of consultant post (district general hospital, teaching hospital, academic appointment) did not significantly affect surgeons views on these issues.

Surgeons were asked "If you were admitted to a hospital not known to yourself for an elective cholecystectomy (albeit an unlikely scenario) and were offered laparoscopic or open cholecystectomy, which procedure would you choose?": 49% chose laparoscopic cholecystectomy, a further 21% chose laparoscopic cholecystectomy only if they could guarantee the surgeon had had substantial experience of laparoscopic cholecystectomy without major complications, while 28% chose open cholecystectomy (2% were undecided).

2.4 DISCUSSION

In contrast to previously expressed views [268,269], this survey showed that in April 1992, there was a body of support for a RCT comparing laparoscopic and open cholecystectomy, with 58% of surgeons expressing the view that a randomised controlled trial was necessary and 45% of surgeons expressing some interest in participating in a RCT. Furthermore, the majority of ethical committees would give approval in 1992 for a RCT to assess laparoscopic cholecystectomy.

Surgeons with more experience of laparoscopic cholecystectomy tended to be less inclined towards the need for a RCT. This finding might be interpreted in two ways. On the one hand, it could be argued that surgeons performing laparoscopic cholecystectomy become aware of a clear and obvious benefit of the laparoscopic technique in terms of a more rapid postoperative recovery, and therefore feel less inclined to the need for a RCT to objectively asess the benefits of the technique. On the other hand, it could be argued that there is a difference in attitude between surgeons who have started performing laparoscopic cholecystectomy, and surgeons who have not; that surgeons with an enthusiasm for new techniques have started performing laparoscopic cholecystectomy before rigorous evaluation, and clear evidence proven advantage for the method. Such surgeons might be less inclined to the use of RCTs, feeling that they restrict the advance of surgical innovation.

In difficult clinical situations, the question a surgeon often has to ask himself, is what decision would he take if he or a close relative of himself was the patient. Interestingly, in this survey less than half of the surgeons would unreservedly have chosen the laparoscopic technique if they were to require cholecystectomy themselves, with over a quarter of surgeons choosing open cholecystectomy.

In conclusion, this survey showed that in April 1992 there was wide support amongst the surgical community for RCTs comparing laparoscopic cholecystectomy and open cholecystectomy, and that contrary to previous suggestions, such trials would receive the approval of ethical committees in the British Isles.

Chapter 3

LAPAROSCOPIC VERSUS MINILAPAROTOMY CHOLECYSTECTOMY: A RANDOMISED TRIAL

3.1 INTRODUCTION

Laparoscopic cholecystectomy was first performed by Mouret in France in 1987. Since then the technique has replaced open cholecystectomy as the standard treatment for symptomatic cholelithiasis [21]. The perceived advantages of laparoscopic cholecystectomy are less postoperative pain, reduced hospital stay and a more rapid return to normal activity. However, without rigorous evaluation, the supposed benefits of the laparoscopic technique remain unproven. Audit has shown an increased incidence of bile duct injury after laparoscopic cholecystectomy [134-136]. Other serious complications include major vascular injury [150,270] and viscus perforation [81,118] during Veress needle or trocar insertion. These increased risks require that the postulated benefits of the laparoscopic technique are assessed objectively [75].

Surgeons have been reluctant to conduct clinical trials comparing conventional with laparoscopic cholecystectomy [268]. However, a small transverse subcostal incision ("minilaparotomy") for open cholecystectomy has been shown to result in a more rapid postoperative recovery than a standard incision [1-7]. A randomised trial was therefore undertaken to compare outcomes following laparoscopic and minilaparotomy cholecystectomy.

3.2 PATIENTS AND METHODS

Seven consultants in five hospitals (Western Infirmary, Royal Infirmary, Gartnavel General Hospital, Southern General Hospital, Glasgow and Crosshouse Hospital, Kilmarnock) participated in this trial, which was approved by the relevant hospital ethical committees. All had previous experience of laparoscopic cholecystectomy and all except one had assisted at or performed more than thirty procedures. Four surgeons began recruiting patients to the trial in August 1991, a further three joined the study in 1992, and recruitment was completed at the end of March 1993. All patients undergoing elective cholecystectomy for symptomatic cholelithiasis were considered for entry into this trial; this included patients with acute cholecystitis and acute pancreatitis who underwent delayed interval cholecystectomy. Patients requiring urgent surgery for empyema or perforation, those with common bile duct stones and those with extensive previous upper abdominal surgery were excluded. Patients with abnormal liver function tests or a dilated common bile duct on ultrasound were recruited into the trial only if a pre-operative intravenous or endoscopic retrograde cholangiogram was normal. After giving informed consent, patients were randomised on the day before operation by the use of numbered sealed envelopes, stratified by surgeon.

Laparoscopic cholecystectomy was performed using a four trocar technique with electrocautery dissection. Minilaparotomy cholecystectomy was performed using a five to ten centimetre transverse subcostal incision depending on body habitus [5]. In both groups, patients received antibiotic prophylaxis (a single dose of intravenous Cefuroxime 1.5g), subcutaneous heparin (5,000 i.u. twice daily), and local anaesthetic wound infiltration at the end of the procedure (20 mls of 0.5% bupivacaine). A consultant was present at all operations. Only one surgeon had a policy of routine cholangiography;

the remainder used it only when there was a suspicion of bile duct stones at operation.

Analgesia requirement and pain scores

Postoperatively, patients were given intravenous morphine by a disposable patient-controlled analgesia device [271,272] (Figure 3.1), which gave a bolus dose of one mg of morphine; the refill time until the next full dose was six minutes, yielding a maximum rate of 10 mg per hour. A standard explanation of how to use this device was given to each patient on the day before operation, along with an information sheet. On the second postoperative day, patients were also given simple oral analgesics on demand. At 24 and 48 hours postoperatively, patients were shown a 100 mm linear analogue pain scale: labelled from "pain free" to "worst pain I could possibly imagine" [273] and asked to mark the pain they experienced on sitting up from the lying position and on coughing. They were also asked to assess this pain on an ordinal four-point scale (none, mild, moderate, severe).

Pulmonary function

Forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and peak expiratory flow rate (PEFR) were assessed using a Respiradyne pulmonary function monitor [274] (Figure 3.2), pre-operatively and 24 and 48 hours postoperatively. All measurements were performed on sitting patients after a standard explanation. Five measurements were taken on each occasion, and the best of the five values was recorded. Postoperative pulmonary function was expressed as a percentage of the pre-operative value.

Oxygen saturation

After patients had returned to the ward from the recovery area, no routine oxygen supplementation was given. Oxygen saturation was monitored continuously with an Ohmeda Biox 3700 Pulse Oximeter after return to the

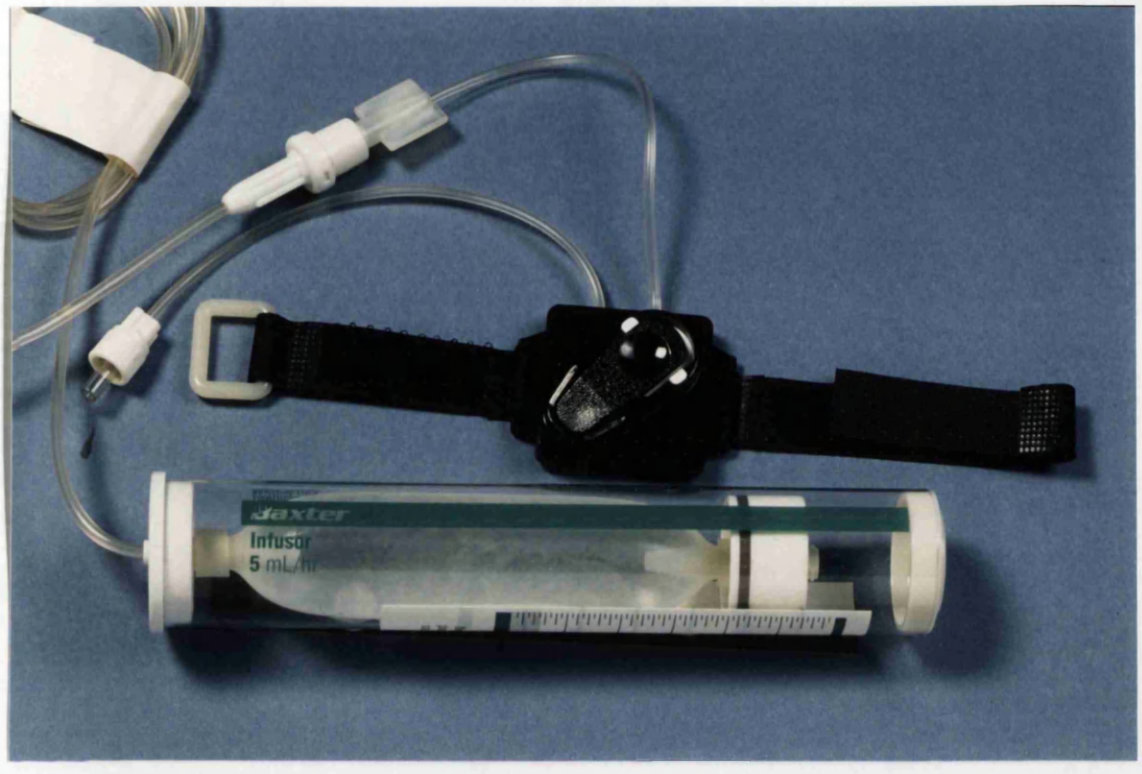

FIGURE 3.1 Disposable patient controlled analgesia device

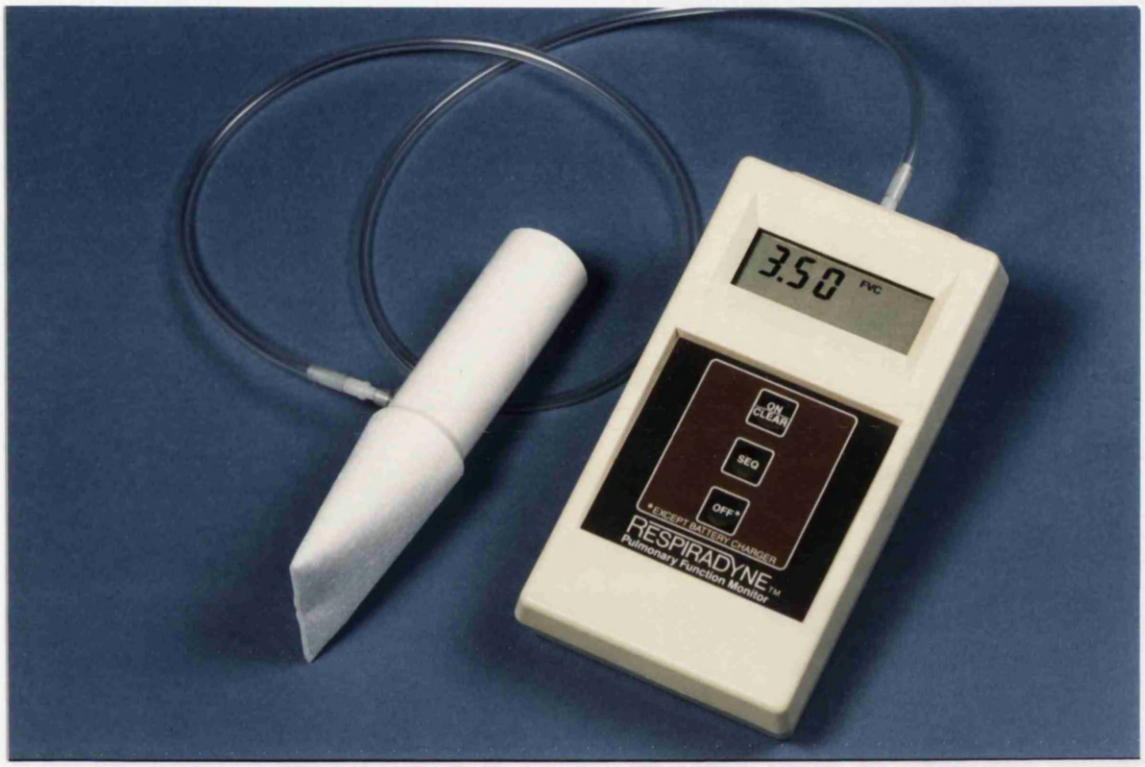

FIGURE 3.2 Respiradyne portable pulmonary function monitor

ward. The audible low saturation alarm was set at 86% [275]. If oxygen saturation fell to this level, oxygen supplementation was given. Oxygen saturation on breathing air was recorded every hour for 16 hours. In the case of patients who required oxygen supplementation, this was performed by removing the oxygen mask for 5 minutes before taking the reading.

Complications

Wound infection was defined as presence of cellulitis, or pus discharge from the wound. A major postoperative complication was defined as any complication which prolonged hospital stay, required admission to intensive care unit, or required a further interventional procedure.

Hospital stay and return to normal activity

Before hospital discharge, patients had to tolerate a full diet, be able to dress themselves, be fully mobile around the ward, require only oral analgesia, and be satisfied that they could manage at home. Patients were reviewed at the outpatient clinic at 10 days and 4 weeks postoperatively.

To assess return to normal activity, patients were sent postal questionnaires at one, four, and twelve weeks after operation, with reminders for non-responders two and four weeks after the last two questionnaires. Self-completion was used rather than interview to avoid observer bias and minimise cost. The questionnaires contained questions about return to their normal activity (paid employment, looking after the home, social life, sex life, interests and hobbies), a modified version of the SF-36 health survey questionnaire [276,277] and the hospital anxiety and depression scale (HADS) [278]. Questions 9 (i-ix) and 10 in the SF-36 were omitted to avoid repetition of similar questions in HADS; the remaining seven SF-36 dimensions were scored from 0 (worst score) to 100 (best). In view of the patients' recent operations, the SF-36 questions in the first questionaire were amended to

focus on the time period since returning home from hospital, and the second and third questionnaires on the week immediately preceding the questionnaire. The HADS responses were converted into two separate scores for anxiety and depression (best score 0, worst 21). Finally, patients were asked to grade the outcome of the operation on a five point scale (excellent, good, fair, poor, very poor) and also their satisfaction with the appearance of the operation scars (very satisfied, moderately satisfied, barely satisfied, moderately dissatisfied, very dissatisfied).

Costs

A detailed breakdown of theatre, ward, investigation, and staffing costs was obtained for the financial year April 1991 to March 1992 from the resource management units of the two main hospitals involved in this study (Western Infirmary and Royal Infirmary, Glasgow). Formulae used to calculate costs are shown in Figure 3.3. Costing breakdowns from both hospitals were similar (Table 3.1). The National Health Service cost of hospital admission for cholecystectomy for each patient was then estimated on the basis of theatre time, hospital stay, and additional tests or treatment using an average of the costs obtained from the Western and Royal Infirmaries. Costing did not include previous investigation or out-patient follow-up. The resulting theatre costs were £369 per hour, and ward costs £73 per day. The disposable laparoscopic instruments cost £303 per set, and other laparoscopic equipment £60 per operation.

Statistical methods

The trial aimed to recruit 300 patients over two years. Using a significance level of five per cent, such a sample would have 80 per cent power to detect differences between laparoscopic and minilaparotomy groups greater than one *third* of the standard deviation of normally distributed outcome measures [279]. For the end-points of post-operative pain and pulmonary function, the study

$$\text{THEATRE COSTS PER MINUTE} = \frac{\text{TOTAL THEATRE COSTS FOR YEAR}}{\text{THEATRE TIME (minutes) UTILIZED IN FINANCIAL YEAR}}$$

$$\text{SURGEON'S COSTS IN THEATRE} = (\text{ANNUAL SALARY + EMPLOYER'S COSTS}) \times \frac{\text{OPERATION TIME}}{\text{(Time Worked in the Year i.e. 46 weeks x 40 hours)}}$$

$$\text{WARD COSTS} = \frac{\text{ANNUAL COST FOR WARD}}{\text{TOTAL BEDSTAY DAYS UTILIZED}}$$

$$\text{JUNIOR HOUSE OFFICER COST FOR WARD COVER PER BEDSTAY DAY} = \frac{\text{(SALARY + EMPLOYER'S COSTS) OF ALL RESIDENTS}}{\text{ANNUAL BEDSTAY DAYS}}$$

$$\text{SENIOR HOUSE OFFICER COST FOR WARD COVER PER BEDSTAY DAY} = 10\% \text{ OF } \frac{\text{(SALARY + EMPLOYER'S COSTS)}}{\text{ANNUAL BEDSTAY DAYS}}$$

$$\text{CONSULTANT SURGEON COST FOR WARD COVER PER BEDSTAY DAY} = 5\% \text{ OF } \frac{\text{(SALARY + EMPLOYER'S COSTS)}}{\text{ANNUAL BEDSTAY DAYS}}$$

$$\text{LAPAROSCOPIC EQUIPMENT COST PER OPERATION} = \frac{\text{TOTAL COST OF EQUIPMENT} + \text{CAPITAL INTEREST OVER PERIOD OF USE}}{\text{NUMBER OF OPERATIONS PER YEAR} \times 5 \text{ YEARS}}$$

$$= \frac{£25{,}000 + £5{,}000}{100 \times 5} = £60$$

FIGURE 3.3 Formulae for calculating theatre, ward and laparoscopic equipment costs.

	Western Infirmary	Royal Infirmary
THEATRE COSTS	**£/minute**	**£/minute**
Theatre Nursing Staff	1.52	n/a
Anaesthetists	2.22	n/a
Theatre Pharmacy	0.93	n/a
Theatre Other	0.44	n/a
Theatre Subtotal	**5.11**	**4.67**
Consultant Surgeon	0.53	0.53
Senior Surgical Registrar	0.41	0.41
Surgical Senior House Officer	0.31	0.31
Total Theatre Costs	**6.37**	**5.92**
WARD COSTS	**£/patient/day**	**£/patient/day**
Ward	67.94	66.33
Consultant Surgeon	0.81	0.81
Senior Surgical Registrar	0.62	0.62
Senior Surgical House Officer	0.47	0.47
Junior Surgical House Offficer	4.08	4.08
Total Ward Costs	**73.92**	**72.31**
INVESTIGATIONS	**£/test**	**£/test**
Chest Xray	11.75	16.87
Electrocardiogram	5.60	5.00
Pathology	39.00	67.38
Bacteriology	21.45	8.85
Full blood count	2.51	1.45
Blood Grouping	11.58	11.58
Biochemistry	2.46	0.34

TABLE 3.1 A breakdown of costings from resource management units at the Western and Royal Infirmaries, Glasgow.

aimed to detect differences greater than one *half* of the standard deviation. To yield 80 per cent power to detect such differences at a significance level of five per cent, a sample of 120 patients was needed [279]. Hence, post-operative pain and pulmonary function were measured only for the first year of the trial - from September 1991 until August 1992.

The trial was pragmatic, i.e. designed to reflect normal clinical practice [280]. In particular, results were analysed by intention to treat, so that patients from both groups requiring conversion to standard cholecystectomy were included. A secondary analysis was performed, after excluding patients requiring conversion to standard cholecystectomy and patients with complications which prolonged hospital stay.

Normally distributed data were analysed by the t test, while those not normally distributed were analysed by the Mann-Whitney U test. Categorical data were analysed by the chi-squared test. Ordinal pain scores and patients' ratings of outcome were analysed by the chi-squared test for linear trend. An analysis of covariance was performed when, despite randomisation, thee was any imbalance in baseline variables between the two groups.

3.3 RESULTS

Informed consent to randomisation was sought from 311 patients eligible for the trial. Nine refused randomisation, leaving 302 who were randomised. Of these, three did not undergo cholecystectomy and were therefore excluded from analysis; two were unexpectedly found to have liver metastases from an unknown primary, and another found to have severe cirrhosis. Randomisation produced two groups with similar pre-operative characteristics (Table 3.2).

Of the patients randomised to laparoscopic cholecystectomy, 15 (10%) required conversion to open cholecystectomy; the reasons were severe cholecystitis or chronic empyema in seven, unclear anatomy in three, dense intrabdominal adhesions in two, bleeding in one, equipment failure in one, and bile duct stones in one. In the minilaparotomy group, the median incision length was 7 cm (interquartile range 5-9cm). An incision greater than 10cm was necessary in 14 patients (10%); the reasons were severe cholecystitis or empyema in four, morbid obesity in four, bile duct stones in two, bleeding in two, cholecysto-choledochal fistula in one, and an intrahepatic gallbladder in one. Complications of cholelithiasis (mucocoele or chronic empyema) were found in 43 (14%) of 299 patients (Table 3.2). One elderly minilaparotomy patient with a large cholecystoduodenal fistula was treated by cholecystostomy and stone removal alone.

The mean (SD) operation time was significantly shorter in the minilaparotomy group (57 (24) minutes versus 71 (20); t test - $p<0.001$) - Figure 3.4. The median (interquartile range) postoperative hospital stay of two (2-4) days after laparoscopic cholecystectomy was significantly shorter than that of four (3-5) days after minilaparotomy (Mann-Whitney U test - $p<0.001$) - Figure 3.5.

	Minilaparotomy group (n=148)		Laparoscopic group (n=151)	
Median (IQR) age (yrs)	52 (41-63)		54 (41-64)	
Sex (% female)	84%		88%	
Mean height [cm] (SD)	161 (8)		162 (8)	
Mean weight [kgs] (SD)	67 (13)		70 (13)	
Mean body mass index [kg/m^2] (SD)	26.1 (4.8)		26.7 (4.8)	
Median (IQR) duration of symptoms (months)	11 (6-24)		10 (6-24)	
	No. of patients (%):		No. of patients (%):	
Indication:				
Biliary colic	91	(61%)	103	(68%)
Previous acute cholecystitis	36	(24%)	36	(24%)
Gallstone pancreatitis	10	(7%)	9	(6%)
Previous choledocholithiasis	11	(7%)	3	(2%)
ASA class 1	66	(45%)	66	(44%)
class 2	51	(34%)	61	(40%)
class 3	25	(17%)	19	(13%)
class 4	6	(4%)	5	(3%)
Employment status :				
Housewife	46	(31%)	54	(36%)
Retired	41	(28%)	45	(30%)
Full-time paid employment	33	(22%)	29	(19%)
Part-time paid employment	14	(9%)	14	(9%)
Unemployed	10	(7%)	7	(5%)
Other	4	(3%)	2	(1%)
Complicated operative findings:				
Chronic empyema	12	(8%)	14	(9%)
Mucocoele (No. of patients (%))	6	(4%)	11	(7%)
Cholecysto-choledochal fistula	1	(1%)	0	(0%)
Cholecysto-duodenal fistula	1	(1%)	0	(0%)

ASA = American Society of Anaesthesiologist's physical fitness classification
IQR=interquartile range.

TABLE 3.2 Patient characteristics of all patients in the trial.

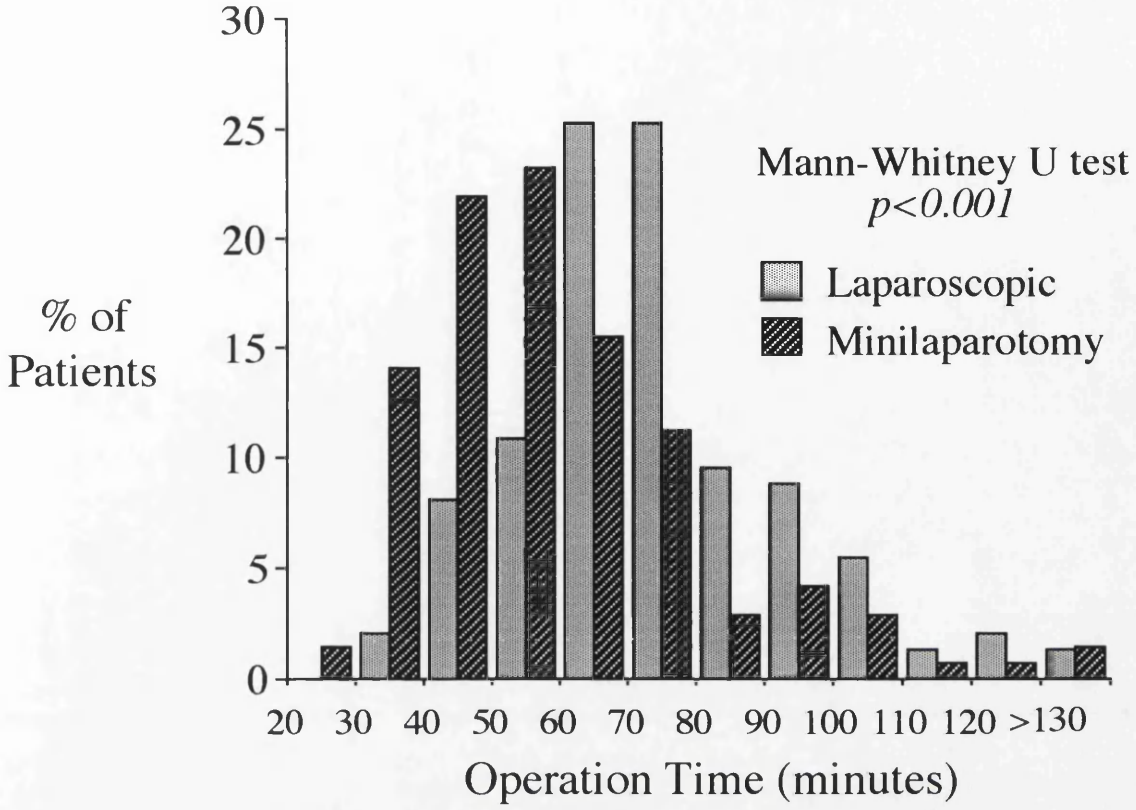

FIGURE 3.4 Operation time in the two groups

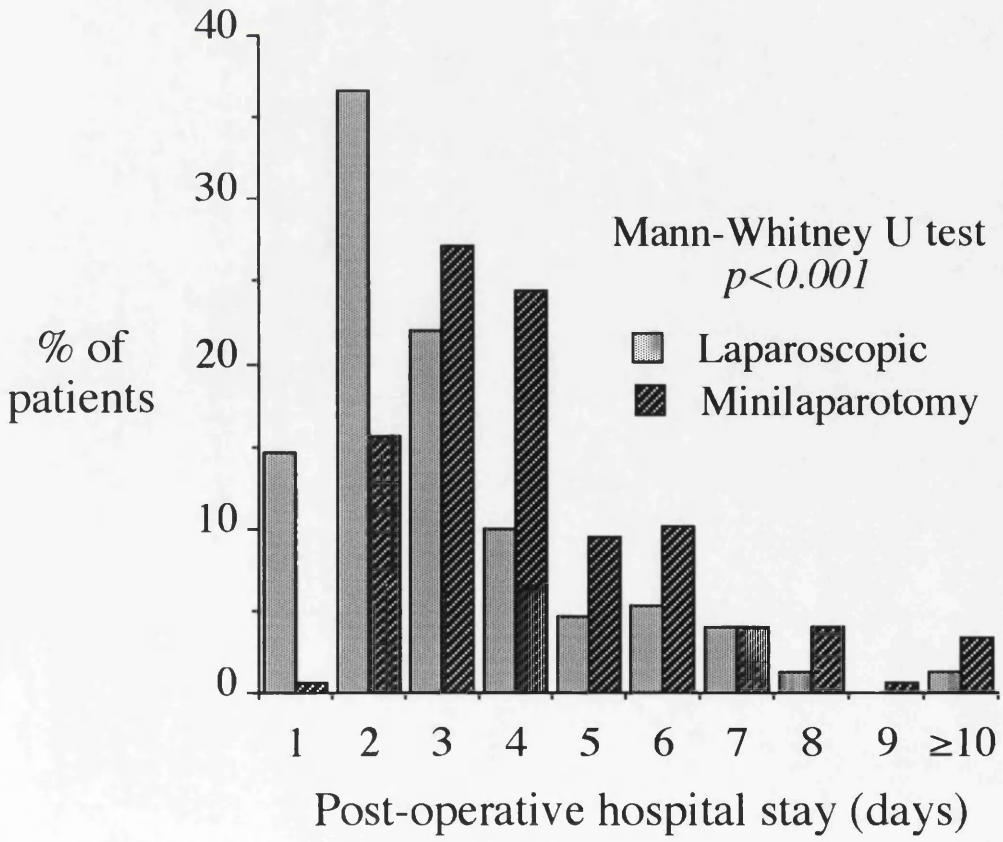

FIGURE 3.5 Post-operative hospital stay in the two groups

In the first year of the randomised trial during which post-operative pain and pulmonary function were assessed, a total of 131 patients were randomised, 65 to minilaparotomy cholecystectomy and 67 to laparoscopic cholecystectomy. The two group of patients evaluated for postoperative pain and pulmonary function were well matched for age, sex, body mass index, American Society of Anaesthesiologists (ASA) class [281], indication for operation, and pre-operative pulmonary function but less well matched for smoking (Table 3.3).

Pain and analgesia consumption

The amount of morphine used in the peri-operative period was similar in both groups (Table 3.4). Patients in the minilaparotomy group had experienced significantly more pain than those in the laparoscopic group at both 24 and 48 hours, as measured by linear analogue and ordinal pain scores (Table 3.5 and Figure 3.6). Patient-controlled morphine consumption was also significantly greater in the minilaparotomy group over both the first and second periods of 24 hours (Table 3.6. and Figure 3.7). Pain referred to the shoulder was experienced postoperatively by 8 (13%) minilaparotomy patients compared with 15 (23%) laparoscopic patients (χ^2=2.2, 1 d.f., p=0.14).

Pulmonary function

In both groups, there was a postoperative fall in all three measures of pulmonary function, most marked at 24 hours, with some improvement at 48 hours. The fall in pulmonary function was significantly greater in the minilaparotomy group at both 24 and 48 hours (Table 3.7 and Figure 3.8). Average oxygen saturation over the first 16 postoperative hours was significantly higher in the laparoscopic patients (Table 3.8 and Figure 3.9). Furthermore, oxygen saturation fell below 86% in a greater proportion of the minilaparotomy patients.

	Minilaparotomy group (n=65)	Laparoscopic group (n=67)
Mean Age (range)	53 (19-82)	54 (23-80)
Number of Males	12 (18%)	11 (16%)
Mean Height [cm] (S.D.)	160 (8.1)	162 (8.2)
Mean Weight [kgs] (S.D.)	67 (15.1)	71 (14.6)
Mean Body Mass Index [kg/m^2] (S.D.)	26 (5.1)	27 (5.3)
Number of Smokers	33 (51%)	23 (34%)
ASA class 1	28	21
class 2	23	29
class 3	11	13
class 4	3	4
Indication :		
Biliary Colic	44	42
Acute Cholecystitis	17	19
Gallstone Pancreatitis	4	6
Mean FVC [litres] (S.D.)	2.80 (0.74)	2.94 (0.77)
Mean FEV_1 [litres] (S.D.)	2.26 (0.70)	2.42 (0.69)
Mean PEFR [ml/sec] (S.D.)	360 (117)	385 (108)

ASA = American Society of Anaesthesiologist's physical fitness classification.

TABLE 3.3 Preoperative characteristics of patients randomised over the first year of the trial and in whom postoperative pain and pulmonary function was assessed.

	Minilaparotomy group (n=58)	Laparoscopic group (n=59)	Statistic
No of patients (%) given opiate premedication	26 (45%)	29 (49%)	χ^2=0.2, 1 d.f., p=0.64
Median intra-operative morphine dose [mg] (median/interquartile range)	5 (3-10)	5 (2.5-10)	p=0.98 (U test)
No of patients (%) requiring bolus of morphine in recovery	11 (19%)	8 (14%)	χ^2=0.6, 1 d.f., p=0.43

TABLE 3.4 Peri-operative morphine administration in the laparoscopic and minilaparotomy groups.

		Minilaparotomy group (n=64)	Laparoscopic group (n=65)	95% confidence interval for the difference in the medians
Linear Analogue Pain Score median (IQR) [mm]:				
24 hours		59 (40-79)	40 (25-54)	10-26***
48 hours		43 (24-64)	21 (10-39)	11-28***
Ordinal Pain Score (number of patients):				
24 hours:	None	0	5	
	Mild	9	16	
	Moderate	18	29	
	Severe	37	15 ###	
48 hours:	None	3	18	
	Mild	15	24	
	Moderate	30	17	
	Severe	16	5###	

*** Mann-Whitney U test p<0.001
Chi-squared Test for Linear Trend p<0.001
IQR=interquartile range

TABLE 3.5 Postoperative linear analogue and ordinal pain scores in the two groups.

	Minilaparotomy group (n=64)	Laparoscopic group (n=65)	95% confidence interval for the difference in the medians
	Median (interquartile range) [mg]		
1st 24 hours	40 (35-47)	22 (20-30)	8-22***
2nd 24 hours	11 (0-31)	0 (0-20)	0-10**

Mann-Whitney U test *** $p<0.001$ **$p<0.01$

TABLE 3.6 Patient-controlled morphine consumption over the first two postoperative days in the two groups.

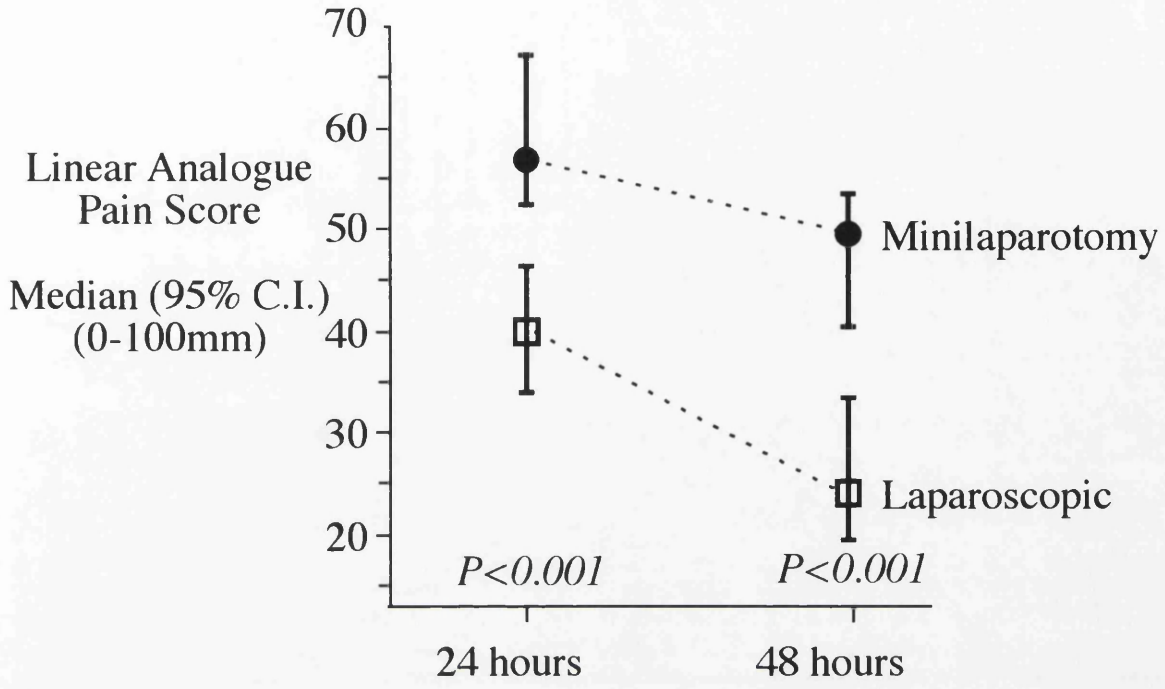

FIGURE 3.6 Post-operative linear analogue pain scores

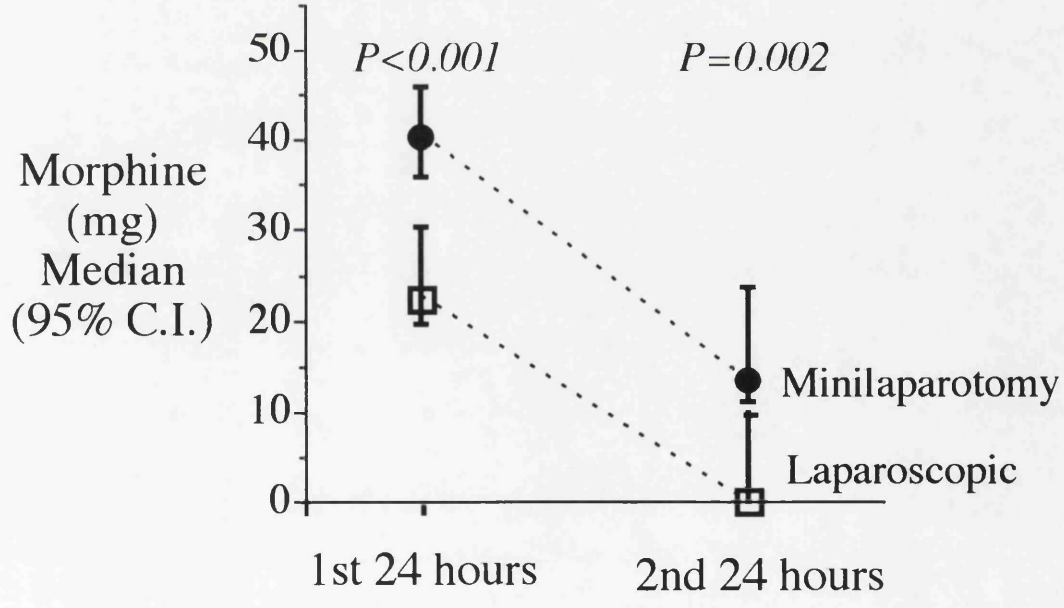

FIGURE 3.7 Post-operative Morphine Consumption

		Minilaparotomy group (n=64)	Laparoscopic group (n=64)	95% confidence interval for the difference in the means
		Mean percentage of pre-operative value (S.D.)		
FVC	24 hours	54 (16)	65 (19)	4-17***
	48 hours	66 (16)	76 (17)	4-16***
FEV_1	24 hours	54 (17)	64 (17)	4-16**
	48 hours.	65 (17)	75 (18)	4-16**
PEFR	24 hours	49 (16)	64 (20)	9-22***
	48 hours	58 (19)	75 (23)	10-25***

FVC = forced vital capacity FEV1 = forced expiratory volume in one second
PEFR = peak expiratory flow rate
Student's t test: *** $p<0.001$ ** $p<0.01$

TABLE 3.7 Pulmonary function on the first two postoperative days in the two groups.

	Minilaparotomy group (n=58)	Laparoscopic group (n=56)	95% confidence interval for the difference
Oxygen saturation Mean (S.D.) [%]	91.2 (3.3)	92.9 (2.7)	0.4-2.6**
Number of patients (%) whose oxygen saturation fell below 86%	30 (52%)	15 (27%)	8-42 %##

Student's t test: ** $p<0.01$ Chi-squared test: ## $p<0.01$

TABLE 3.8 Average oxygen saturation over the first 16 post-operative hours in the two groups

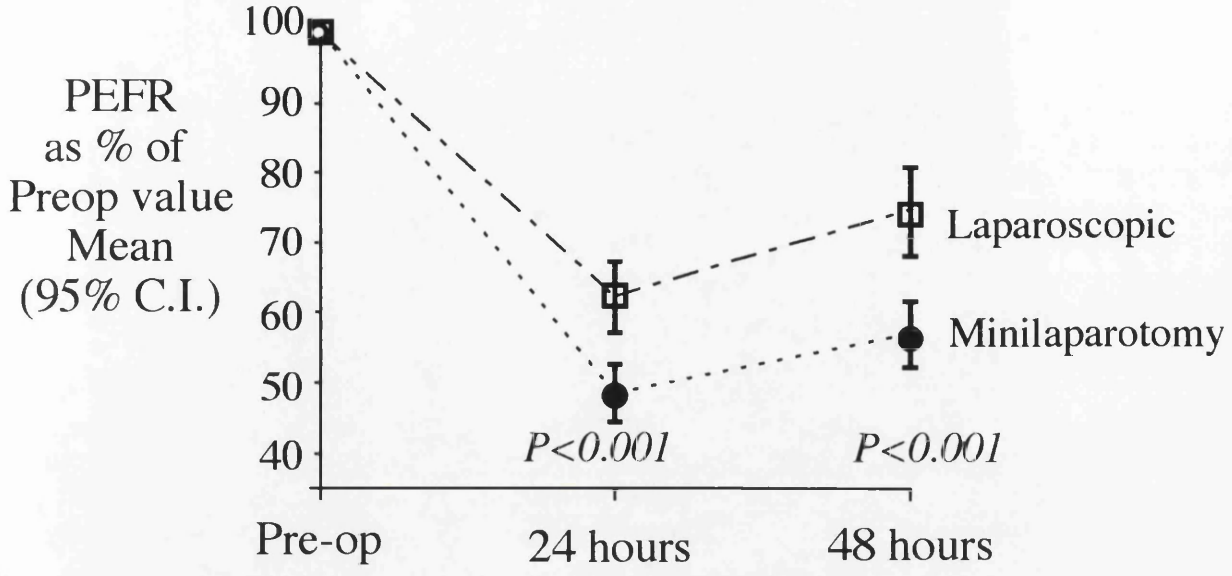

Figure 3.8 Post-operative Peak Expiratory Flow Rate

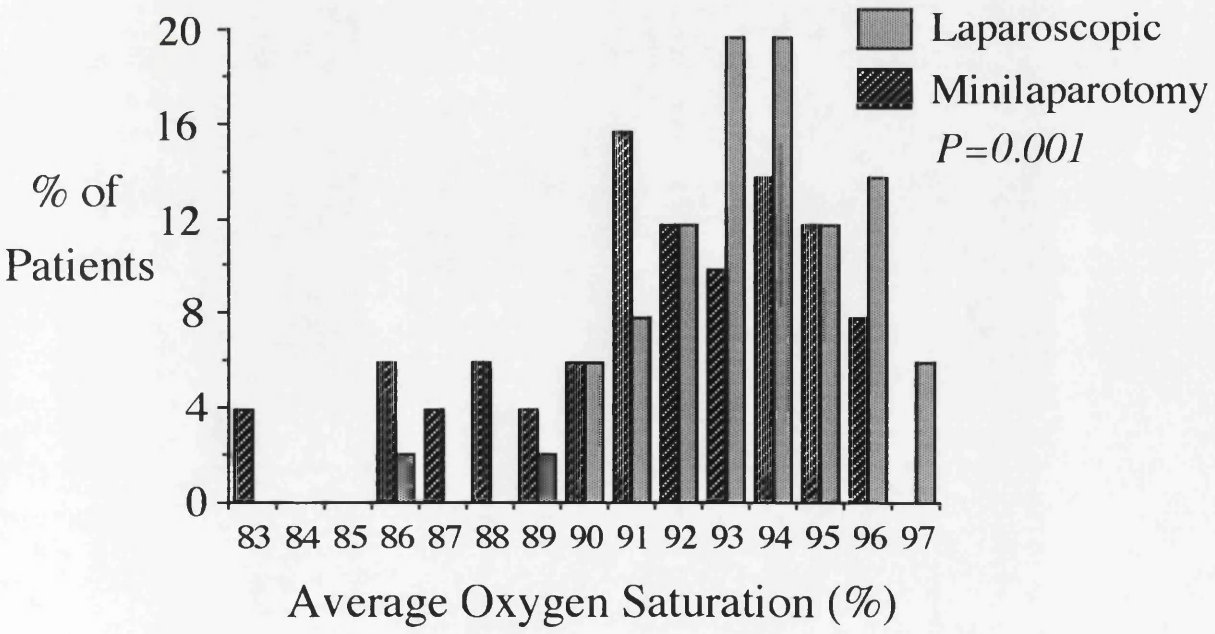

FIGURE 3.9 Mean O2 Saturation (without O2 Supplementation) in the first 18 post-operative hours

Although there was a difference in the proportion of smokers in the two groups, it did not achieve statistical significance. Nevertheless, the effect of smoking on postoperative pulmonary function and oxygen saturation was examined. There was no significant difference between smokers and non-smokers in postoperative pulmonary function but, oxygen saturation was significantly lower in smokers. After taking the effect of smoking into account, the difference in oxygen saturation between the two groups remained significant; the adjusted mean oxygen saturation was 92.8% in the laparoscopic group, and 91.3 in the minilaparotomy group (p=0.003).

Although the main analysis of post-operative pain and pulmonary function was by "intention to treat", a secondary analysis was also carried out from which the nine minilaparotomy patients who required an incision greater than 10cm, and the nine laparoscopic patients who required conversion to open cholecystectomy were excluded. As in the main analysis, all outcome measures were significantly better in the laparoscopic group. Mean linear analogue pain score, mean oxygen saturation and median morphine consumption in both groups were almost identical with those in the main analysis, while mean pulmonary function was 1% higher in the minilaparotomy group, and 2% higher in the laparoscopic group.

Complications

The incidence of both major and minor complications was similar in both groups (Table 3.9).

In the minilaparotomy group two minor bile duct injuries occurred. In the first, a 3 mm transverse incision was made in the common hepatic duct; this injury was immediately repaired with two interrupted sutures. In the second, a similar injury occurred at the junction of the cystic and common bile ducts; this was managed by inserting a T tube at the site of injury. Both patients

Complication	Minilaparotomy (n=148) No.	(%)	Laparoscopic (n=151) No.	(%)
Wound infection	11	(7.4)	13	(8.6)
Wound haematoma	0	(0)	3	(1.3)
Urinary retention	6	(4.1)	2	(1.3)
Minor chest infection	5	(3.4)	1	(0.7)
Post-operative haemorrhage	3	(3.0)	3	(2.0)
Urinary tract infection	2	(1.4)	0	(0)
Septicaemic shock	1	(0.7)	0	(0)
Adhesive obstruction	1	(0.7)	0	(0)
Retained bile duct stone	0	(0)	1	(0.7)
Major bile duct injury	0	(0)	1	(0.7)
Minor bile duct injury	2	(1.4)	0	(0)
Cystic duct bile leak	0	(0)	1	(0.7)
Subvesical bile duct leak	1	(0.7)	2	(1.4)
Readmission	3	(2.0)	5	(3.3)
Total number of patients with complications	30	(20%)	26	(17%)

TABLE 3.9 Postoperative complications.

remain well one year later. Percutaneous ultrasound drainage was required in a minilaparotomy patient for a subvesical bile duct leak demonstrated by endoscopic retrograde cholangiography (ERCP). One patient developed septicaemic shock post-operatively and had a negative re-laparotomy. Three patients required transfusion post-operatively for bleeding. Re-operation was required in one patient for adhesive obstruction at one month. There was one death from myocardial infarction in a minilaparotomy patient on the second post-operative day.

In the laparoscopic group, a patient presented with jaundice one week after cholecystectomy, and ERCP demonstrated complete division and clipping of the common hepatic duct; this was repaired by primary anastamosis over a T tube, and after six months follow-up the patient remains well. A laparoscopic patient developed a bile leak and jaundice post-operatively: the bile collection was drained percutaneously, and ERCP revealed a subvesical bile duct leak and a stone in the common bile duct, which was removed endoscopically. A laparoscopic patient who developed biliary peritonitis two weeks postoperatively from a subvesical bile duct leak required laparotomy and drainage. A cystic bile duct leak in a laparoscopic patient was treated by percutaneous drainage and endoscopic placement of a biliary stent. Three patients required transfusion post-operatively for bleeding.

Patient questionnaires

The response rate to the one, four, and twelve week questionnaires was 78%, 88%, and 81% respectively in both groups. The times to return to normal activities after surgery are shown in Table 3.10. Laparoscopic patients returned more quickly to hobbies, work in the home (Figure 3.10 and social activities, but there was no difference in the time to return to sexual activity or paid employment.

	Minilaparotomy median (IQR)	n	Laparoscopic median (IQR)	n	Significance level (U test)
Hobbies	**12** (7-21)	118	**7** (4-14)	128	0.0014
Work in the home	**15** (10-24)	114	**10** (5-19)	122	<0.001
Social activities	**21** (11-28)	111	**14** (7-21)	125	<0.001
Sexual activity	**21** (12-28)	64	**21** (11-24)	60	0.33
Paid employment	**41** (21-60)	37	**36** (28-60)	31	0.86

IQR = interquartile range

TABLE 3.10 Time (days) to return to normal activities after cholecystectomy.

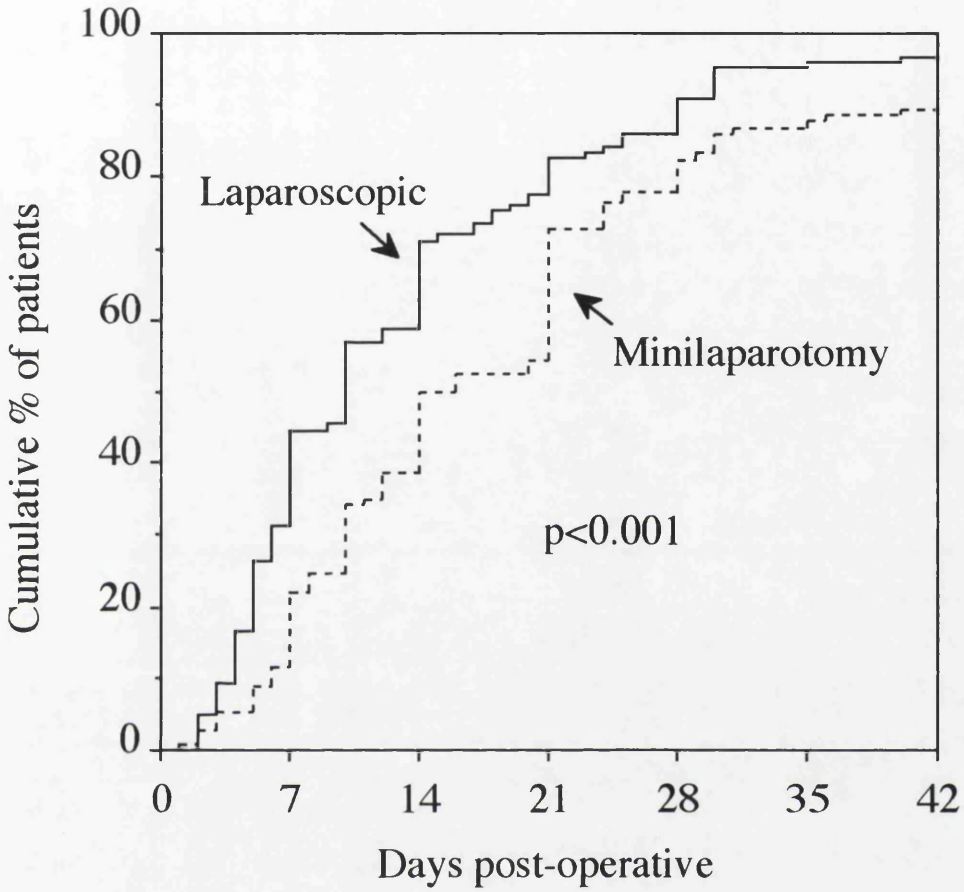

Figure 3.10: Time to return to work in the home after cholecystectomy

In general, the SF-36 and HADS scores improved from the first to the twelfth postoperative week (Table 3.11). One week after surgery laparoscopic patients had significantly better perceived health, better physical and social functioning, less role limitation due to physical problems, less pain (Figure 3.11), and less depression than minilaparotomy patients. (Although median/IQR social functioning scores were the same in both groups at one week, the mean (SD) was significantly higher in the laparoscopic group: 74 (29) versus 67 (30)). At four weeks, laparoscopic patients still had better physical functioning and less depression, but by twelve weeks there were no significant differences between the groups in any of the patient-reported scores.

Patients' ratings of outcome after cholecystectomy is shown in Table 3.12. At twelve weeks, the majority of patients (minilaparotomy 93%, laparoscopic group 92%) thought the outcome of their operation was "good" or "excellent". Nevertheless, at one week, laparoscopic patients were significantly more satisfied with the outcome of their operation than patients in the minilaparotomy group, with a tendency to greater satisfaction at four and twelve weeks also. Similarly, although more than 95% of patients in both groups were satisfied with the appearance of their scar, laparoscopic patients were significantly more satisfied at four and twelve weeks with a tendency to greater satisfaction at one week also. At three months, 97% of laparoscopic patients would recommend the operation they had had to somebody with the same gallbladder problem compared with 94% in the minilaparotomy group.

Cost

Theatre costs were higher for laparoscopic cholecystectomy because of longer theatre time, and higher equipment costs, including disposable instruments (Table 3.12). Ward costs were higher for minilaparotomy because of longer hospital stay. The mean total cost per patient was £396 greater for the

	Minilaparotomy (median/IQR)			Laparoscopic (median (IQR)		
	1 week (n≥93)	4 weeks (n≥102)	12 weeks (n≥94	1 week n≥80	4 weeks n≥108	12 weeks n≥101
General health perception	**50** (25-75)	**75** (50-75)	**75** (50-75)	**50** (50-75)	**75** (50-75)	**75** (50-75)
Change in health since before the operation	**75** (50-75)*	**75** (50-100)	**75** (75-100)	**75** (50-100)*	**75** (50-100)	**100** (75-100)
Physical functioning	**43** (20-63)*	**60** (47-67)*	**67** (57-70)	**57** (37-67)*	**67** (55-70)*	**67** (67-70)
Role limitation: physical problems	**0** (0-25)**	**75** (75-100)	**100** (75-100)	**13** (0-88)**	**100** (0-100)	**100** (100-100)
Role limitation: emotional problems	**67** (0-100)	**100** (0-100)	**100** (100-100)	**100** (0-100)	**100** (33-100)	**100** (100-100)
Social functioning	**75** (50-100)*	**100** (75-100)	**100** (75-100)	**75** (50-100)*	**100** (75-100)	**100** (100-100)
Pain	**44** (33-67)***	**78** (56-100)	**94** (67-100)	**67** (44-78)***	**89** (56-100)	**100** (78-100)
HADS anxiety score	**4** (2-9)	**5** (1-8)	**4** (1-7)	**3** (1-7)	**3** (1-8)	**4** (1-8)
HADS depression score	**3** (1-6)**	**2** (1-6)*	**1** (0-4)	**2** (1-5)**	**1** (0-5)*	**1** (0-3)

Mann-Whitney U test (laparoscopic versus minilaparotomy) * P<0.05 ** P<0.01 *** P<0.001

IQR = interquartile range

TABLE 3.11 SF-36 and HADS scores after cholecystectomy

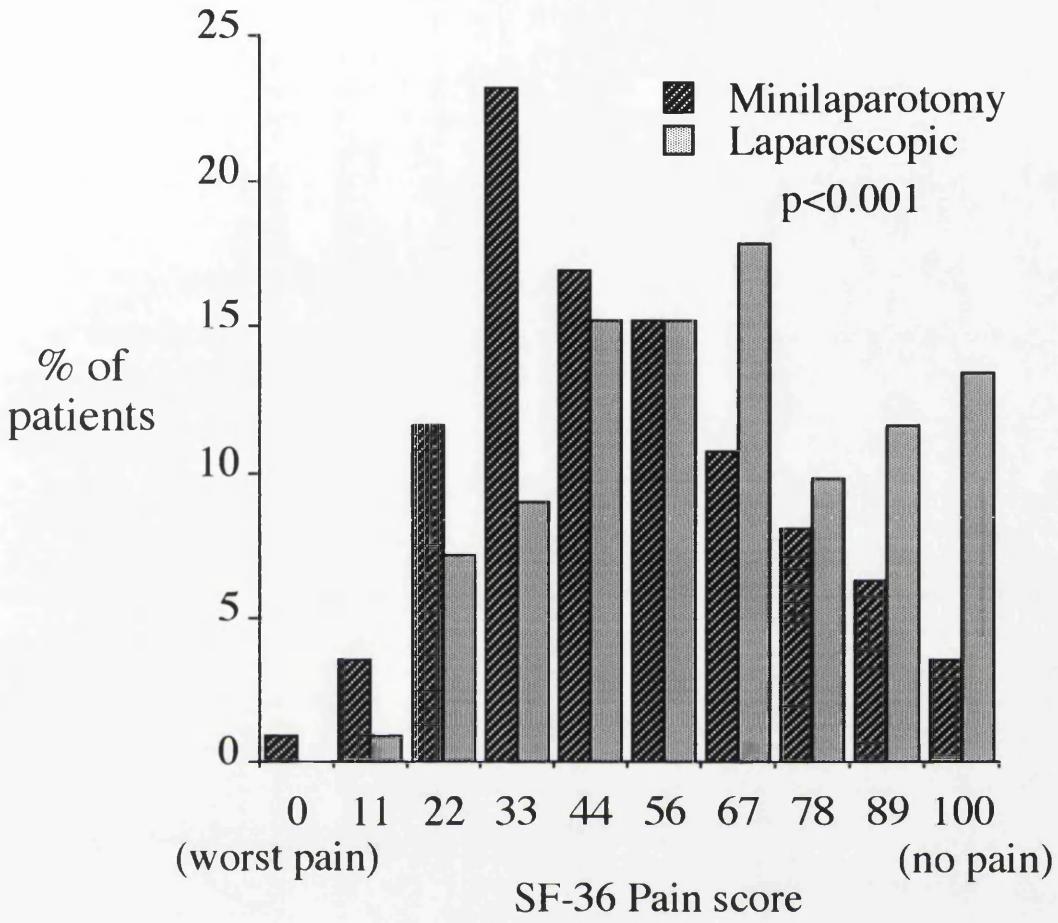

FIGURE 3.11 Histogram of SF-36 pain scores one week after cholecystectomy

	Minilaparotomy			Laparoscopic		
	1 week n (%)	4 weeks n (%)	12 weeks n (%)	1 week n (%)	4 weeks n (%)	12 weeks n (%)
Outcome of operation:						
Excellent	45 (41%)*	66 (52%)	61 (54%)	68 (60%)*	81 (62%)	79 (69%)
Good	50 (45%)*	48 (38%)	45 (39%)	30 (26%)*	38 (29%)	27 (23%)
Fair, Poor, or Very Poor	16 (14%)*	13 (10%)	8 (7%)	16 (14%)*	12 (9%)	9 (8%)
Appearance of scar:						
Very satisfied	79 (71%)	92 (74%)*	84 (74%)*	88 (77%)	114 (87%)*	98 (84%)*
Moderately satisfied	28 (25%)	30 (24%)*	24 (21%)*	20 (18%)	13 (10%)*	16 (14%)*
Barely satisfied or worse	5 (4%)	4 (3%)*	5 (4%)*	6 (5%)	4 (3%)*	2 (2%)*
Recommend operation						
Yes	101 (92%)	118 (93%)	104 (94%)	109 (96%)	123 (94%)	111 (97%)
No	9 (8%)	9 (7%)	7 (6%)	5 (5%)	7 (6%)	3 (3%)

* Chi-squared test for linear trend (laparoscopic versus minilaparotomy) $p<0.05$

TABLE 3.12 Patients' ratings of outcome after cholecystectomy

	Minilaparotomy mean (SD)	Laparoscopic mean (SD)	t test: p value
Theatre	£577 (149)	£687 (126)	<0.001
Laparoscopic disposables	-	£303	
Laparoscopic equipment	-	£60	
Ward costs	£393 (190)	£299 (168)	<0.001
Pathology/Bacteriology	£87	£87	
ECG & Chest Xray	£15 (8)	£15 (8)	
Additional (complications)	£17 (94)	£35 (176)	0.28
TOTAL (excluding disposables)	£1090 (296)	£1183 (296)	0.008
TOTAL (including disposables)	£1090 (296)	£1486 (296)	<0.001

ECG = electrocardiogram

TABLE 3.13 Cost per patient for cholecystectomy.

laparoscopic method (95 % CI £328 to £465). However, if disposable instruments had not been used, the difference in mean cost would have been only £93 (95% CI £ 25 to £162).

Secondary analysis

Although the main analysis was by "intention to treat", we also carried out a secondary analysis from which minilaparotomy patients who required an incision greater than 10cm, laparoscopic patients who required conversion to open cholecystectomy, and patients with a complication prolonging hospital stay were excluded, leaving 120 in the minilaparotomy group, and 131 in the laparoscopic group. Median postoperative stay was two days (interquartile range 2-3) in the laparoscopic group compared to three (interquartile range 3-4) in the minilaparotomy group (Mann-Whitney U test $p<0.001$).

Nonrandomised patients

During the study period, 42 patients who did not fit the study criteria required cholecystectomy . The reasons for exclusion were common bile duct stones in 15, perforated gallbladder empyema in 5, gallbladder empyema in 6, acute cholecystitis requiring urgent surgery in 6, severe upper abdominal adhesions in 3, and similtaneous operative procedure in 7. Three of these were found to have a cholecystocholedochal fistula. Major complications in these patients were retained bile duct stone (1), bile leak from a choledochoduodenostomy (1), subhepatic abscess (1), and pulmonary embolism (1). One patients who presented with cholangitis, septic shock and respiratory failure died from multi-organ failure. There were also 9 patients eligible for the study who refused consent. All of these patients underwent laparoscopic cholecystectomy without complication.

3.4 DISCUSSION

This is the first randomised trial to compare laparoscopic and minilaparotomy cholecystectomy with a sample size of over a hundred patients and to use objective assessment of pain with patient-controlled delivery of analgesia. The findings demonstrate a significant advantage for laparoscopic cholecystectomy in terms of postoperative pain, pulmonary function, hospital stay and return to normal activity. Although the laparoscopic operation resulted in less postoperative pain than minilaparotomy cholecystectomy, 15 (23%) of 65 laparoscopic patients complained of severe pain, and 14 used more than 40 mg of morphine in the first 24 hours. A significant reduction in pulmonary function also occurred after laparoscopic cholecystectomy - more than a third in all three measures on the first postoperative day.

Postoperative oxygen desaturation may be due to a number of different mechanisms: hypoventilation [193], obstructive sleep apnoea [194] (both of which may induced by anaesthetic agents or opiates), or intrapulmonary shunting from small airway closure [192]. In the present study, it is not clear which of these factors resulted in the lower oxygen saturation levels and the higher incidence of desaturation in the minilaparotomy group, but it was probably a combination of all three factors. Morphine consumption in the minilaparotomy group was twice that in the laparoscopic group; this is likely to have contributed to a higher incidence of episodes of obstructive apnoea, and respiratory depression. The greater reduction in postoperative pulmonary function in the minilaparotomy group is likely to have been associated with more small airway collapse and therefore increased intrapulmonary shunting.

There has been only one other randomised trial of laparoscopic versus minilaparotomy cholecystectomy reported in the English literature [99]. However, the small sample size (62 patients), loss to follow-up (only 36

patients completed questionnaires) and difficulties with randomisation limit the value of this Canadian study [232,233]. There were no significant differences between the groups in the patient-assessed outcome measures (McGill pain scores, the Nottingham Health Profile, a quality of life index, and a visual analogue scale) but this may have been entirely due to the small number of patients; in particular, the laparoscopic group did report earlier improvements in quality of life, even though the difference was not statistically significant. These results accord with those of the present study, in which laparoscopic patients reported significantly better SF-36 and HADS scores at one week, smaller inter-group differences at one month, and no differences by three months. In the Canadian study, the modest advantage of the laparoscopic method over minilaparotomy in hospital stay (median 3 versus 4 days) and duration of convalescence (median 8 versus 13 days) was also consistent with the findings of the present study.

The median hospital stay for laparoscopic cholecystectomy in our study is similar to that reported from other European centres [32,77,145], whereas a median stay of one day is more typical for American centres [76,81]. While outpatient open cholecystectomy has been reported [4,207], the median postoperative stay of four days after minilaparotomy cholecystectomy in this study is comparable with that reported in several studies [6,60,98,99]. The average postoperative stay for standard cholecystectomy has been falling over the past decade and in audit reports from Britain [204] and America [95] is now six and four days respectively.

The period taken to return to normal activities after laparoscopic cholecystectomy in this study was between one and two weeks - similar to that widely reported [77,101,114,282]. Return to normal activity for open cholecystectomy has not been accurately measured but is commonly perceived to be at least six weeks [205]. In this study, patients returned to

normal activites between 10 days and three weeks after minilaparotomy cholecystectomy. Less than a third of patients were in paid employment, about a third worked in the home, and another third were retired. There was a marked discrepancy between the median time to return to work in the home (10 days for laparoscopy, and 15 days for minilaparotomy) and the median of five to six weeks to return to paid employment. This probably reflects general practitioners' and patients' pre-conceived ideas about the appropriate duration of convalescence after surgery.

The laparoscopic conversion rate in this study was higher than in reports from specialist centres [77], but less than than the 14% reported in a large prospective audit in the UK [135]. This conversion rate reflected three factors: the severity of biliary disease, a low threshold for conversion, and the fact that some surgeons were still on the "learning curve".

In this study, minilaparotomy was significantly cheaper than laparoscopic cholecystectomy, and would still have been cheaper if reusable instruments had been used for laparoscopic surgery. There are conflicting reports on the comparative cost of laparoscopic and open cholecystectomy: several studies have reported that the costs of laparoscopic cholecystectomy are less than open cholecystectomy [101,125,213,283], while one has reported increased costs [205]. Operation time and hospital stay, which are the two main determinants of the cost of cholecystectomy, vary from centre to centre. Another important factor is whether disposable instruments are used during laparoscopic cholecystectomy, re-usable instruments being substantially cheaper.

This study has shown a similar incidence of complications after both procedures. However, the low incidence of major complications means that only rigorous large scale audit can accurately estimate the incidence of iatrogenic complications. Audit has shown a higher incidence of bile duct

injury after laparoscopic cholecystectomy [134-136] compared with open cholecystecytomy [78,90,93,95]. Furthermore, the bile duct injuries from laparoscopic cholecystectomy tend to be more extensive and higher in the duct system [107-109] than those from open cholecystectomy, thus reducing the chance of a successful outcome to reconstruction [86]. As most studies of minilaparotomy have been small, it is unclear whether the minilaparotomy technique also results in a higher bile duct injury rate. However, in the published results of over 2500 operations there have been only two bile duct injuries [1-7]. The two injuries occurring during our trial were both minor, and did not cause significant morbidity to the patient.

In conclusion, this study has shown that laparoscopic cholecystectomy confers moderate benefits on patients in comparison with minilaparotomy cholecystectomy. These benefits take the form of reduced postoperative pain and pulmonary dysfunction, shorter hospital stay, and earlier return to normal activity. However, the laparoscopic operation was more expensive to the National Health Service (NHS). It seems likely that, as surgeons complete the learning curve, the relative benefit to patients will increase, while the relative cost to the NHS will decrease. Rigorous large-scale audit is needed to ensure that the apparent superiority of laparoscopic cholecystectomy is maintained in the long term.

Chapter 4

METABOLIC RESPONSES TO LAPAROSCOPIC AND MINILAPAROTOMY CHOLECYSTECTOMY

4.1 INTRODUCTION

The stress of surgery evokes a wide variety of biochemical and physiological changes including production of cytokines and acute phase proteins, increase in the levels of "stress" hormones, loss of muscle protein, increased vascular permeability, and changes in white cell count subsets. Although some of these responses are considered to be a homeostatic defence mechanism, some of the consequences, such as the catabolic state, are thought to be deleterious [241]. Hence, in recent years, many investigators have sought to find ways of reducing the metabolic response to surgery [239,240,284-286].

With reference to cholecystectomy, attempts have also been made to reduce the degree of surgical trauma. Indeed, the use of a small transverse incision for open cholecystectomy (minilaparotomy) has been shown to result in a more rapid postoperative recovery than a standard incision [1-7]. More recently, laparoscopic cholecystectomy has been introduced rapidly into routine clinical practice, and is replacing open cholecystectomy as the procedure of choice for symptomatic cholelithiasis [124]. The claimed advantages are less postoperative pain [203], and a more rapid return to normal activity [124].

It has been shown that the magnitude of the metabolic response to injury is proportional to the degree of the surgical trauma [8-11]. It has been postulated, therefore, that the reduction of "access trauma" by the laparoscopic technique might diminish the metabolic response to cholecystectomy [145]. However, diagnostic laparoscopy alone is associated with a substantial hormonal and glycaemic response, which is thought to be evoked by the stimulus of peritoneal distension [246]. Furthermore, the magnitude of the metabolic response has been shown to correlate with the duration of surgery [9,287] which, for laparoscopic cholecystectomy, is longer than open cholecystectomy [81].

Therefore, the aim of this randomised study was to compare both the pattern and the magnitude of the metabolic response to injury after laparoscopic and minilaparotomy cholecystectomy.

4.2 PATIENTS AND METHODS

This study was carried out as part of the randomised controlled trial comparing minilaparotomy and laparoscopic cholecystectomy described in Chapter 3. The metabolic study was approved by the local hospital ethical committees and informed consent obtained from all patients. Detailed metabolic studies were performed in ten consecutive patients in each arm of the trial. In the metabolic study, patients requiring conversion to standard cholecystectomy, patients with medical conditions or on treatment that might result in an altered metabolic response to surgery, and patients who developed complications were excluded. The median age (range) in the laparoscopic group was 58 (30-71) years and 44 (25-70) in the minilaparotomy group. There was one male in each group.

Anaesthetic techniques were similar in both groups. Agents used were thiopentone or propofol for induction, suxamethonium for initial muscle relaxation, morphine and ethrane for maintenance, atrocurium besylate or vecuronium for muscle relaxation, and neostigmine bromide for reversal. Minilaparotomy cholecystectomy was performed through a five to seven centimetre subcostal incision [5], while laparoscopic cholecystectomy was performed using a four trocar technique using electrocautery. All wounds in both groups were infiltrated with 20mls of 0.5% bupivacaine at the end of the procedure. The median operation time was longer in the laparoscopic group (median 65 versus 46 minutes, p=0.01). Postoperatively, patients received morphine by a disposable patient-controlled analgesia device [272]. Over the first 24 hours, patients were given intravenous fluids (1 litre normal saline, and 2 litres 5% dextrose), with nil orally, and thereafter allowed free fluids and a normal diet. All patients made an uneventful postoperative recovery.

A blood sample was collected from an indwelling venous cannula on the morning of surgery (before premedication), and at 3, 6, 9, 12, 18, 24, 48, 72, and

168 hours after incision. Blood samples were immediately separated by centrifugation, and aliquots of serum and plasma frozen and stored at -20°C. Twenty-four hour urine samples were collected the day before surgery, and over the first, second and third postoperative days. An additional urine sample was collected on the 7th postoperative day. Samples were preserved with thymol, and after recording volumes, aliquots frozen and stored at -20°C.

The cytokine, interleukin-6 (IL-6), which is thought to play a central role in the development of the metabolic response [116], was measured by the hybridoma growth stimulation assay using the mouse B-cell hybridoma 7TD1 line [9,237,288]. Cell numbers were evaluated colorimetrically using 3-(4,5,-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (Thiazolyl Blue) [289], a tetrazolium salt cleaved by dehydrogenase enzymes present in living cells. Standardization was performed using recombinant IL-6 [290] (obtained from the National Institute of Biomedical Standards and Controls, Potters Bar, Hertfordshire, UK). Serum samples were heat-treated at 56°C for 30 minutes before analysis to inactivate any inhibitors. The detection limit of this bioassay was approximately 14 units/ml, and the imprecision (co-efficient of variation) calculated from 20 consecutive assays was 19%. The specificity of the assay was confirmed using a polyclonal anti-IL-6 antibody.

The positive acute phase proteins, C reactive protein (CRP) and fibrinogen, and the negative acute phase proteins, albumin and transferrin (whose fall reflects increased vascular permeability and loss to the tissue spaces [242]), were measured by nephelometry. The detection limit for serum CRP was 5 mg/l. Serum iron, which falls after surgery [291], was measured colorimetrically using a Hitachi 737 analyser (Boehringer, Mannheim, Germany).

Neutrophil and lymphocyte counts were measured with a Coulter Blood Analyser. Plasma cross-linked fibrin degradation products (FDPs), a measure of fibrin turnover, were measured using an enzyme linked immuno-absorbancy

assay (AGEN, Parsippany, New Jersey, USA). The "stress" hormone, cortisol, was measured by fluorescence polarization immunoassay. Polymorphonuclear (PMN) elastase, which is released by activated neutrophils [292], was measured using the PMN elastase IMAC immuno-activation kit (Diagnostica Merk, Frankfurt, Germany).

Urinary 3-methylhistidine, which is a measure of muscle protein breakdown [293], was measured by ion-exchange chromatography with ninhydrin detection. Urinary creatinine was measured using the alkaline picrate reaction and urea measured electrochemically using a Beckman CX-3 instrument. Urinary nitrogen was calculated on the basis that urea loss comprises 80 per cent of total nitrogen loss.

Unlike methylhistidine and urea, urinary samples for catecholemine measurement required to be acidified. Therefore, 24 hour urine collections (acidified with 20mls of concentrated hydrochloric acid) for catecholamine measurement were collected from a second group of 20 patients, 10 in each arm of the study. In this group of patients, the median age (range) was 56 (27-72) in the laparoscopic group, and 45 (19-82) in the minilaparotomy group with no males in the laparoscopic group and two in the minilaparotomy group. Urinary catecholamines were measured using high performance liquid chromatography with electrochemical detection [294].

As part of the study of postoperative pain and pulmonary function described in Chapter 3, peak expiratory flow rate was measured the day before operation and 24 hours postoperatively using a Respiradyne pulmonary function monitor (Sherwood Medical, Crawley, W. Sussex, UK). Analgesia consumption over the first 24 hours was assessed using patient-controlled delivery of morphine (Baxter PCA infusor system, Baxter Healthcare Ltd, Norfolk, UK), and pain assessed by a linear analogue pain score at 24 hours.

Statistics

In order to produce summary measures [295], each parameter was plotted against time and the area under the curve calculated for each individual patient using the programme, Multifit, on an Apple Macintosh computer. For the two negative acute phase reactants, albumin and transferrin, the falls from pre-operative values were plotted. Areas under the curve in the two groups were compared using the Mann-Whitney U test. The magnitude of changes in each metabolic variable (areas under the curve) were compared using Pearson's correlation. Values of white cell counts, urinary nitrogen, 3-methylhistidine and catecholamines in the two groups were compared at each time point with the Mann-Whitney U test (with the Bonferroni correction as appropriate). Comparison of postoperative and pre-operative catecholamines and 3-methylhistidine was performed with the Wilcoxon matched pairs test (with the Bonferroni correction).

4.3 RESULTS

The time course of the metabolic changes is shown in Figures 4.1-4.9 and Table 4.1. IL-6 rose within 3 hours, peaking at 6 hours, with levels only beginning to fall after 24 hours, and returning to near normal levels at 7 days (Figure 4.1). CRP began to rise after 9 hours, peaking at 48 hours, and returning to near normal levels at 7 days (Figure 4.2). Albumin and transferrin fell over the first 24 hours, remaining depressed over the first 3 days, but rising by day 7 (Figures 4..3 and 4.4). The iron/transferrin ratio fell within 6 hours and remained depressed at 7 days (Figure 4.5). Fibrinogen and FDPs rose steadily over the first 3 days, remaining elevated at 7 days (Figures 4.6 and 4.7). Cortisol levels were elevated pre-operatively reflecting anxiety, and rose to peak levels at 3-9 hours, returning to normal by 24 hours (4.8). Neutrophil counts were elevated at 6 hours, slightly raised at 48 hours, and near normal at 7 days (Table 4.1). PMN elastase was elevated modestly at all postoperative time points, compared to pre-operative values (Wilcoxon matched pairs test $p<0.01$) - Figure 4.9. Lymphocyte counts were depressed at 6 and 48 hours, and returned to near base-line values at 7 days (Table 4.1). A similar time course of metabolic changes occurred in the two groups.

The calculated areas under the curves are shown in Table 4.2. Although there were considerable within group variations, there were no significant differences in the magnitude of the changes between the two groups. By contrast, the laparoscopic patients had better postoperative pulmonary function, consumed less morphine and had lower pain scores than the minilaparotomy patients (Table 4.3).

Urinary nitrogen loss was similar in both groups (Table 4.4). Food intake was not measured, and nitrogen balance could not therefore be calculated. However, both groups started eating on the first postoperative day.

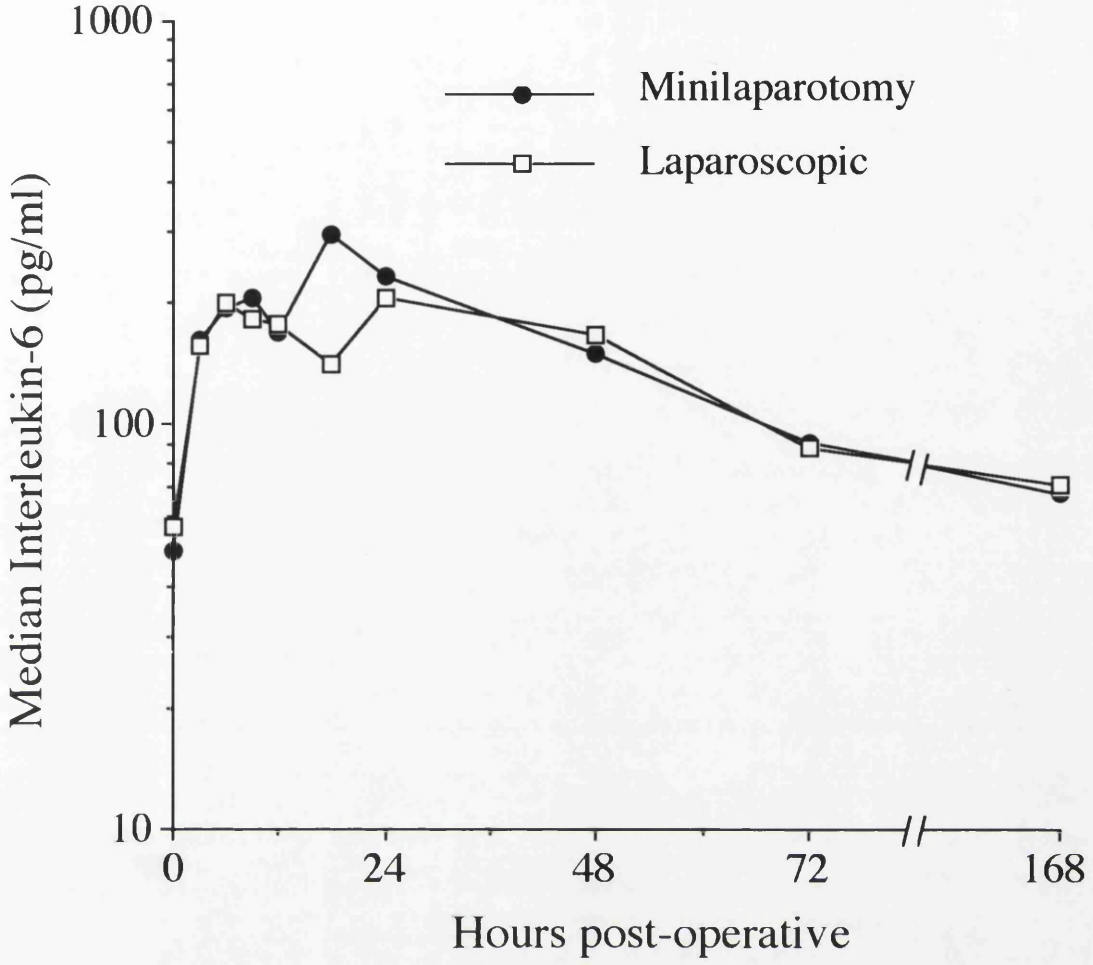

FIGURE 4.1a Changes in serum interleukin-6 after cholecystectomy

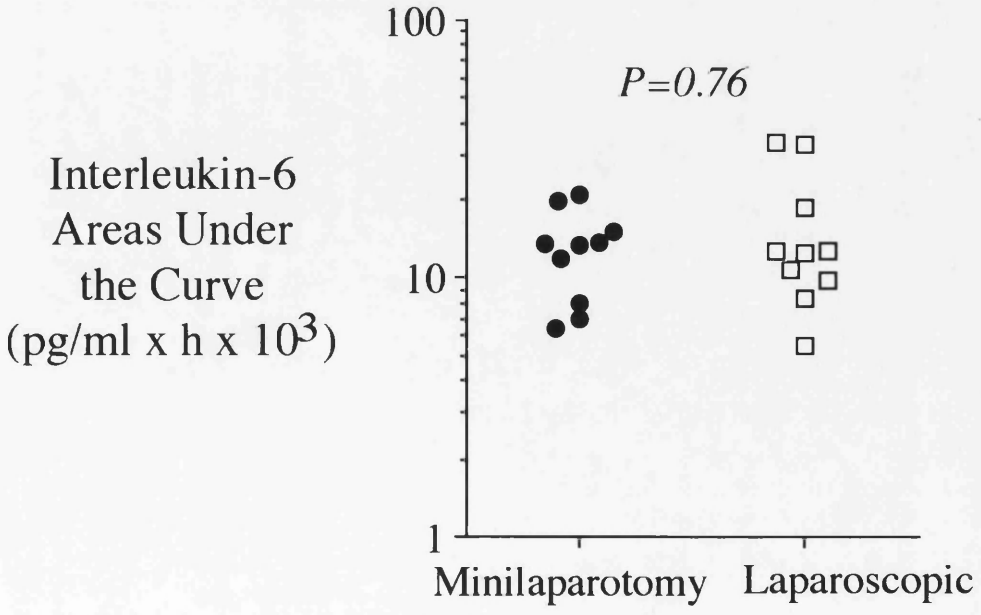

FIGURE 4.1b Areas under the curve for individual patients of interleukin-6 changes in the first 72 hours

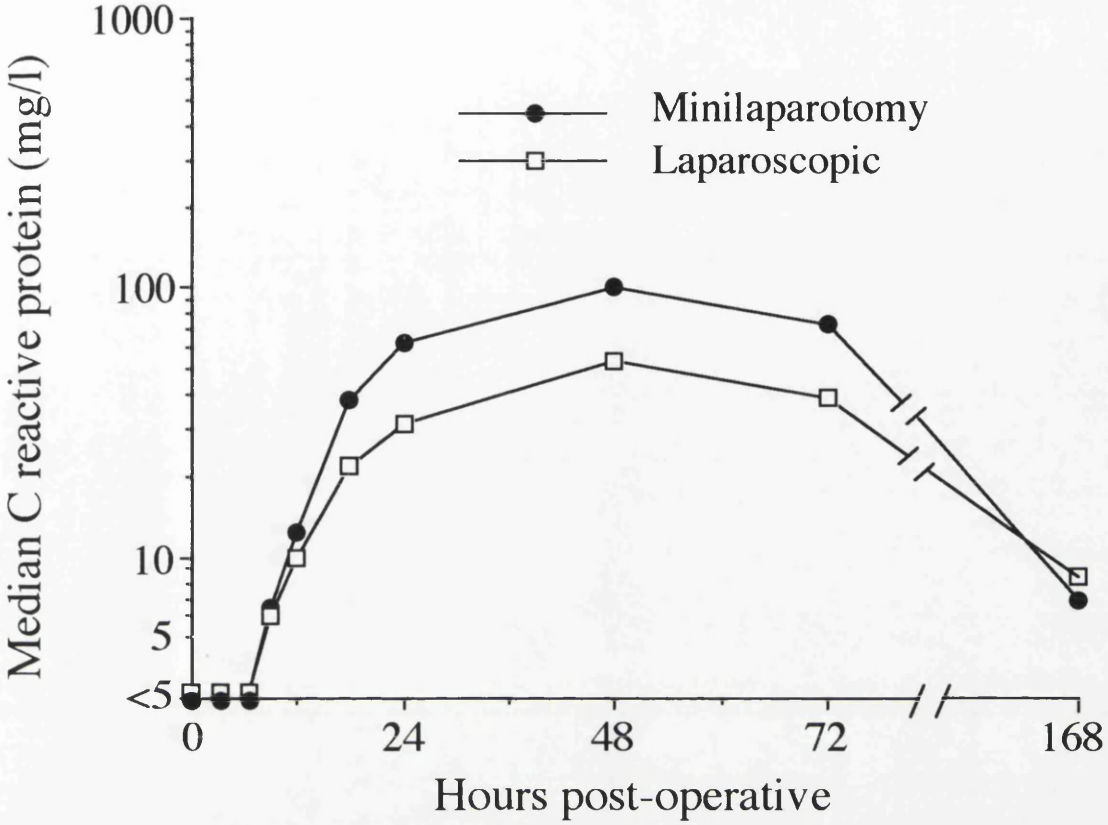

FIGURE 4.2a Changes in serum C reactive protein after cholecystectomy (detection limit 5mg/l).

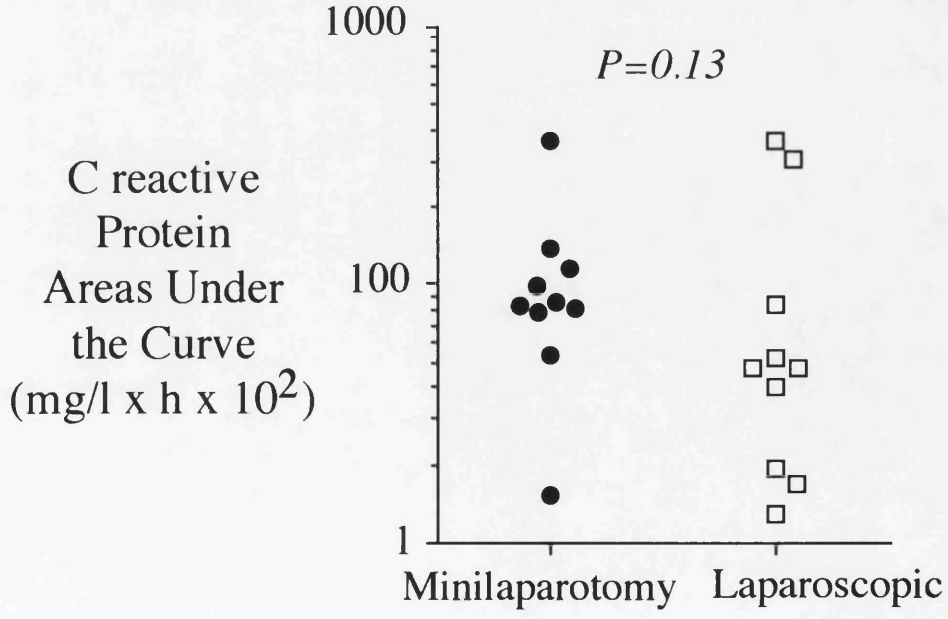

FIGURE 4.2b Areas under the curve for individual patients of C reactive protein changes

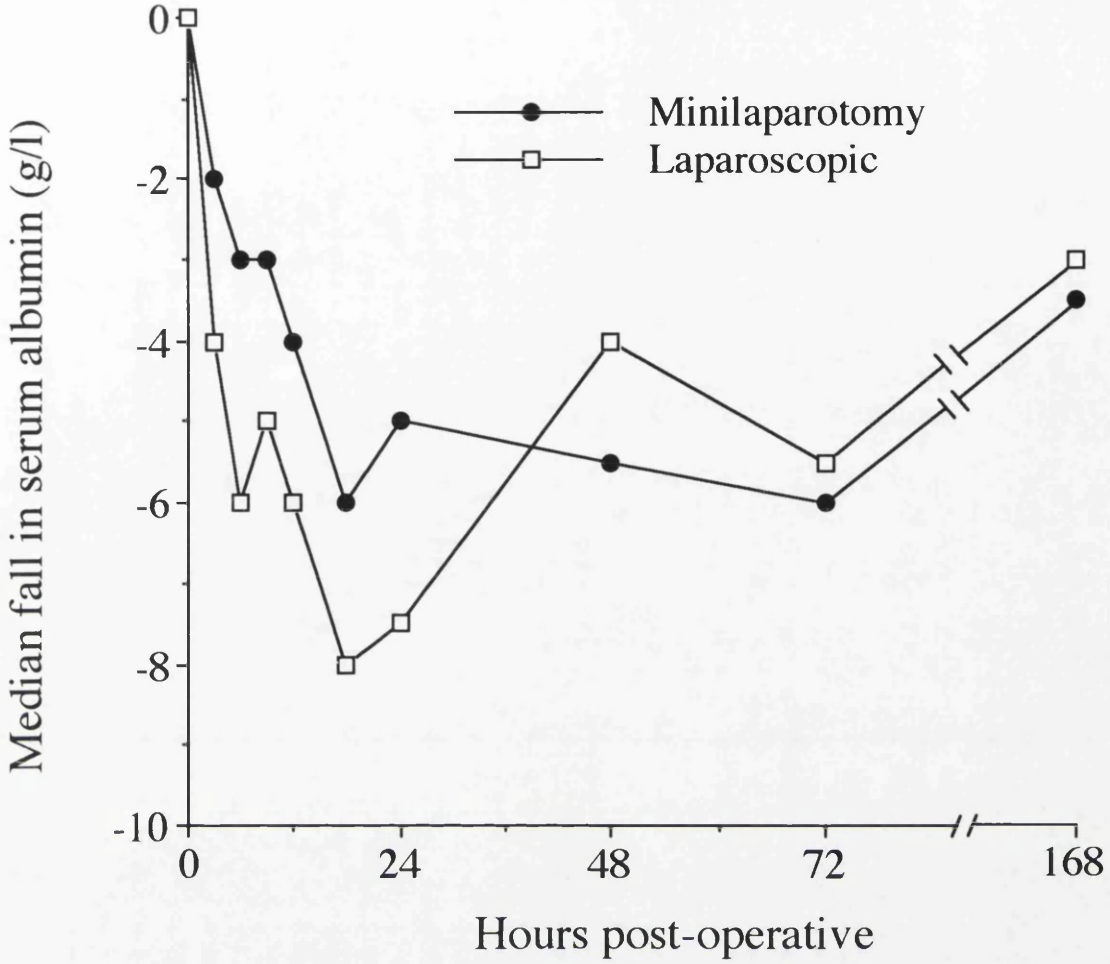

FIGURE 4.3a Changes in serum albumin after cholecystectomy

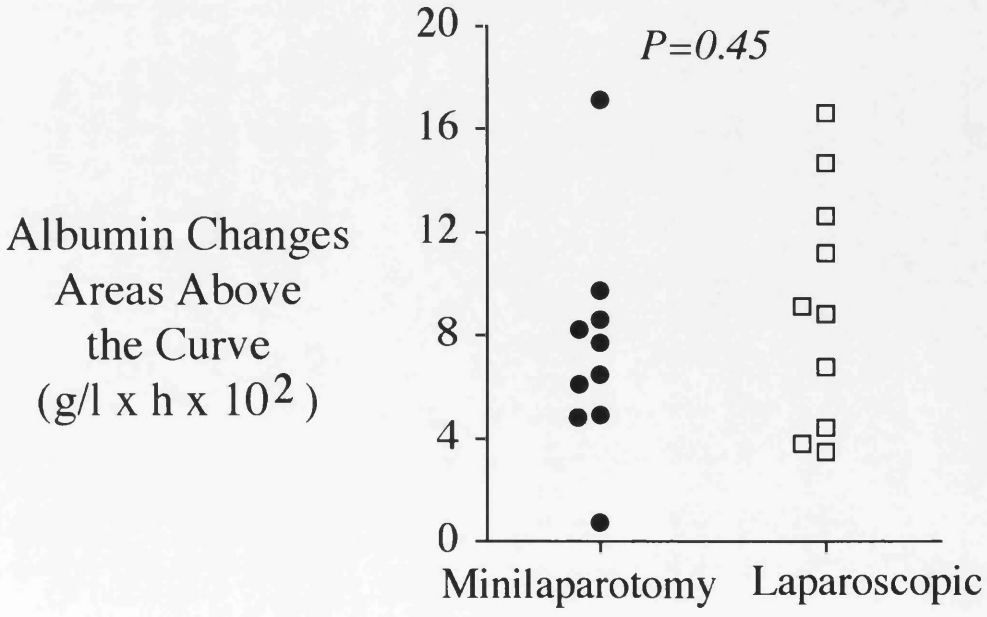

FIGURE 4.3b Areas above the curve for individual patients of albumin changes

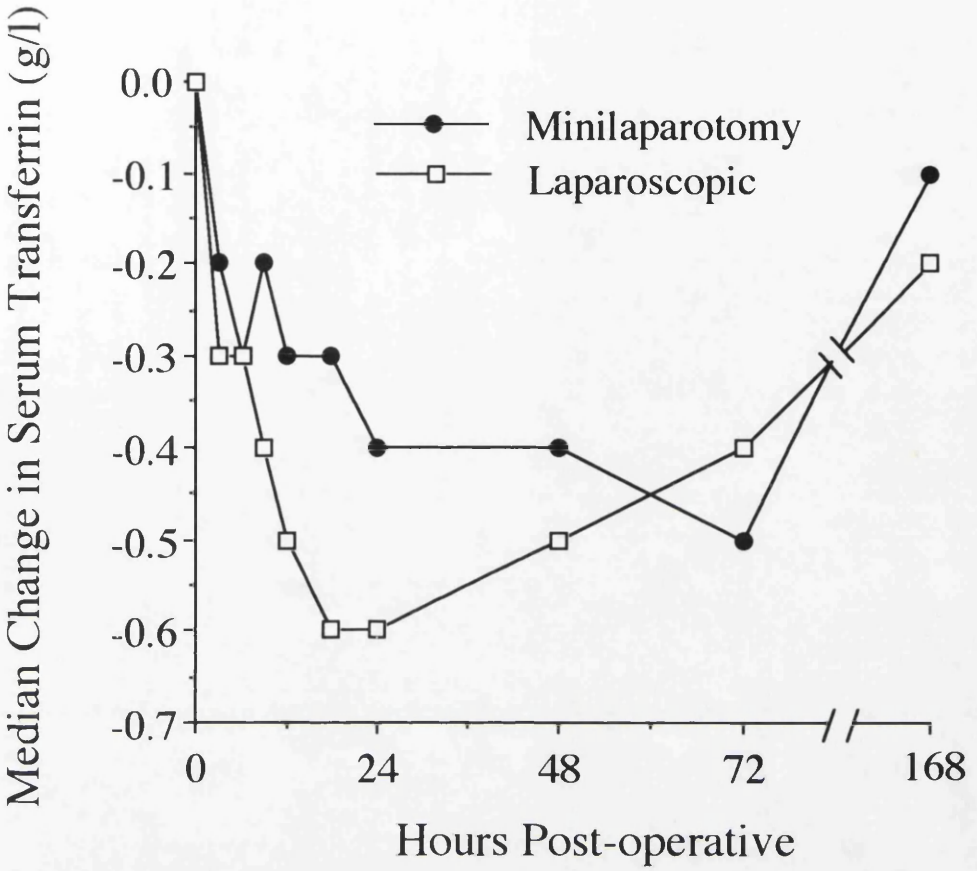

FIGURE 4.4a Changes in serum transferrin after cholecystectomy

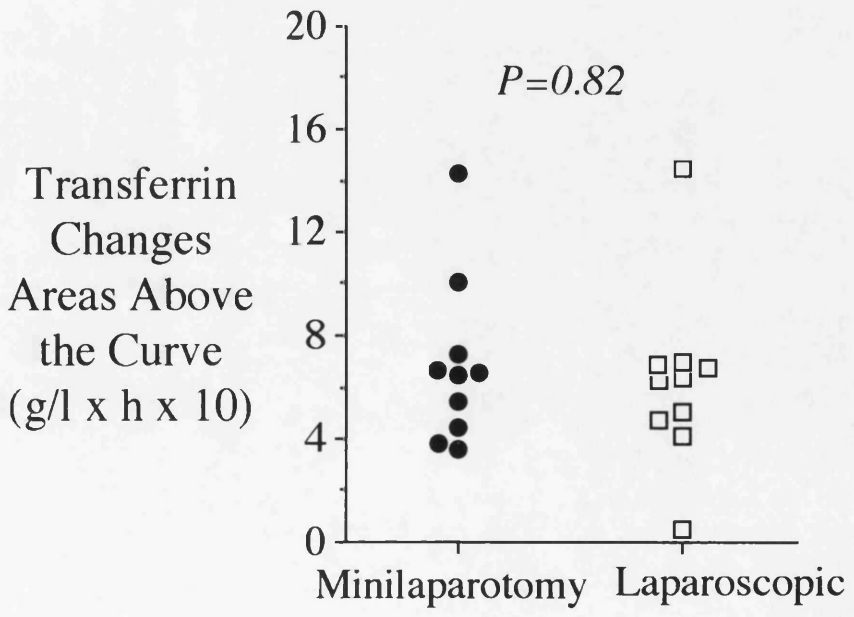

FIGURE 4.4b Areas above the curve for individual patients of transferrin changes

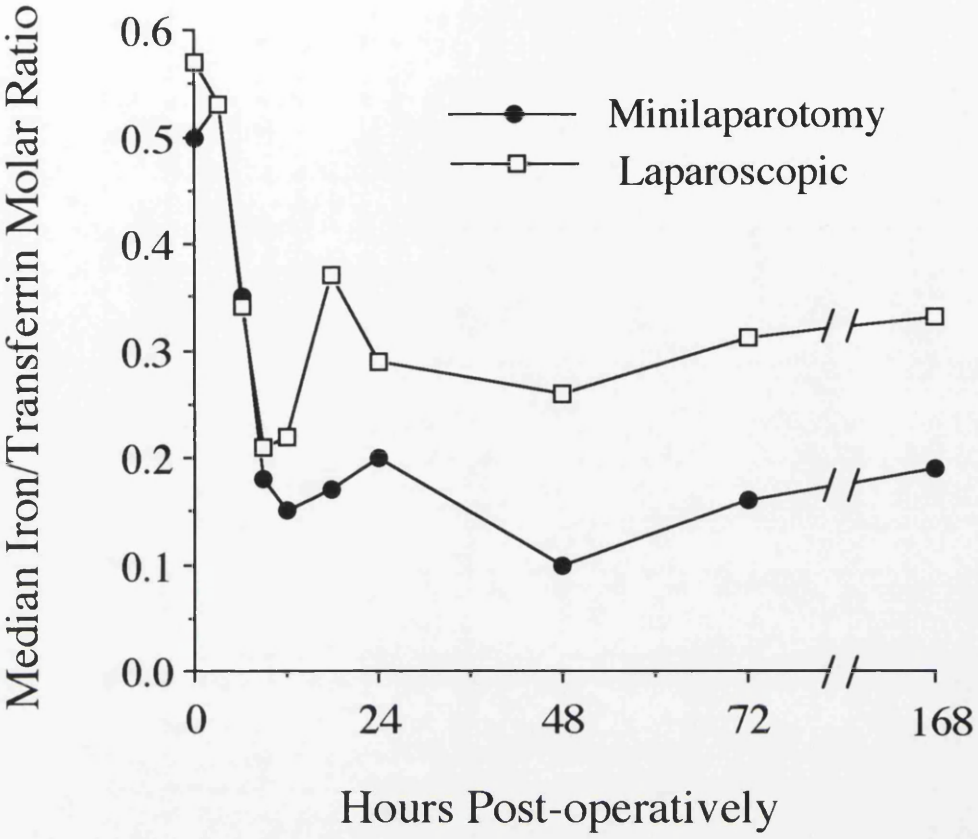

FIGURE 4.5a Changes in iron/transferrin ratio after cholecystectomy

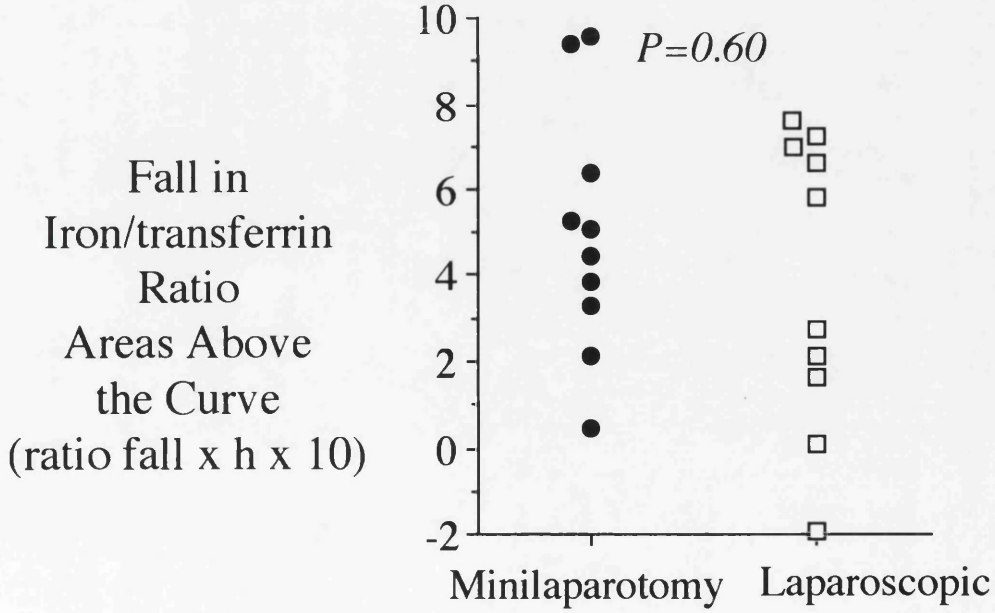

FIGURE 4.5b Areas above the curve for individual patients of the fall in iron/transferrin ratio

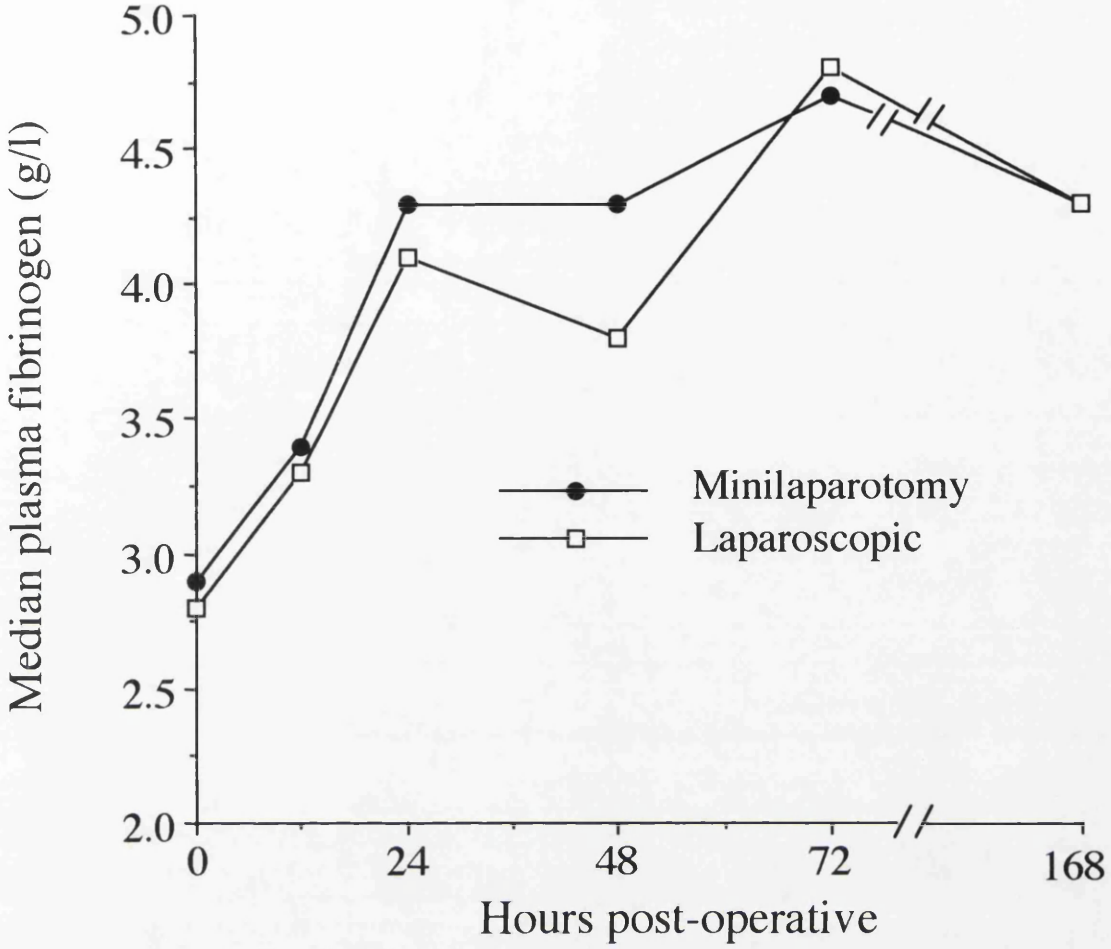

FIGURE 4.6a Changes in plasma fibrinogen after cholecystectomy

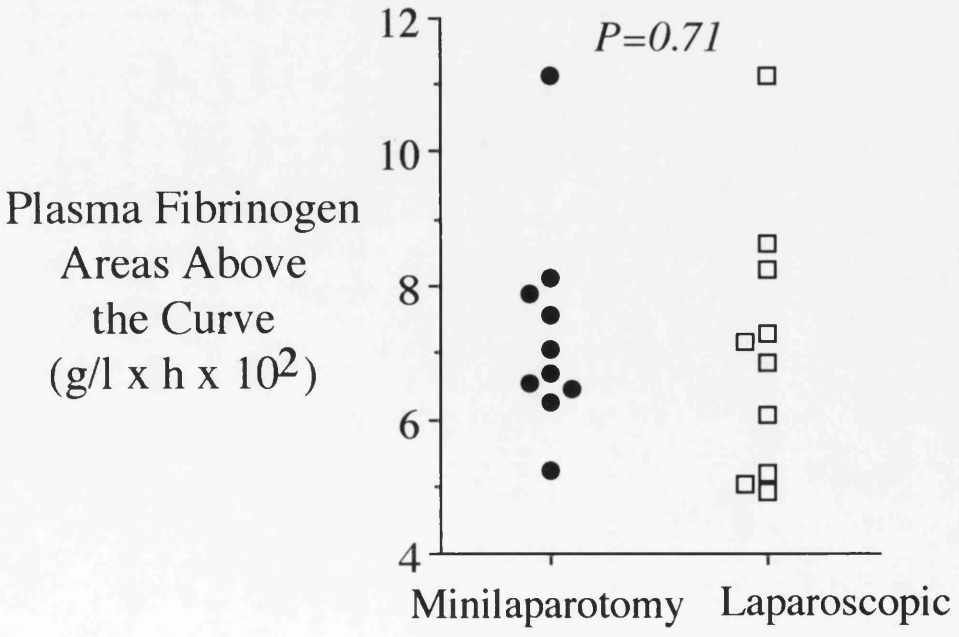

FIGURE 4.6b Areas below the curve for individual patients of the plasma fibrinogen changes

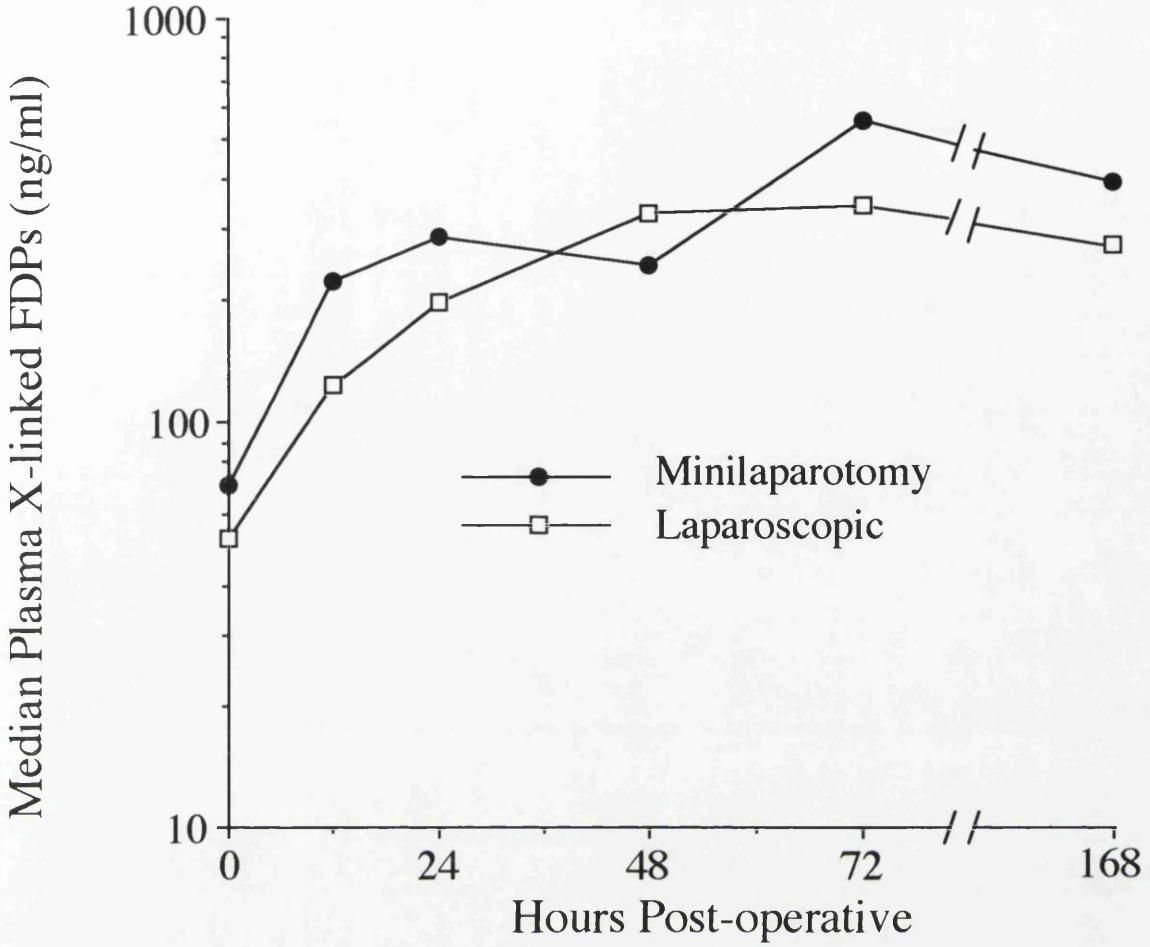

FIGURE 4.7a Changes in plasma cross-linked fibrin degradation products after cholecystectomy

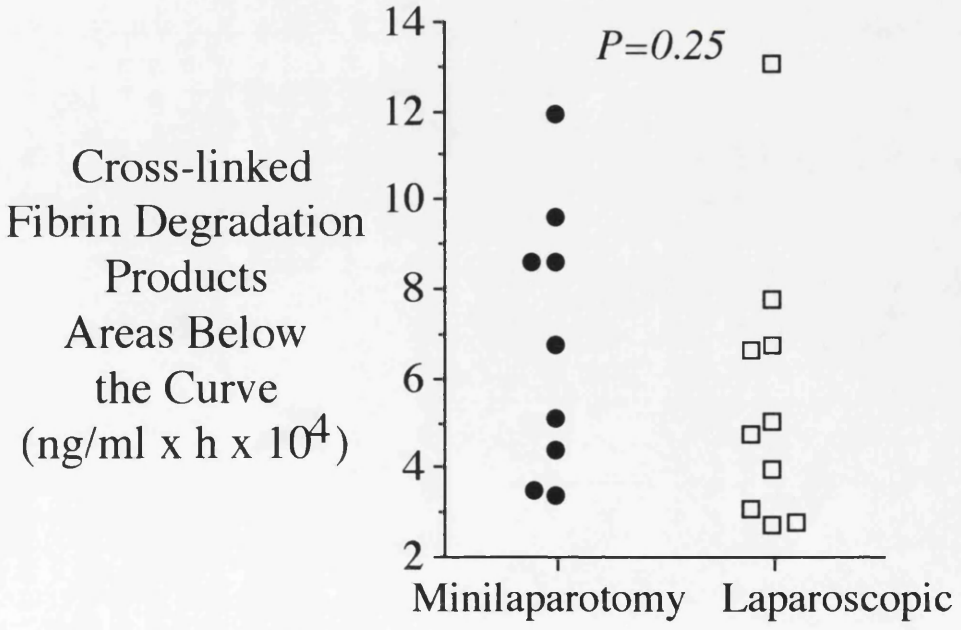

FIGURE 4.7b Areas below the curve for individual patients of the plasma fibrinogen changes (one missing value in minilaparotomy group)

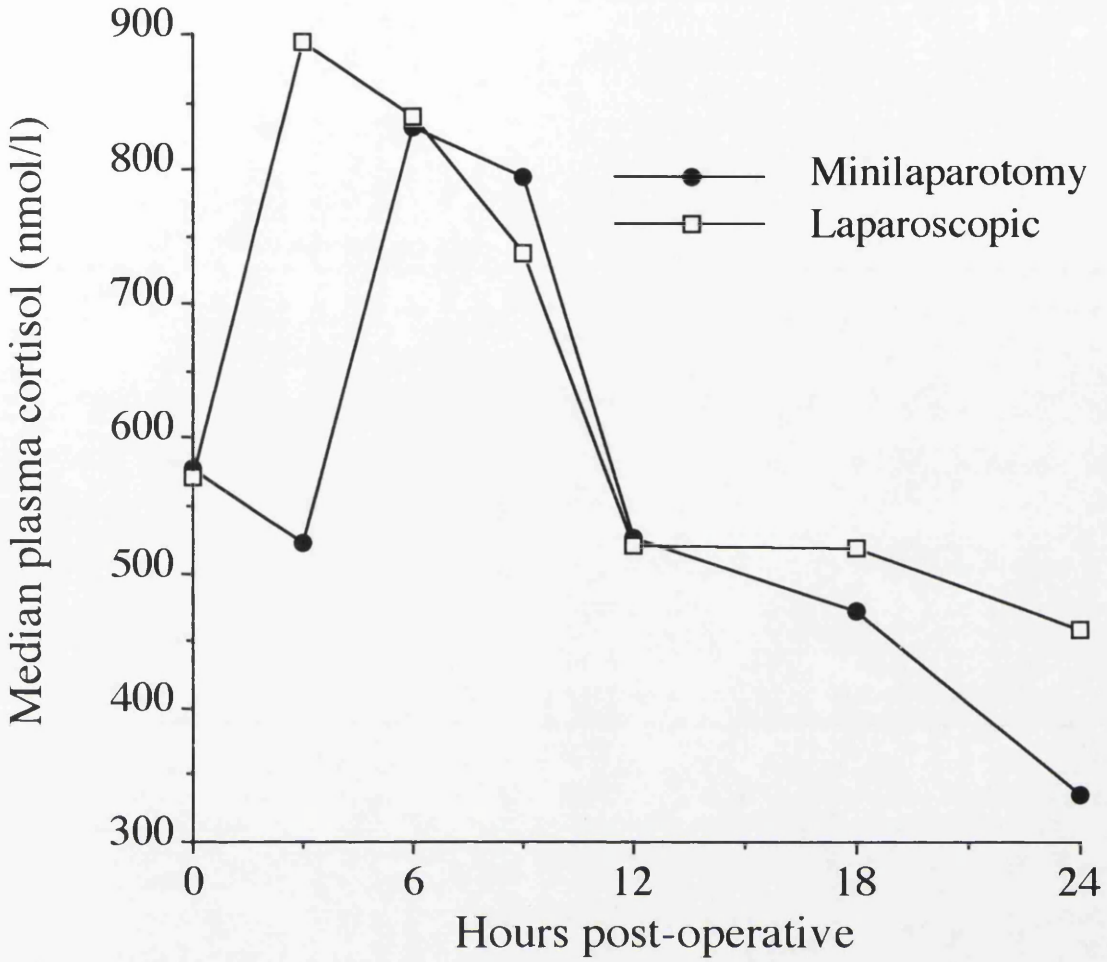

FIGURE 4.8a Changes in plasma cortisol after cholecystectomy

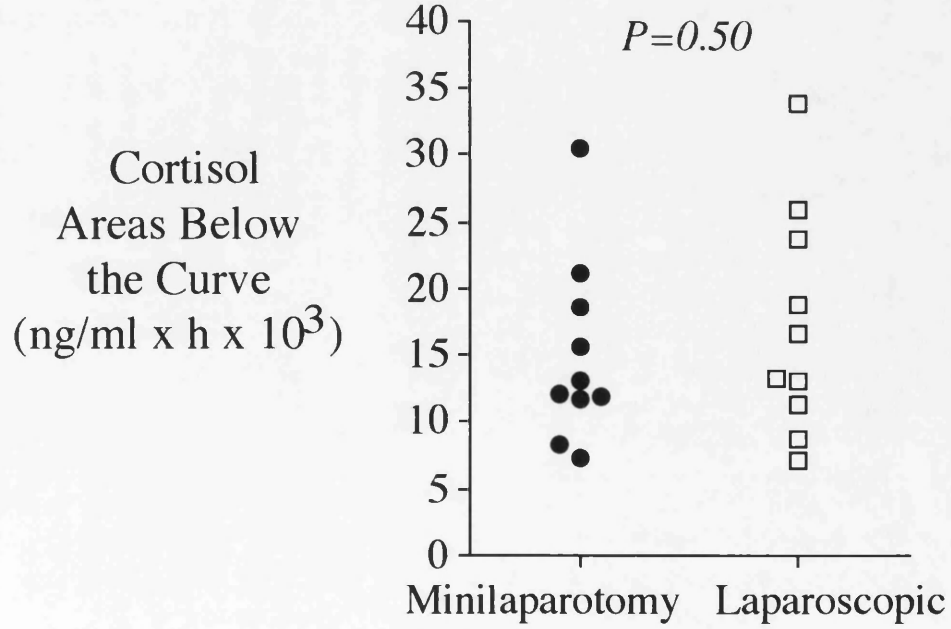

FIGURE 4.8b Areas below the curve for individual patients of the plasma cortisol changes

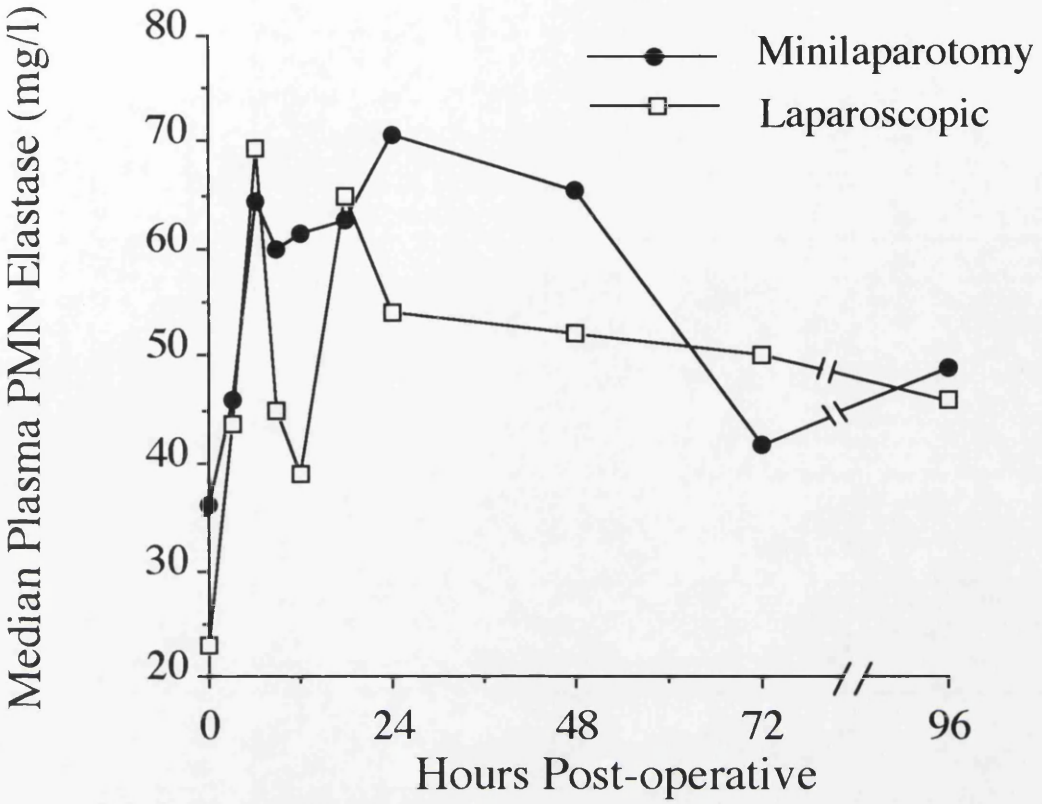

FIGURE 4.9a Changes in plasma polymorphonuclear elastase after cholecystectomy

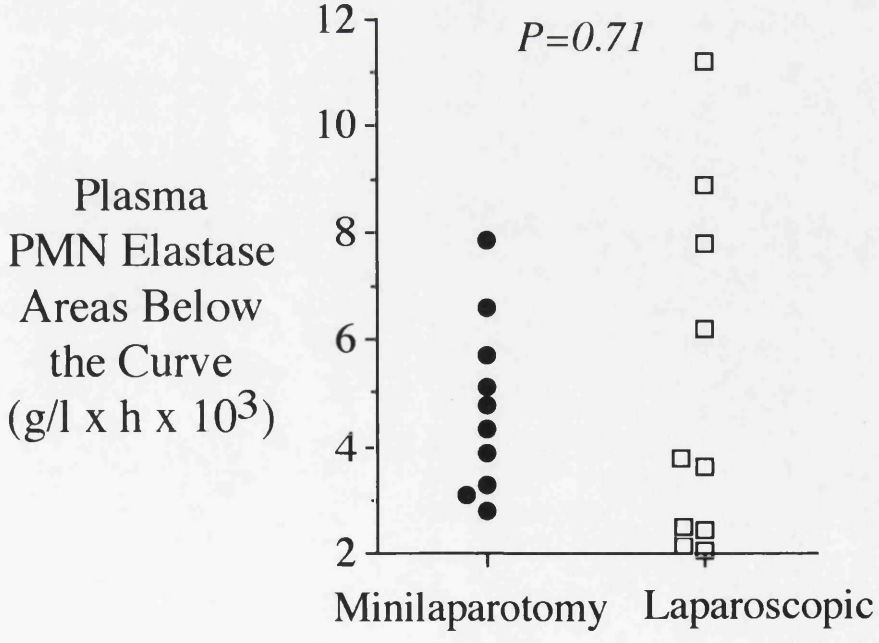

FIGURE 4.9b Areas below the curve for individual patients of the plasma polymorphonuclear elastase changes

		Pre-op	6 hours	48 hours	7 days
Neutrophil count * (x 10^9/l)	**M**	4.1 (2.2-7.4)	11.9 (8.6-15.0)	6.9 (1.7-13.2)	6.1 (3.3-8.5)
	L	3.4 (2.6-4.1)	10.3 (6.1-15.4)	5.9 (2.8-13.0)	4.3 (3.5-10.7)
Lymphocyte count * (x 10^9/l)	**M**	2.1 (1.1-3.7)	1.5 (0.6-2.3)	1.8 (1.0-2.6)	2.2 (1.6-6.8)
	L	2.6 ((1.1-3.5)	1.3 (0.3-6.5)	1.7 (0.6-5.9)	1.9 (1.9-4.5)

Values median (range) M=minilaparotomy, L=laparoscopic
Mann-Whitney U test: no significant intergroup differences at any time point.

TABLE 4.1 Neutrophil and lymphocyte count changes after cholecystectomy

	Units	**Minilaparotomy**		**Laparoscopic**		P value *
		Median	Range	Median	Range	
C reactive protein	(mg/l x hrs x 10^2)	**84**	15-359	**48**	13-365	0.13
Interleukin-6	(pg/ml x hrs x10^2)	**135**	66-212	**117**	54-336	0.76
Fall in Albumin	(g/l x hrs x 10)	**71**	7-171	**90**	35-166	0.45
Fall in Transferrin	(g/l x hrs)	**65**	36-142	**63**	5-145	0.82
Fibrinogen	(g/l x hrs x 10)	**69**	52-111	**70**	49-111	0.71
Fibrin Degradation Products	(ng/ml x hrs x 10^3)	**68**	34-119	**49**	27-130	0.25
Cortisol	(nmol/l x hrs x 10^3)	**13**	7-30	**15**	7-34	0.50
PMN ELastase	(mg/l x hrs x 10^2)	**46**	28-78	**37**	20-112	0.60
Fall in Iron/ transferrin ratio	(ratio fall x hrs)	**48**	4-96	**43**	(-19)-76	0.60

* Mann-Whitney U test

TABLE 4.2 Areas under the curve of the metabolic changes after cholecystectomy

	Minilaparotomy Median (IQ range)	**Laparoscopic** Median (IQ range)	**P value***
Morphine Consumption (mg morphine)	44 (24-62)	16 (10-26)	0.021
Peak Expiratory Flow Rate (percentage of pre-op. value)	44 (36-49)	78 (53-80)	0.012
Linear Analogue Pain Score (0-100mm)	58 (30-85)	37 (30-40)	0.074

* Mann-Whitney U test

TABLE 4.3 Post-operative pain and pulmonary function 24 hours after cholecystectomy.

		Pre-op	Day 1	Day 2	Day 3	Day 7
24h Urinary *	**M**	5.0 (4.6-9.3)	3.5 (3.0-6.5)	7.4 (4.5-11.5)	7.4 (2.1-11.8)	-
Nitrogen * (g/24h)	**L**	7.5 (3.6-11.8)	6.9 (3.8-9.7)	6.0 (3.3-14.6)	6.9 (3.8-13.6)	-
3-Methylhistidine *	**M**	23 (16-36)	22 (13-31)	23 (14-29)	27 (20-33)	19 (14-36)
(mmol/mmol creatinine)	**L**	23 (13-28)	22 (13-25)	23 (13-31)	26 (17-41)	17 (12-20)
(RR: 12-42)						
Noradrenaline *	**M**	18 (4-119)	40 (7-188)	39 (15-126)	-	-
(nmol/mmol creatinine)	**L**	21 (5-152)	42 (13-101)	22 (13-163)	-	-
(URL: 100)						
Adrenaline *	**M**	7 (3-103)	16 (1-68)	14 (6-50)	-	-
(nmol/mmol creatinine)	**L**	38 (1-92)	29 (2-92)	32 (4-76)	-	-
(URL: 30)						
Dopamine *	**M**	136 (58-234)	129 (75-292)	195 (126-282)	-	-
(nmol/mmol creatinine)	**L**	124 (66-252)	137 (42-268)	118 (70-306)	-	-
(URL: 400)						

Values median (range), M=minilaparotomy, L=laparoscopic RR=reference range, URL=upper reference limit
* Mann-Whitney U test: no significant intergroup difference at any time-point.

Table 4.4 Urinary nitrogen, 3-methylhistidine, and catecholamines pre- and post-operatively in the two groups.

	CRP	IL-6	Albumin	Trans-ferrin	Fibrin-ogen	FDPs	Cortisol	PMN Elastase	Fe/Tf ratio	PEFR ratio	Pain Score
IL-6	0.83***										
Albumin	0.24	0.29									
Transferrin	0.30	0.51*	0.69***								
Fibrinogen	0.76***	0.48*	-0.10	-0.11							
FDPs	0.53*	0.52*	-0.08	-0.20	0.36						
Cortisol	0.17	0.21	-0.05	-0.30	0.11	0.49*					
PMN elastase	0.75***	0.79***	0.24	0.34	0.46*	0.34	0.45				
Fe/Tf ratio	0.17	0.16	0.12	0.15	0.21	-0.01	0.13	0.24			
PEFR ratio	-0.24	0.07	-0.07	0.15	-0.45	-0.12	-0.08	-0.04	-0.27		
Pain Score	0.09	0.07	0.09	0.04	-0.05	0.32	0.15	0.03	-0.08	-0.30	
Morphine Consumption	0.40	0.46*	0.28	0.54*	0.15	0.16	-0.39	0.20	0.08	-0.11	0.30

* P<0.05, *** P<0.001
Fe/Tf = iron/transferrin ratio PEFR ratio = peak expiratory flow rate as a ratio of pre-op. value

TABLE 4.5 Correlation matrix of areas under the curve of metabolic changes, post-operative pain and pulmonary function

Postoperative urinary 3-methylhistidine levels did not differ significantly from pre-operative values, and were all within the normal range (Table 4.4).

There were no significant inter-group differences in catecholamine levels at the three time points (even without Bonferroni correction - Table 4.4). All but one noradrenaline value in each group at each time point were below the upper reference limit. However, noradrenaline levels on the first and second postoperative day were significantly higher than on the pre-operative day (first day $p=0.04$, second day $p<0.001$). Adrenaline levels on the pre-operative day were above the upper reference limit in 5 patients in the laparoscopic group and 2 in the minilaparotomy group probably reflecting anxiety. Postoperative values were not significantly different from pre-operative values. All urinary dopamine levels were within the normal range and postoperative values did not differ significantly from pre-operative values.

There was a significant association between the response areas of several metabolic variables, in particular IL-6, CRP and PMN elastase (Table 4.5). There was also a strong correlation between the albumin and transferrin fall. There was a weak correlation between duration of surgery and IL-6 response ($r=0.50$ $p=0.040$), but not with CRP response ($r=0.36$ $p=0.15$). There was no correlation between pain scores and pulmonary function and the metabolic variables, but there was a weak correlation between morphine consumption and IL-6 and transferrin changes.

4.4 DISCUSSION

This study has demonstrated a significant metabolic response to both laparoscopic and minilaparotomy cholecystectomy, with no significant differences between the two types of surgery. By contrast, in Chapter 2 it was found that laparoscopic cholecystectomy results in less postoperative pain than minilaparotomy cholecystectomy, a smaller reduction in postoperative pulmonary function, better postoperative oxygen saturation, and a more rapid return to normal activity. Furthermore, in the present study, there was no correlation between the more clinical end-points, postoperative pain and pulmonary function, and the magnitude of the metabolic response. This accords with the finding that elimination of postoperative pain by epidural infusion of bupivacaine does not significantly alter the metabolic response to cholecystectomy [284,286]. Postoperative pain is thus only one of a number of factors affecting the magnitude of the metabolic response to surgery.

The metabolic response to minilaparotomy cholecystectomy has not been previously described. The peak CRP response to minilaparotomy documented in this study (CRP at 48 hours mean 122, median 101mg/l) was within the range of results reported after standard cholecystectomy (mean 87-210 mg/l) [9,201,202,237,238,296,297]. The IL-6 response to both operations in our study was similar to that recently reported after standard cholecystectomy using the same bioassay [236]. The fall in albumin, transferrin and the iron/transferrin ratio was also similar to that previously reported after standard cholecystectomy [298]. However, the peak cortisol response to both operations in this study (835nmol/l) was lower that that reported after standard cholecystectomy in several studies (1050-1400) [198,285,286,297].

Three recent studies have compared selected aspects of the metabolic response to laparoscopic and standard cholecystectomy (using historical [201]

and non-randomised [198,202] controls). The CRP response to laparoscopic cholecystectomy reported in two of the studies (CRP at 48 hours mean 21 [202] and 40 [201] mg/l) was lower that that found in our study (CRP median 54, mean 118 mg/l), and significantly lower than standard cholecystectomy. Furthermore, using an immunoradiometric assay, Joris *et al.* found lower IL-6 levels after laparoscopic compared to standard cholecystectomy (12 versus 70 pg/ml), although measurements were made at only three time points and the control group was historical [201].

Two of these three published studies showed a similar cortisol response after open and laparoscopic cholecystectomy [198,201]. One of the studies reported a trend towards lower plasma levels of adrenaline after laparoscopic cholecystectomy [201], while another of these three studies found higher urinary catecholamine breakdown products (vanillylmandelic acid) after laparoscopic cholecystectomy [202].

In addition to the above mentioned published studies, there have been two further studies reported in abstract form comparing the metabolic responses to laparoscopic and open cholecystectomy [299,300]. Both of these found a lower CRP response to laparoscopic cholecystectomy, and one found a lower IL-6 response [300].

A number of the above studies contradict the findings of the present study. In particular, four studies reported a reduced CRP response [201,202,299,300] and two studies a reduced IL-6 response [201,300] after laparoscopic compared to standard cholecystectomy . A defect of the present study was the small number of patients studied, although unlike any of the other studies the patients were randomised. It is possible that the lack of a statistically significant difference between the CRP and IL-6 responses to the two operations was due to a type II statistical error, due to the small number of patients studied. There was a trend to lower CRP response in the

laparoscopic group, but the median/range of the IL-6 response was similar in both groups. The present study found a very wide variation the magnitude of the metabolic response to each operation. Therefore, factors other than the method of surgery must have a greater influence in determining the magnitude of the metabolic response.

The relationship between the different metabolic changes in this study is similar to those previously described. In particular, the sequential time course of IL-6 which preceded the rise of C reactive protein and fibrinogen, and the strong correlation between these three markers, is consistent with IL-6 being the primary stimulus to the acute phase response [116]. The author is not aware of any previous report of changes in PMN elastase after surgical trauma. Values were elevated throughout the postoperative period compared with pre-operative levels, but changes were modest compared to those seen in severe sepsis [301]. While monocytes, endothelial cells and fibroblasts are thought to be the major *in vivo* source of IL-6, some recent evidence suggests that circulating neutrophils contribute significantly to IL-6 production [302]. The highly significant correlation between changes in IL-6 and PMN elastase (which is released by activated neutrophils [292]) and the immediate rise in PMN elastase, found in this study would be consistent with this hypothesis.

In conclusion, this study demonstrates that the laparoscopic technique does not reduce the metabolic response when compared with open surgery using a small incision. This contrasts with the clinical benefits of less postoperative pain and more rapid recovery after the laparoscopic procedure. These findings suggest that factors other than the metabolic response are important in determining recovery following surgery.

Chapter 5

VENTILATORY AND BLOOD GAS CHANGES DURING LAPAROSCOPIC AND MINILAPAROTOMY CHOLECYSTECOMY

5.1 INTRODUCTION

Until the advent of extended therapeutic laparoscopic procedures such as laparoscopic cholecystectomy, most laparoscopies were brief and performed in young, otherwise healthy, gynaecological patients. Ventilatory changes in these patients have been extensively studied and found to be clinically unimportant [247-250]. With the increasing popularity of minimally invasive general surgery, many laparoscopic procedures now require long periods of peritoneal insufflation, and are often performed on patients who are older and have respiratory disease. Two recent studies have suggested that greater ventilatory changes occur in these patients [13,14].

End-tidal CO_2 partial pressure ($P_{E'CO2}$) monitoring is increasingly used during anaesthesia as an indirect measure of arterial CO_2 tension (Pa_{CO2}), and therefore the relationship between these two variables is of considerable interest. The arterial to end-tidal P_{CO2} difference ($Pa_{CO2} - P_{E'CO2}$) is dependent upon many factors including the relative distribution of ventilation and perfusion within the lung, and the functional residual capacity [303]. During laparoscopic procedures, changes in ventilation and perfusion distribution due to basal lung compression might be expected to occur because of the pneumoperitoneum. Thus, ($Pa_{CO2} - P_{E'CO2}$) might be expected to change.

The aim of the present study was to assess ventilatory and arterial blood gas changes during laparoscopic cholecystectomy (using open cholecystectomy as a control group), and to assess the accuracy of capnography in monitoring arterial CO_2 tension changes.

5.2 PATIENTS AND METHODS

This study was approved by the local hospital ethics committees. Informed consent was obtained from all patients in this study, who were participating in the randomised trial comparing laparoscopic cholecystectomy and minilaparotomy cholecystectomy as described in Chapter 3. Thirty consecutive patients in each arm of the randomised trial were studied. Three patients in the laparoscopic group who required early conversion to open cholecystectomy were excluded.

Patients underwent general anaesthesia and were paralysed and ventilated. Anaesthetic techniques were similar in both groups (agents used were thiopentone or propofol for induction, suxamethonium for initial muscle relaxation, morphine and ethrane for maintenance, and atracurium besylate or vecuronium for muscle relaxation). An Ohmeda OAV 7750 ventilator (Ohmeda, Hatfield, Hertfordshire, UK) with a non-rebreathing circuit was used. Minute ventilation was recorded by a flow transducer on the expiratory side of the circuit. Peak airway pressure was recorded by an aneroid pressure gauge in the ventilator. End-tidal CO_2 tension ($P_{E'CO2}$) was measured throughout the operation using an infrared analyzer (Datex Capnomac Ultima, Instrumentation Corporation, Helsinki, Finland). The coefficient of variation for $P_{E'CO2}$ measurement of values within the normal range is 0.2%. Minute ventilation was adjusted to obtain a $P_{E'CO2}$ within the range 4.0 to 6.0 kPa. When $P_{E'CO2}$ was stable, and just before commencing surgery, baseline recordings were made of minute ventilation, peak airway pressure, $P_{E'CO2}$, and inspired oxygen concentration (F_{IO2}). At the same time, an arterial blood sample was taken and analysed for oxygen tension (P_{aO2}), carbon dioxide tension (P_{aCO2}), hydrogen ion ($[H^+]$), and bicarbonate concentration ($[HCO_3^-]$). The coefficient of variation for P_{aCO2} measurements of values within the normal range is 1.4%.

In the laparoscopic group, pneumoperitoneum was achieved with CO_2 insufflation through a Veress needle to a maximum pressure of 15 mm Hg. No patients developed surgical emphysema due to a misplaced Veress needle. The operation was performed with the patient either horizontal or with a slight reverse Trendelenburg tilt. During surgery, ventilation settings in both groups were adjusted according to changes in $P_{E'CO2}$ (arterial blood gas results were not available to the anaesthetist). At the time of removal of the gallbladder, all measurements were repeated along with arterial blood gas sampling.

Statistics

Measures between groups were compared with the unpaired t test, and within group changes, with the paired t test. The 95% confidence intervals (95% CI) of the range of (Pa_{CO2} - $P_{E'CO2}$) values were calculated to assess the accuracy of capnography in monitoring Pa_{CO2} changes [304].

5.3 RESULTS

The groups were well matched for pre-operative patient characteristics (Table 5.1). The results are summarised in Tables 5.2 and 5.3.

Baseline results

On baseline measurements, both groups were well matched for ventilatory and blood gas values. $P_{E'CO2}$ was of low accuracy in predicting Pa_{CO2} (95% CI of the range of (Pa_{CO2} - $P_{E'CO2}$) -0.61 to +1.93 kPa. In other words, 95% of patients had a Pa_{CO2} between 0.61 kPa lower, and 1.93 kPa higher than the $P_{E'CO2}$ - Figure 5.1).

Measurements at time of gallbladder removal

The mean time between beginning of surgery and the second set of measurements was 40 minutes (range 20-95) in the open cholecystectomy group, compared to 61 (30-115) in the laparoscopic cholecystectomy group ($t=4.1$, $p<0.001$). All patients remained haemodynamically stable throughout surgery.

In the minilaparotomy cholecystectomy group, no clinically significant changes occurred in ventilatory or arterial blood gas values (Table 5.2).

In the laparoscopic group, induction of a CO_2 pneumoperitoneum resulted in a progressive rise in $P_{E'CO2}$ in the majority of patients. Despite a significant increase in minute ventilation, Pa_{CO2} and arterial [H^+] both increased significantly. There was no correlation between the duration of pneumoperitoneum and the rise in either minute ventilation (Pearson linear regression analysis $r=0.27$, $p=0.15$) or Pa_{CO2} ($r=0.25$, $p=0.18$). The pneumoperitoneum was also associated with a mean rise of 6 cm H_20 in peak airway pressure. There were no significant changes in (Pa_{CO2} - $P_{E'CO2}$), Pa_{O2} or F_{IO2}.

	Minilaparotomy group (n=30)	Laparoscopic group (n=30)
Mean Age (range)	51 (19-82)	54 (31-80)
Male:Female Sex ratio	5:1	6.5:1
Height (mean/S.D.)	160 (8)	161 (6)
Weight (mean/S.D.)	65 (10.0)	69 (11)
FVC (litres - mean/S.D.)	2.87 (0.64)	2.94 (0.84)
$FEV_{1\ (litres}$ - mean/S.D.)	2.32 (0.61)	2.39 (0.77)
PEFR (ml/sec - mean/S.D.)	370 (112)	369 (128)
Asthma	3	4
Chronic Bronchitis	1	1

TABLE 5.1 Pre-operative patient characteristics, and pulmonary function in the two groups.

	Open group (n=30)	Laparoscopic group (n=30)	t test	
			t	p value
Beginning of surgery				
Minute Ventilation (l)	5.4 (1.2)	5.7 (1.4)	0.8	0.44
$P_{E'}CO_2$ (kPa)	4.6 (0.5)	4.6 (0.6)	0.2	0.81
P_aCO_2	5.2 (0.7)	5.3 (0.9)	0.6	0.57
Arterial $[H^+]$ (nM)	40 (4)	41 (6)	0.9	0.38
(P_aCO_2 - $P_{E'}CO_2$) (kPa)	0.6 (0.6)	0.7 (0.7)	0.9	0.38
P_aO_2 (kPa)	22.7 (7.6)	19.1 (7.1)	1.9	0.063
F_IO_2 (%)	38 (10)	38 (7)	0.0	0.98
Peak Air Pressure (cm H_20)	17 (4)	17 (4)	0.3	0.79
$[HCO_3^-]$ (mM)	25 (2)	25 (2)	0.2	0.86
At removal of Gallbladder				
Minute Ventilation (l)	5.1 (1.1)	6.1 (1.2)	3.4	p<0.001
$P_{E'}CO_2$ (kPa)	4.8 (0.4)	5.4 (0.7)	3.9	p<0.001
P_aCO_2 (kPa)	5.5 (0.7)	6.0 (0.9)	2.0	0.046
Arterial $[H^+]$ (nM)	42 (5)	46 (5)	2.9	0.006
(P_aCO_2 - $_{E'}CO_2$) (kPa)	0.8 (0.5)	0.6 (0.5)	0.0	0.36
P_aO_2 (kPa)	19.6 (4.7)	19.1 (5.7)	0.3	0.76
F_IO_2 (%)	37 (7)	39 (6)	-0.9	0.37
Peak Air Pressure (cm H_20)	18 (4)	23 (4)	5.3	p<0.001
$[HCO_3^-]$ (mM)	24 (2)	24 (2)	0.4	0.64

TABLE 5.2 Ventilation and blood gas measurements at the beginning of surgery, and at the time of removal of the gallbladder.

	Open group		Laparoscopic group	
	t	p value	t	p value
Minute Ventilation	1.4	0.16	2.0	0.0491
$P_{E'}CO_2$	1.0	0.31	6.5	<0.001
P_aCO_2	2.4	0.021	4.5	<0.001
Arterial $[H^+]$	3.3	0.002	6.5	<0.001
(P_aCO_2 - $P_{E'}CO_2$)	1.8	0.069	0.9	0.35
P_aO_2	1.7	0.10	0.7	<0.51
F_IO_2 (%)	1.2	0.22	0.4	0.68
Peak Air Pressure	2.3	0.025	11.4	<0.001

TABLE 5.3 Statistical comparison (paired t test) within-patients of ventilatory and blood gas changes (readings at baseline compared with those at gall bladder removal).

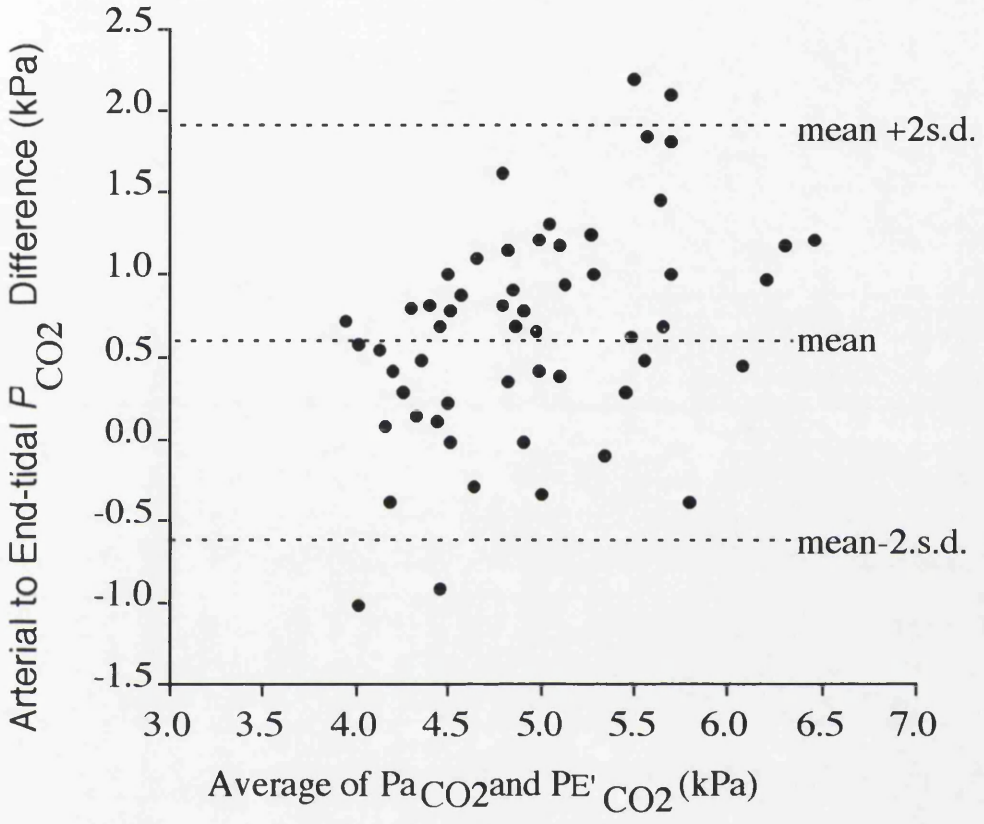

FIGURE 5.1 Graph of (Pa_{CO2} - PE'_{CO2}) against average of Pa_{CO2} and PE'_{CO2} in all patients at the beginning of surgery, with 95% confidence interval of the range of (Pa_{CO2} - PE'_{CO2}).

As in baseline measurements, $P_{E'CO2}$ at the time of gallbladder removal was of low accuracy in predicting Pa_{CO2} (95% CI of the range of (Pa_{CO2} - $P_{E'CO2}$) -0.4 to +1.6 kPa in both groups). Furthermore, there was poor concordance between the arterial to end-tidal P_{CO2} difference at the two time-points (95% CI of agreement between baseline and second measurement: minilaparotomy cholecystectomy group -0.8 to +1.21 kPa, and laparoscopic group -1.5 to +1.3 kPa).

5.4 DISCUSSION

Our findings accord with the three reported studies of blood gas changes during laparoscopic cholecystectomy using a carbon dioxide pneumoperitoneum [13,14,305]. Wittgen *et al* compared the changes in 20 normal patients to that in 10 patients with cardiorespiratory disease [13]. During laparoscopic cholecystectomy, Pa_{CO2} rose by 0.8kPa in the normal patients (without increasing ventilation), while in patients with cardiopulmonary disease Pa_{CO2} rose by 2.0 kPa despite an increase in minute ventilation of 1.2 litres. The corresponding changes in $P_{E'CO2}$ were much less and did not fully reflect the changes in Pa_{CO2}: in normal patients $P_{E'CO2}$ increased by only 0.3 kPa, while in the patients with cardiorespiratory disease, it increased by only 0.6 kPa. In contrast, in our study, and in a study of gynaecological laparoscopy [252], mean (Pa_{CO2} - $P_{E'CO2}$) did not change significantly with CO_2 pneumoperitoneum. Nevertheless, our findings of poor concordance between baseline (Pa_{CO2} - $P_{E'CO2}$) and (Pa_{CO2} - $P_{E'CO2}$) at the end of the procedure would support the conclusion of Wittgen *et al* that end-tidal measurement of P_{CO2} was a poor indicator of changes in Pa_{CO2} [13]. Marked within-patient variability in (Pa_{CO2} - $P_{E'CO2}$) during anaesthesia has also been shown in a study of patients undergoing major surgery [255]. Indeed, within-patient variations in (Pa_{CO2} - $P_{E'CO2}$) were comparable with or greater than the inter-patient differences.

In the other study of blood gas and ventilatory changes during laparoscopic cholecystectomy, Liu *et al* [14] found that $P_{E'CO2}$ and Pa_{CO2} both increased by a mean of 1.4 kPa during laparoscopic cholecystectomy, with 13 out of 16 patients requiring an increase in minute ventilation to maintain $P_{E'CO2}$ below 6 kPa. In contrast to our findings, they claimed that there was good agreement between paired $P_{E'CO2}$ and Pa_{CO2} measurements, but their data do not support this statement. On analysing their results, it can be calculated that

95% of patients had a Pa_{CO2} between 0.42 kPa lower to 1.08 kPa higher than paired $P_{E'CO2}$ measurements.

In a pig model of laparoscopic cholecystectomy, Pa_{CO2} increased by 1.9 kPa and carbon dioxide output by 30% of baseline values [12]. In a canine model of prolonged laparoscopy (2 hours), the effects of CO_2 and helium pneumoperitoneum were compared [256]. Even with a 57% increase in minute ventilation to maintain a constant $P_{E'CO2}$, CO_2 pneumoperitonum was associated with a significant rise in Pa_{CO2} and (Pa_{CO2} - $P_{E'CO2}$). The rise in minute ventilation requirement, Pa_{CO2}, and (Pa_{CO2} - $P_{E'CO2}$) was greater in dogs with papain-induced pulmonary emphysema, supporting the previously mentioned findings of Wittgen *et al* in patients with pulmonary disease undergoing laparoscopic cholecystectomy [13]. Intra-operative blood gas monitoring may be advisable in patients with severe respiratory disease, as they may have larger differences between Pa_{CO2} and $P_{E'CO2}$ and a greater tendency to retain CO_2 [13].

During laparoscopic procedures, changes in ventilation and perfusion distribution might be expected to occur because of the raised intrabdominal pressure. However, in this study (Pa_{CO2} - $P_{E'CO2}$) or Pa_{O2} during the pneumoperitoneum were not significantly different from values pre-insufflation or values in the open surgery group. In the present study, it was not possible to calculate the alveolar-arterial oxygen gradient (PA_{O2}-Pa_{O2}) from the standard formula: $PA_{O2} = (FI_{O2} \times P_B) - Pa_{CO2}/R$, because absorption of carbon dioxide from the peritoneum would have resulted in changes in the respiratory quotient. Collection of exhaled gases would have been necessary to calculate the new respiratory quotient.

In conclusion, laparoscopic cholecystectomy using a CO_2 pneumoperitoneum is associated with a significant increase in carbon dioxide output, requiring a significant but variable increase in minute ventilation to prevent hypercarbia. $P_{E'CO2}$ is of low accuracy in predicting Pa_{CO2}. It is therefore suggesed that in patients undergoing laparoscopic cholecystectomy with a carbon dioxide pneumoperitoneum, ventilation be increased to maintain $P_{E'CO2}$ towards the lower end of the normal range (4-5 kPa).

Chapter 6

HELIUM PNEUMOPERITONEUM FOR LAPAROSCOPIC CHOLECYSTECTOMY: VENTILATORY AND BLOOD GAS CHANGES

6.1 INTRODUCTION

Carbon dioxide (CO_2) is the gas most widely used for laparoscopic procedures. In Chapter 5, it was shown that CO_2 is absorbed from the pneumoperitoneum into the blood stream, and in order to avoid significant respiratory acidosis during laparoscopic cholecystectomy, a substantial increase in the minute ventilation is required [12-14]. In patients with severe cardiac or respiratory disease, it may be impossible to eliminate the increased CO_2 burden by hyperventilation [13,15], and the ensuing hypercarbia and acidosis, which can result in cardiac arrhythmias [306], may necessitate the procedure being converted to an open surgical operation. This has prompted a search for an alternative to carbon dioxide for insufflation of the abdomen in this subgroup of patients.

Helium is an inert gas, which is chemically, physiologically and pharmacologically inert, and does not support combustion. Its physical property of low airflow resistance is utilized in patients with narrowed airways [265], and also to operate intra-aortic balloon pumps. It is thus readily available in hospitals. Two animal model studies have confirmed the suitability of helium for insufflating the abdomen during laparoscopy, and showed that it does not alter ventilation requirements [256,266], but there has been only one report of its use in humans for laparoscopy, in a study with ten patients [305].

The aim of this study, therefore, was to compare the effects of helium and carbon dioxide pneumoperitoneum on ventilatory and arterial blood gas changes during laparoscopic cholecystectomy.

6.2 PATIENTS AND METHODS

This study was approved by the local hospital ethics committees. Informed consent was obtained from all patients in this study. In this study, ventilatory and blood gas changes were assessed in thirty consecutive patients who underwent laparoscopic cholecystectomy using a helium pneumoperitoneum (helium group). The methods were as described in the study in Chapter 5. The thirty patients who underwent laparoscopic cholecystectomy using a CO_2 pneumoperitoneum in Chaper 5 were used as a non-randomised historical control group (CO_2 group).

Ventilatory and blood gas measurements were made after stabilization of anaesthesia and ventilation, but before commencing surgery. Pneumoperitoneum was achieved with either CO_2 or helium insufflation to a maximum intraperitoneal pressure of 15 mm Hg. This was performed with either a Storz electronic Laparoflator model 264300 20 (Karl Storz GMBH and Co., Tuttlingen, Germany) or a Olympus Surgical Insufflator (KeyMed, Southend-on-Sea, Essex, UK). The Helium cylinders (British Oxygen Company, Guilford, Surrey, UK) filled at 135 barr were connected to the insufflator via an external valve which reduced the pressure to 10 barr. The operation was performed with the patient either horizontal or with a slight reverse Trendelenburg tilt. During surgery, ventilation settings in both groups were adjusted according to changes in $P_{E'CO2}$ (arterial blood gas results were not available to the anaesthetist). At the time of removal of the gallbladder, all measurements were repeated along with arterial blood gas sampling.

The alveolar-arterial oxygen gradient (PA_{O2}-Pa_{O2}) was calculated using the formula for calculating alveolar oxygen partial pressure [307]:

$$PA_{O2} = (FI_{O2} \times P_B) - Pa_{CO2}/R$$

where P_B = barometric pressure minus water vapour pressure saturated at body temperature, R = respiratory quotient estimated at 0.8. Because the calculation of (PA_{O2}-Pa_{O2}) was dependent on a estimate of the respiratory quotient, (PA_{O2}-Pa_{O2}) could only be calculated for the helium insufflation group, because CO_2 absorption from the peritoneum in the CO_2 insufflation would have altered the respiratory quotient.

Statistics

Measures between groups were compared with the unpaired t test, and within group changes, with the paired t test.

6.3 RESULTS

There were no significant differences between the two groups in pre-operative patient characteristics (Table 6.1). The results are summarised in Table 6.2 and Table 6.3.

Baseline results

On baseline measurements, both groups were well matched for ventilatory and blood gas values.

The mean (SD) time between beginning of surgery and the second set of measurements was 61 minutes (21) in the helium group, and 61 (20) in the carbon dioxide group. All patients remained haemodynamically stable throughout surgery.

In the helium group, minute ventilation was reduced slightly, but no significant changes occurred in Pa_{CO2} or $P_{E'CO2}$ values (Table 6.2). However, peak airway pressure rose by 7 cm H_2O and there was a significant rise in both (Pa_{CO2} - $P_{E'CO2}$) and (P_{AO2}-Pa_{O2}).

In the CO_2 group, despite a significant increase in minute ventilation, Pa_{CO2} and arterial [H^+] both increased significantly. The pneumoperitoneum was also associated with a mean rise of 6 cm H_20 in peak airway pressure. There were no significant changes in (Pa_{CO2} - $P_{E'CO2}$), Pa_{O2} or F_{IO2}.

Four patients in the helium group, in whom gas was accidentally insufflated into the abdominal wall, had surgical emphysema in the anterior abdominal wall, which remained for three to five days. This was not associated with any discomfort, and did not impede patient recovery.

	Helium group (n=30)	Carbon Dioxide group (n=30)
Mean Age (range)	49 (24-73)	54 (31-80)
No. of females (%)	28 (93%)	26 (87%)
Height (mean/S.D.)	160 (8)	161 (6)
Weight (mean/S.D.)	74 (24)	69 (11)
Asthma	1	4
Chronic Bronchitis	4	1

TABLE 6.1 Pre-operative patient characteristics in the two groups.

	Helium group (n=30)	Carbon Dioxide group (n=30)	t test: t	p value
Beginning of surgery				
Minute Ventilation (l)	5.8 (1.2)	5.7 (1.4)	0.5,	0.63
$P_{E'CO2}$ (kPa)	4.5 (0.6)	4.6 (0.6)	-0.4	0.72
P_{aCO2}	5.2 (0.7)	5.3 (0.9)	-0.4	0.67
Arterial $[H^+]$ (nM)	38 (3)	41 (6)	-2.1	0.037
(P_{aCO2} - $P_{E'CO2}$) (kPa)	0.7 (0.4)	0.7 (0.7)	-0.2	0.81
P_{aO2} (kPa)	21.4 (6.9)	19.1 (7.1)	1.2	0.22
F_{IO2} (%)	40 (6)	38 (7)	1.2	0.23
(P_{AO2}-P_{aO2}) (kPa)	10.3 (7.3)	10.6 (6.1)	0.1	0.88
Peak Air Pressure (cm H_2O)	18 (5)	17 (4)	0.2	0.87
$[HCO_3^-]$ (mM)	26 (2)	25 (2)	1.8	0.077
At removal of Gallbladder				
Minute Ventilation (l)	5.5 (1.2)	6.1 (1.2)	3.4	<0.001
$P_{E'CO2}$ (kPa)	4.5 (0.6)	5.4 (0.7)	3.9	<0.001
P_{aCO2} (kPa)	5.3 (0.6)	6.0 (0.9)	2.0	0.046
Arterial $[H^+]$ (nM)	40 (3)	46 (5)	2.9	0.006
(P_{aCO2} - $P_{E'CO2}$) (kPa)	0.9 (0.6)	0.6 (0.5)	1.7	0.096
P_{aO2} (kPa)	17.9 (5.0)	19.2 (5.7)	0.3	0.76
F_{IO2} (%)	40 (7)	39 (6)	-0.9	0.37
(P_{AO2}-P_{aO2}) (kPa)	13.5 (8.8)	-	-	-
Peak Air Pressure (cm H_2O)	25 (7)	23 (4)	5.3	<0.001
$[HCO_3^-]$ (mM)	25 (2)	24 (2)	0.4	0.64

TABLE 6.2 Ventilation and blood gas measurements at the beginning of surgery, and at the time of removal of the gallbladder.

	Helium group		Carbon dioxide group	
	t	p value	t	p value
Minute Ventilation	2.2	0.036	2.0	0.0491
$P_{E'}CO_2$	0.8	0.43	6.5	<0.001
P_aCO_2	-0.6	0.52	4.5	<0.001
Arterial $[H^+]$	-3.3	0.003	6.5	<0.001
(P_aCO_2 - $P_{E'}CO_2$)	-2.1	0.047	0.9	0.35
P_aO_2	3.3	0.003	0.7	0.51
F_IO_2 (%)	0.3	0.74	0.4	0.68
(P_AO_2-P_aO_2) (kPa)	-2.9	0.006	-	-
Peak Air Pressure	-12.8	<0.001	11.4	<0.001
$[HCO_3^-]$ (mM)	4.9	<0.001	2.5	0.019

TABLE 6.3 Statistical comparison (paired t test) within-patients of ventilatory and blood gas changes (readings at baseline compared with those at gall bladder removal).

6.4 DISCUSSION

This study has shown that helium can be effectively used for laparoscopy and avoids the problem of carbon dioxide absorption.

The only drawback in using helium for laparoscopy is that it is not very water-soluble. Hence, in four patients in this study where the gas was accidentally insufflated into the abdominal wall, surgical emphysema was present for three to five days after operation. Secondly, it is likely that it has a lower safety margin than CO_2 in the very rare event of gas embolism [308]. In order to reduce the risk of gas embolism when using a helium pneumoperitoneum, the open technique of laparoscopy might be used [151], which avoids the risk of insufflation into a blood vessel through a misplaced Veress needle.

Helium pneumoperitoneum resulted in a increase in both (Pa_{CO2} - $P_{E'CO2}$) and (PA_{O2}-Pa_{O2}). The likely mechanism of this effect is that splinting of the diaphragm by the increased intra-abdominal pressure might have resulted in collapse of basal airways, which together with the increased ventilation pressure requirement might have altered the ventilation and perfusion distribution, resulting in increased right to left shunt, and an increased dead space. An animal model study also demonstrated that pneumoperitoneum with either CO_2 or helium resulted in an increase in (PA_{O2}-Pa_{O2}), the effect being more marked in animals with papain-induced emphysema [256].

In conclusion, this study has shown that laparoscopy with helium peritoneal insufflation does not result in significant changes in ventilation requirements. However, the theoretical risks resulting from its low water-solubility preclude its routine use for most patients. Nevertheless, it may be a suitable alternative for patients with severe cardiorespiratory disease undergoing laparoscopic procedures in whom carbon dioxide insufflation results in excessive

hypercarbia and acidosis. Animal model studies are required to compare the effects of gas embolism with helium to that of carbon dioxide to clarify whether helium is associated with a higher theoretical risk in the rare event of accidental insufflation into a blood vessel.

CONCLUSIONS

Although laparoscopic cholecystectomy was first performed only five years ago, it has been introduced into routine practice in most western countries, and has become the treatment of choice for symptomatic cholelithiasis. Its rapid introduction occurred without rigorous scientific evaluation comparing it with the gold standard, open cholecystectomy. The randomised trial described in this thesis has confirmed that laparoscopic cholecystectomy has significant advantages over open cholecystectomy, even when the latter is performed through a minilaparatomy incision. The advantages compared with minilaparotomy cholecystectomy are:

1) Reduced postoperative pain, with a significant reduction for up to at least a week after surgery.
2) Reduced requirements for opiate analgesics in the postoperative period.
3) Less reduction in postoperative pulmonary function and therefore better oxygen saturation.
4) Post-operative hospital stay is halved from a median of four days to two days.
5) The time to return to normal activity in the home is reduced from fifteen days to ten days.
6) General health survey measures such as physical and social functioning, role limitation due to physical problems and depression scores are all significantly better in the week following surgery. Even a month after surgery, laparoscopic patients have better physical functioning and better depression scores.

The randomised trial described in this thesis found that the laparoscopic cholecystectomy was nearly £400 more expensive than minilaparotomy cholecystectomy. However, this difference could be reduced to less than £100 if re-usable instruments are used in preference to disposables. It is likely

that as surgeons complete the learning curve, operation times are likely to become shorter. As surgeons becomme more confident in early hospital discharge, average hospital stay in this country may be reduced further to approach the average one day stay reported in many centres in America. These two factors should reduce the costs of laparosocopic cholecystectomy to a figure comparable to or less than minilaparotomy cholecystectomy.

A randomised trial of three hundred patients cannot make much comment on the relative incidence of complications of cholecystectomy. Large scale audit studies have shown that laparoscopic cholecystectomy has been associated with a higher incidence of bile duct injuries, bile leaks, and deaths due to technical complications. However, there is evidence to suggest that this may be due in part to the learning curve. Rigorous large-scale audit is needed to ensure that the apparent superiority of laparoscopic cholecystectomy is maintained in the long term.

With the increasing experience of surgeons with the technique of laparoscopic cholecystectomy, many of the absolute contraindications of the technique have become relative. Most patients with acute cholecystitis or previous upper abdominal surgery can now safely undergo cholecystectomy by the laparoscopic approach. However, there will always be a proportion of patients with symptomatic cholelithiasis in whom the technique cannot be performed. In some of these patients, minilaparotomy may be a reasonable alternative. This study has shown that minilaparotomy cholecystectomy results in a median hospital stay of four days and return to work in the home in about two weeks, which is significantly shorter than that the usual recovery period expected after standard open cholecystectomy in the UK. The technique is also a suitable alternative for surgeons who feel unable to

learn the laparoscopic technique or who do not have access to laparoscopic equipment.

The role of laparoscopic cholecystectomy in patients with evidence of common bile duct (CBD) stones remains to be clarified. At present most of these patients are managed by endoscopic sphincterotomy and stone clearance before proceeding to laparoscopic cholecystectomy. However, the incidence of complications from endoscopic sphincteotomy is independent of age. Thus patients at low risk from open surgery (aged under 60) who undergo laparoscopic cholecystectomy and endoscopic treatment of duct stones may suffer greater morbidity and mortality than they would if they underwent open operation. Further studies are required to clarify this area.

In Chapter 4, it was shown that both laparoscopic and minilaparotomy are associated with a significant metabolic response. The time course and magnitude of changes are similar for both procedures, but there is wide inter-individual variation in the magnitude of the response. The similar metabolic response of the two procedures contrasts with the clinical benefits of less postoperative pain and more rapid recovery after the laparoscopic procedure. These findings suggest that factors other than the metabolic reponse are important in determining recovery following surgery.

The study in Chapter 5 has demonstrated that laparoscopic cholecystectomy using a CO_2 pneumoperitoneum is associated with a significant increase in carbon dioxide output, requiring a significant but variable increase in minute ventilation to prevent hypercarbia. Capnography may underestimate the rises in arterial carbon dioxide levels, and it is therefore suggested that minute ventilation be increased to maintain end-tidal carbon dioxide levels towards the lower end of the normal range (4-5 kPa). The study in Chapter 6 has

shown that helium is a suitable alternative to carbon dioxide for peritoneal insufflation, and that helium does not result in significant changes in ventilation requirements. However, the theoretical risks resulting from its low water-solubility, preclude its routine use for most patients. Nevertheless, it may be a suitable alternative for patients with severe cardiorespiratory disease undergoing laparoscopic procedures, in whom carbon dioxide insufflation results in excessive hypercarbia and acidosis. Animal model studies are required to compare the effects of air embolism with helium to that of carbon dioxide to clarify whether helium is associated with a higher theoretical risk in the rare event of accidental insufflation into a blood vessel.

APPENDIX I

QUESTIONNAIRE ABOUT SURGEONS' VIEWS ON RANDOMISED TRIALS COMPARING LAPAROSCOPIC AND OPEN CHOLECYSTECTOMY

ARE YOU A GENERAL SURGEON
(If NOT, do not complete questionnaire)

Yes ☐ **No** ☐

1 Do you work in:

District General Hospital ☐
Teaching Hospital (NHS appointment) ☐
Teaching Hospital (Academic appointment) ☐

2 How many years have you been appointed as a consultant surgeon? ☐

3 Approximately how many laparoscopic cholecystectomies have you performed? ☐

4 Are you satisfied with the safety of laparoscopic cholecystectomy?

Very satisfied ☐
Satisfied ☐
Unsure ☐
Concerned ☐
Very concerned ☐

5 Do you think there is a necessity for a randomised trial comparing *standard* cholecystectomy with laparoscopic cholecystectomy?

Very necessary ☐
Probably necessary ☐
Unsure ☐
Probably not necessary ☐
Totally unnecessary ☐

6 Do you think there is a necessity for a randomised trial comparing *minilaparotomy* cholecystectomy with laparoscopic cholecystectomy?

Very necessary ☐
Probably necessary ☐
Unsure ☐
Probably not necessary ☐
Totally unnecessary ☐

APPENDIX I (continued)

7 Is a randomised trial of standard cholecystectomy versus laparoscopic cholecystectomy possible on a practical level (e.g. getting patient consent):

Yes	No	Unsure
☐	☐	☐

8 Is a randomised trial of standard cholecystectomy versus laparoscopic cholecystectomy ethical:

Highly unethical	☐
A little unethical	☐
Unsure	☐
Ethical	☐

9 If you think that a randomised trial is unethical, Why?

10 Hypothetically, would you be interested in participating in a randomised trial of laparoscopic cholecystectomy?

Very interested	☐
Moderately interested	☐
Unsure	☐
Not interested	☐

11 If you were admitted to a hospital not known to yourself for an elective cholecystectomy (albeit an unlikely scenario) and were offered laparoscopic or open cholecystectomy, which procedure would you choose:

Laparoscopic cholecystectomy	☐
Open cholecystectomy	☐

12 Any other comments:

Appendix II

Questionnaire sent to patients one week after laparoscopic or minilaparotomy cholecystectomy

THE EFFECT OF YOUR RECENT OPERATION

1 Have you returned to your job of work (that is, paid employment) since your operation?
(Please tick the bos which best applies to you)

Yes ☐ **No** ☐ **I have no paid job** ☐

If 'yes', how long after your operation did you return to work? ☐☐ **days**

2 Are you able to look after the home since your operation (for example, cleaning and cooking, repairs, odd jobs around the home, and so on)?
(Please tick the box which best applies to you)

Yes ☐ **No** ☐ **I do not look after the home** ☐

If 'yes', how long after your operation did you return to work? ☐☐ **days**

3 Are you able to enjoy your usual social life (for example, going out, seeing friends, going to the pub, etc) since your operation?
(Please tick the box which best applies to you)

Yes ☐ **No** ☐ **Not applicable** ☐

If 'yes', how long after your operation were you able to enjoy your usual social life again? ☐☐ **days**

4 Are you able to enjoy your usual sex life since your operation?
(Please tick the box which best applies to you)

Yes ☐ **No** ☐ **Not applicable** ☐

If 'yes', how long after your operation were you able to enjoy your usual sex life again? ☐☐ **days**

5 Are you able to enjoy your usual interests and hobbies (for example, sports, watching television, arts and crafts, do it yourself, etc) since your operation?
(Please tick the box which best applies to you)

Yes ☐ **No** ☐ **Not applicable** ☐

If 'yes', how long after your operation were you able to return to your usual interests? ☐☐ **days**

Appendix II (continued)

6 Do you think the outcome of the operation itself has been:
(Please tick the box which best describes you)

- **Excellent** ☐
- **Good** ☐
- **Fair** ☐
- **Poor** ☐
- **Very poor** ☐

7 How satisfied are you with the appearance of your operation scars?
(Please tick the box which best describes you

- **Very satisfied** ☐
- **Moderately satisfied** ☐
- **Barely satisfied** ☐
- **Moderately dissatisfied** ☐
- **Very dissatisfied** ☐

8 If someone else had the same gallbladder problem as you, would you recommend the operation you had?
(Please tick one box)

Yes ☐ **No** ☐

YOUR HEALTH SINCE YOUR OPERATION

The following questions ask for your views about your health and how you have felt about life in general since returning home after your operation. If you are unsure about how to answer any question, try and think about your health in general and give the best answer you can. Do not spend too much time over each answer as your immediate responses are likely to be the most helpful.

9 In general, would you say your health now is:
(Tick the box which best describes you)

- **Excellent** ☐
- **Good** ☐
- **Fair** ☐
- **Poor** ☐
- **Very poor** ☐

Appendix II (continued)

10 How is your health now compared with before your operation?
(Tick the box which best describes you)

Much better	☐
Somewhat better	☐
About the same	☐
Somewhat worse	☐
Much worse	☐

11 The following questions are about activities you might do during a typical day. Has your health limited you in these activities at any time since returning home? If so, how much?
(Tick one answer for each activity)

		A lot more limited than before	A little more limited than before	About the same as before	Less limited than before
i	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐	☐
ii	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐	☐
iii	Lifting or carrying groceries	☐	☐	☐	☐
iv	Climbing several flights of stairs	☐	☐	☐	☐
v	Climbing one flight of stairs	☐	☐	☐	☐
vi	Bending, kneeling or stooping	☐	☐	☐	☐
vii	Walking more than a mile	☐	☐	☐	☐
viii	Walking half a mile	☐	☐	☐	☐
ix	Walking 100 yards	☐	☐	☐	☐
x	Bathing and dressing yourself	☐	☐	☐	☐

Appendix II (continued)

12 At any time since returning home, have you had any of the following problems with your work or other regular daily activities as a result of your operation?
(Tick one answer for each activity)

		Yes	No
i	Cut down on the amount of time you spent on work or other activities	☐	☐
ii	Accomplished less than you would like	☐	☐
iii	Were limited in the kind of work or other activities	☐	☐
iv	Had difficulty performing the work or other activities (e.g. it took extra effort)	☐	☐

13 At any time since returning home, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
(Tick one answer for each activity)

		Yes	No
i	Cut down on the amount of time you spent on work or other activities	☐	☐
ii	Accomplished less than you would like	☐	☐
iii	Didn't do work or other activities as carefully as usual	☐	☐

14 At any time since returning home, have your physical or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?
(Tick the box which best describes you)

- **Not at all** ☐
- **Slightly** ☐
- **Moderately** ☐
- **Quite a bit** ☐
- **Extremely** ☐

15 What is the worst bodily pain you have had since returning home after your operation?
(Tick the box which best describes this pain)

- **None** ☐
- **Very mild** ☐
- **Mild** ☐
- **Moderate** ☐
- **Severe** ☐
- **Very severe** ☐

Appendix II (continued)

16 At any time since returning home, how much has pain interfered with your normal work (including work both outside the home and housework)? *(Tick the box which best describes you)*

- **Not at all** ☐
- **A little bit** ☐
- **Moderately** ☐
- **Quite a bit** ☐
- **Extremely** ☐

HOW YOU ARE FEELING IN GENERAL

17 I feel tense

- **Most of the time** ☐
- **A lot of the time** ☐
- **From time to time, occasionally** ☐
- **Not at all** ☐

18 I still enjoy the things I used to enjoy

- **Definitely as much** ☐
- **Not quite so much** ☐
- **Only a little** ☐
- **Hardly at all** ☐

19 I get a sort of frightened feeling as if something awful is about to happen

- **Very definitely and quite badly** ☐
- **Yes, but not too badly** ☐
- **A little, but it doesn't worry me** ☐
- **Not at all** ☐

20 I can laugh and see the funny side of things

- **As much as I always could** ☐
- **Not quite so much now** ☐
- **Definitely not so much now** ☐
- **Not at all** ☐

Appendix II (continued)

21	Worrying thoughts go through my mind	**A great deal of the time**	☐
		A lot of the time	☐
		From time to time but not too often	☐
		Only occasionally	☐
22	I feel cheerful	**Not at all**	☐
		Not often	☐
		Sometimes	☐
		Most of the time	☐
23	I can sit at ease and feel relaxed	**Definitely**	☐
		Usually	☐
		Not often	☐
		Not at all	☐
24	I feel as if I am slowed down	**Nearly all the time**	☐
		Very often	☐
		Sometimes	☐
		Not at all	☐
25	I get a sort of frightened feeling like 'butterflies' in the stomach	**Not at all**	☐
		Occasionally	☐
		Quite often	☐
		Very often	☐
26	I have lost interest in my appearance	**Definitely**	☐
		I don't take as much care as I should	☐
		I may not take quite as much care	☐
		I take just as much care as ever	☐

Appendix II (continued)

27	I feel restless as if I have to be on the move	**Very much indeed**	☐
		Quite a lot	☐
		Not very much	☐
		Not at all	☐
28	I look forward with enjoyment to things	**As much as I ever did**	☐
		Rather less than I used to	☐
		Definitely less than I used to	☐
		Hardly at all	☐
29	I get sudden feelings of panic	**Very often indeed**	☐
		Quite often	☐
		Not very often	☐
		Not at all	☐
30	I can enjoy a good book or radio or TV programme	**Often**	☐
		Sometimes	☐
		Not often	☐
		Very seldom	☐

Thank you for completing this questionnaire

REFERENCES

1 Dubois F, Berthelot B. Cholecystectomie par mini-laparotomie. *Nouve Presse Med* 1982; **11**: 1139-41.

2 Goco IR, Chambers LG. Dollars and cents: minicholecystectomy and early discharge. *South Med J* 1988; **81**: 161-3.

3 Merrill JR. Minimal trauma cholecystectomy (a "no-touch" procedure in a "well"). *Am Surg* 1988; **54**: 256-61.

4 Ledet WP,Jr.. Ambulatory cholecystectomy without disability. *Arch Surg* 1990; **125**: 1434-5.

5 O'Dwyer PJ, Murphy JJ, O'Higgins NJ. Cholecystectomy through a 5 cm subcostal incision. *Br J Surg* 1990; **77**: 1189-90.

6 O'Kelly TJ, Barr H, Malley WR, Kettlewell M. Cholecystectomy through a 5 cm subcostal incision. *Br J Surg* 1991; **78**: 762.

7 O'Dwyer PJ, McGregor JR, McDermott EWM, Murphy JJ, O'Higgins NJ. Patients recovery following cholecystectomy through a 6cm or 15cm transverse subcostal incision: a prospective randomised clinical trial. *Postgrad Med J* 1992; **68**: 817-9.

8 Dominioni L, Dionigi R, Cividini F. Determination of C-reactive protein and alpha-1-antitrypsin for quantitative assessment of surgical trauma (abstract). *Eur Surg Res* 1980; **12**: 133.

9 Cruickshank AM, Fraser WD, Burns HJ, Van Damme J, Shenkin A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. *Clin Sci* 1990; **79**: 161-5.

10 Chernow B, Alexander HR, Smallridge RC, et al. Hormonal responses to graded surgical stress. *Arch Intern Med* 1987; **147**: 1273-8.

11 Baigrie RJ, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ. Systemic cytokine response after major surgery. *Br J Surg* 1992; **79**: 757-60.

12 Ho HS, Gunther RA, Wolfe BM. Intraperitoneal carbon dioxide insufflation and cardiopulmonary functions. Laparoscopic cholecystectomy in pigs. *Arch Surg* 1992; **127**: 928-32.

13 Wittgen CM, Andrus CH, Fitzgerald SD, Baudendistel LJ, Dahms TE, Kaminski DL. Analysis of the hemodynamic and ventilatory effects of laparoscopic cholecystectomy. *Arch Surg* 1991; **126**: 997-1000.

14 Liu SY, Leighton T, Davis I, Klein S, Lippmann M, Bongard F. Prospective analysis of cardiopulmonary responses to laparoscopic cholecystectomy. *J Laparoendosc Surg* 1991; **1**: 241-6.

15 Wittgen CM, Naunheim KS, Andrus CH, Kaminski DL. Preoperative pulmonary function evaluation for laparoscopic cholecystectomy. *Arch Surg* 1993; **128**: 880-6.

16 Ammon HV, Hofmann AF. The Langenbuch paper. I - An historical perspective and comments of the translators. *Gastroenterology* 1983; **85**: 1426-33.

17 Langenbuch C. Ein Fall von Extstirpation der gallenblase wegen chronischer Cholelithiasis, Heilung. *Berliner Klinsche Wochenschritt* 1882; **19**: 725-7.

18 Ammon HV, Hofmann AF. The Langenbuch paper: II - A translation (Successful treatment of chronic cholelithiasis by cholecystectomy: a case report). *Gastroenterology* 1983; **85**: 1430-3.

19 Schien, C.J. *Acute Cholecystitis*.New York: Harper and Row, 1972.

20 Glenn F, Grafe WR. Historical events in biliary tract surgery. *Arch Surg* 1966; **93**: 848-52.

21 Gallstones and laparoscopic cholecystectomy. *NIH Consens Statement* 1992; **10 (3)**: 1-28.

22 Walsh TN, Russell RC. Cholecystectomy and gallbladder conservation. *Br J Surg* 1992; **79**: 4-5.

23 Jorgensen T. Prevalence of gallstones in a Danish population. *Am J Epidemiol* 1987; **126**: 912-21.

24 Jorgensen T. Abdominal symptoms and gallstone disease: an epidemiological investigation. *Hepatology* 1989; **9**: 856-60.

25 Bates T, Ebbs SR, Harrison M, A'Hern RP. Influence of cholecystectomy on symptoms. *Br J Surg* 1991; **78**: 964-7.

26 Bates T, Mercer JC, Harrison M. Symptomatic gallstone disease: before and after cholecystectomy. *Gut* 1984; **25**: 579-80.

27 Jorgensen T, Teglbjerg JS, Wille Jorgensen P, Bille T, Thorvaldsen P. Persisting pain after cholecystectomy. A prospective investigation. *Scand J Gastroenterol* 1991; **26**: 124-8.

28 Konsten J, Gouma DJ, Von Meyenfeldt MF, Menheere P. Long-term follow-up after open cholecystectomy. *Br J Surg* 1993; **80**: 100-2.

29 Orlando R, Russell JC, Lynch J, Mattie A, for the Connecticut Laparoscopic Cholecystectomy Registry . Laparoscopic cholecystectomy: a statewide experience. *Arch Surg* 1993; **128**: 494-9.

30 Legorreta AP, Silber JH, Costantino GN, Kobylinski RW, Zatz SL. Increased cholecystectomy rate after the introduction of laparoscopic cholecystectomy. *JAMA* 1993; **270**: 1429-32.

31 Spangenberger W, Klein J, Troidl H. Laparoskopische cholezystektomie - erste erfahrungen und ergenbnisse. *Langenbecks Arch Chir* 1990; suppl II: 1361-8.

32 Troidl H, Spangenberger W, Langen R, et al. Laparoscopic cholecystectomy: technical performance, safety and patient's benefit. *Endoscopy* 1992; **24**: 252-61.

33 Spiro HM. Diagnostic laparoscopic cholecystectomy. *Lancet* 1992; **339**: 167-8.

34 Brown TH, Walton G, Cheadle WG, Larson GM. The alkaline shift in gastric pH after cholecystectomy. *Am J Surg* 1989; **157**: 58-65.

35 Johnson AG. Pyloric function and gall-stone dyspepsia. *Br J Surg* 1972; **59**: 449-54.

36 Gadacz TR, Zuidema GD. Bile acid composition in patients with and without symptoms of postoperative reflux gastritis. *Am J Surg* 1978; **135**: 48-52.

37 Walsh TN, Jazrawi S, Byrne PJ, Hennessy TPJ. Cholecystectomy and gastro-oesophageal reflux. *Br J Surg* 1991; **78**: 753A.

38 Jazrawi S, Walsh TN, Li H, Lawlor P, Hennessy TPJ. Cholecystectomy and oesophageal reflux: a prospective evaluation. *Br J Surg* 1993; **80**: 50-3.

39 Thaysen EH, Pedersen L. Idiopathic bile acid catharsis. *Gut* 1976; **17**: 965-70.

40 Moorehead RJ, McKelvey ST. Cholecystectomy and colorectal cancer. *Br J Surg* 1989; **76**: 250-3.

41 Jorgensen T, Rafaelsen S. Gallstones and colorectal cancer - there is a relationship, but it is hardly due to cholecystectomy. *Dis Colon Rectum* 1992; **35**: 24-8.

42 Danzinger R, Hofmann AF, Schoenfield LJ, Thistle JL. Dissolution of cholesterol gallstones by chenodeoxycholic acid. *N Engl J Med* 1972; **286**: 1-8.

43 Neoptolemos JP, Hofmann AF, Moossa AR. Chemical treatment of stones in the biliary tree. *Br J Surg* 1986; **73**: 515-24.

44 Maton PN, Iser JH, Rueben A, Saxton HM, Murphy GM, Dowling RH. Outcome of chenodeoxycholic acid (CDCA) treatment in 125 patients with radiolucent gallstones. *Medicine* 1982; **61**: 85-96.

45 O'Donnell LD, Heaton KW. Recurrence and re-recurrence of gall stones after medical dissolution: a longterm follow up. *Gut* 1988; **29**: 655-8.

46 Sauerbruch T, Delius M, Paumgartner G, et.al. . Fragmentation of gallstones by extracorporeal shock waves. *N Engl J Med* 1986; **314**: 818-22.

47 Sackmann M, Delius M, Sauerbruch T, et al. Shock-wave lithotripsy of gallbladder stones. The first 175 patients. *N Engl J Med* 1988; **318**: 393-7.

48 Brink JA, Simeone JF, Mueller PR, Richter JM, Prien EL, Ferrucci JT. Physical characteristics of gallstones removed at cholecystectomy: implications for extracorporeal shock-wave lithotripsy. *AJR Am J Roentgenol* 1988; **151**: 927-31.

49 Nicholl JP, Brazier JE, Milner PC, et al. Randomised controlled trial of cost-effectiveness of lithotripsy and open cholecystectomy as treatments for gallbladder stones. *Lancet* 1992; **340**: 801-7.

50 Chiverton SG, Inglis JA, Hudd C, Kellett MJ, Russell RC, Wickham JE. Percutaneous cholecystolithotomy: the first 60 patients. *BMJ* 1990; **300**: 1310-2.

51 Kellett MJ, Wickham JE, Russell RC. Percutaneous cholecystolithotomy. *BMJ* 1988; **296**: 453-5.

52 Norrby S, Schonebeck J. Long-term results with cholecystolithotomy. *Acta Chir Scand* 1970; **136**: 711-3.

53 Armstrong PJ, Burgess RW. Choice of incision and pain following gallbladder surgery. *Br J Surg* 1990; **77**: 746-8.

54 Garcia-Valdecasas JC, Almenara R, Cabrer C, et al. Subcostal incision versus midline laparotomy in gallstone surgery: a prospective and randomized trial. *Br J Surg* 1988; **75**: 473-5.

55 Maingot, R. *Abdominal Operations.*7th ed. New York: Appleton Century-Crofts, 1988; 1033-55.

56 Goco IR, Chambers LG. "Mini-cholecystectomy" and operative cholangiography. A means of cost containment. *Am Surg* 1983; **49**: 143-5.

57 Morton CE. Cost containment with the use of "mini-cholecystectomy" and intraoperative cholangiography. *Am Surg* 1985; **51**: 168-9.

58 Moss G. Discharge within 24 hours of elective cholecystectomy. The first 100 patients. *Arch Surg* 1986; **121**: 1159-61.

59 Moss G, Regal ME, Lichtig L. Reducing postoperative pain, narcotics, and length of hospitalization. *Surgery* 1986; **99**: 206-10.

60 Russell RC, Shankar S. The stabilized ring retractor: a technique for cholecystectomy. *Br J Surg* 1987; **74**: 826.

61 Fink DL, Budd DC. Rectus muscle preservation in oblique incisions for cholecystectomy. *Am Surg* 1984; **50**: 628-36.

62 Kelling G. Zur Colioskopie. *Archiv Klinische Chirurgie* 1923; **126**: 226-8.

63 Jacobeus HC. Kurze Ubersicht ubermeine Erfahrungen mit der Laparoskopie. *Munchen Medizinische Wochenschrift* 1911; **58**: 2017-9.

64 Semm K. Die endoskopische Appendektomie. *Gynakologische Praxis* 1983; **7**: 131-40.

65 Mouret G. From the first laparoscopic cholecystectomy to the frontiers of laparoscopic surgery: the future perspectives. *Dig Surg* 1991; **8**: 124-5.

66 Dubois F, Berthelot G, Levard H. Cholecystectomie par coelioscopie. *La Presse Medicale* 1989; **18**: 980-2.

67 Dubois F, Icard P, Berthelot G, Levard H. Coelioscopic cholecystectomy. Preliminary report of 36 cases. *Ann Surg* 1990; **211**: 60-2.

68 Perissat J, Collet D, Belliard R. Gallstones: laparoscopic treatment, intracorporeal lithotripsy followed by cholecystostomy or cholecystectomy - a personal technique. *Endoscopy* 1989; **21** Suppl 1: 373-374.

69 Perissat J, Collet D, Belliard R. Laparoscopic surgery for gallbladder stones. *Ann Med* 1991; **23**: 233-6.

70 Perissat J, Collet D, Belliard R. Gallstones: laparoscopic treatment - cholecystectomy, cholecystostomy, and lithotripsy. Our own technique. *Surg Endosc* 1990; **4**: 1-5.

71 Reddick EJ, Olsen DO, Daniell JF, Saye WB, McKernen BMuller,W., Hoback M. Laparoscopic laser cholecystectomy. *Laser Med Surg News* 1989; **7**: 38-40.

72 Reddick EJ, Olsen DO. Laparoscopic laser cholecystectomy. A comparison with mini-lap cholecystectomy. *Surg Endosc* 1989; **3**: 131-3.

73 Cheslyn Curtis S, Russell RC. New trends in gallstone management. *Br J Surg* 1991; **78**: 143-9.

74 Holohan TV. Laparoscopic cholecystectomy. *Lancet* 1991; **338**: 801-3.

75 Surgical innovation under scrutiny. *Lancet* 1993; **342**: 187-8.

76 Larson GM, Vitale GC, Casey J, et al. Multipractice analysis of laparoscopic cholecystectomy in 1,983 patients. *Am J Surg* 1992; **163**: 221-6.

77 Cuschieri A, Dubois F, Mouiel J, et al. The European experience with laparoscopic cholecystectomy. *Am J Surg* 1991; **161**: 385-7.

78 Morgenstern L, Wong L, Berci G. Twelve hundred open cholecystectomies before the laparoscopic era. A standard for comparison. *Arch Surg* 1992; **127**: 400-3.

79 Gilliland TM, Traverso LW. Modern standards for comparison of cholecystectomy with alternative treatments for symptomatic cholelithiasis with emphasis on long-term relief of symptoms. *Surg Gynecol Obstet* 1990; **170**: 39-44.

80 McSherry CK, Glenn F. The incidence and causes of death following surgery for nonmalignant biliary tract disease. *Ann Surg* 1980; **191**: 271-5.

81 The Southern Surgeons Club . A prospective analysis of 1518 laparoscopic cholecystectomies. *N Engl J Med* 1991; **324**: 1073-8.

82 Levine DW. Comment - An analysis of laparoscopic cholecystectomy . *N Engl J Med* 1991; **325**: 967-8.

83 Nussbaum R, Fromm H. Laparoscopic cholecystectomy: a new procedure in need of further study. *Gastroenterology* 1992; **102**: 362-4.

84 Barone JE, Lincer RM. Correction: A prospective analysis of 1518 laparoscopic cholecystectomies (letter). *N Engl J Med* 1991; **325**: 1517-8.

85 Nahrwold DL. Laparoscopic cholecystectomy - invited comment. *Arch Surg* 1992; **127**: 403.

86 Moossa AR, Mayer AD, Stabile B. Iatrogenic injury to the bile duct: who, how, where? *Arch Surg* 1990; **125**: 1028-30.

87 Vanderpool D, Lane BW, Winter JW, Bone GE. Cholecystectomy. *South Med J* 1989; **82**: 450-2.

88 Ganey JB, Johnson PA,Jr., Prillaman PE, McSwain GR. Cholecystectomy: clinical experience with a large series. *Am J Surg* 1986; **151**: 352-7.

89 Warwick DJ, Thompson MH. Six hundred patients with gallstones. *Ann R Coll Surg Engl* 1992; **74**: 218-21.

90 Clavien P-A, Sanabria JR, Mentha G, et al. Recent results of elective open cholecystectomy in a North American and a European centre. *Ann Surg* 1992; **216**: 618-26.

91 Davies MG, O'Broin E, Mannion C, et al. Audit of open cholecystectomy in a district general hospital. *Br J Surg* 1992; **79**: 314-6.

92 Saltzstein EC, Mercer LC, Peacock JB, Dougherty SH. Twenty-four hour hospitalization after cholecystectomy. *Surg Gynecol Obstet* 1991; **173**: 367-70.

93 Herzog U, Pesmer P, Sutter M, Tondelli P. Surgical treatment for cholelithiasis. *Surg Gynecol Obstet* 1992; **175**: 238-92.

94 Cox MR, Gunn IF, Eastman MC, Hunt RF, Heinz AW. Open cholecystectomy: a control group for comparison with laparoscopic cholecystectomy. *Aust N Z J Surg* 1992; **62**: 795-801.

95 Roslyn JJ, Binns GS, Hughes EFX, Saunders-Kirkwood K, Zinner MJ, Cates JA. Open cholecystectomy: a contemporary analysis of 42,474 patients. *Ann Surg* 1993; **218**: 129-37.

96 Raute M, Podlech P, Jaschke W, Manegold BC, Trede M, Chir B. Management of bile duct injuries and strictures following cholecystectomy. *World J Surg* 1993; **17**: 553-62.

97 Harte PJ, Kirwan WO, Hennessy TP, Gaffney PR, Brady MP. Biliary surgery for benign disease: a study of 500 consecutive operations. *Ir J Med Sci* 1979; **148**: 297-302.

98 Kunz R, Orth K, Vogel J, et al. Laparoskopische cholecystektomie versus mini-lap-cholecystektomie. *Chirurg* 1992; **63**: 291-5.

99 Barkun JS, Barkun AN, Sampalis JS, et al. Randomised controlled trial of laparoscopic versus mini cholecystectomy. *Lancet* 1992; **340**: 1116-9.

100 Assalia A, Schein M, Kopelman D, Hashmonai M. Laparoscopic versus mini-incision cholecystectomy. *Lancet* 1990; **341**: 47.

101 Peters JH, Ellison EC, Innes JT, et al. Safety and efficacy of laparoscopic cholecystectomy: a prospective analysis of 100 initial patients. *Ann Surg* 1991; **213**: 3-12.

102 Smith R. Injuries to the common bile duct during laparoscopic cholecystectomy. *BMJ* 1991; **303**: 1475.

103 Shanahan D, Knight M. Laparoscopic cholecystectomy. *BMJ* 1992; **304**: 776-7.

104 Traverso LW. Endoscopic cholecystectomy: an analysis of complications - comment. *Arch Surg* 1991; **126**: 1197.

105 Peck JJ. Endoscopic cholecystectomy: an analysis of complications - see comment. *Arch Surg* 1991; **213**: 3-12.

106 Lightfoot L, Rogers L. Keyhole surgery could double risk of damage to patients. *Sunday Times* April 11, 1993; p5.

107 Rossi RL, Schirmer WJ, Braasch JW, Sanders LB, Munson JL. Laparoscopic bile duct injuries: risk factors, recognition, and repair. *Arch Surg* 1992; **127**: 596-601.

108 Moossa AR, Easter DW, Van Sonnenberg E, Casola G, D'Agostino H. Laparoscopic injuries to the bile duct: a cause for concern. *Ann Surg* 1992; **215**: 203-8.

109 Davidoff AM, Pappas TN, Murray EA, et al. Mechanisms of major biliary injury during laparoscopic cholecystectomy. *Ann Surg* 1992; **215**: 196-202.

110 Asbun HJ, Rossi RL, Lowell JA, Munson JL. Bile duct injury during laparoscopic cholecystectomy: mechanism of injury, prevention, and management. *World J Surg* 1993; **17**: 547-52.

111 Branum G, Schmitt C, Baillie J, et al. Management of major biliary complications after laparosopic cholecystectomy. *Ann Surg* 1993; **217**: 532-41.

112 Cates JA, Tompkins RK, Zinner MJ, Busuttil RW, Kallman C, Roslyn JJ. Biliary complications of laparoscopic cholecystectomy. *Am Surg* 1993; **59**: 243-7.

113 Ko ST, Airan MC. Review of 300 consecutive laparoscopic cholecystectomies: development, evolution, and results. *Surg Endosc* 1991; **5**: 103-8.

114 Graves HA,Jr., Ballinger JF, Anderson WJ. Appraisal of laparoscopic cholecystectomy. *Ann Surg* 1991; **213**: 655-62.

115 Davidoff AM, Branum GD, Murray EA, et al. The technique of laparoscopic cholecystectomy in children. *Ann Surg* 1992; **215**: 186-91.

116 Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. *Biochem J* 1990; **265**: 621-6.

117 Wilson RG, Macintyre IMC, Nixon SJ, Saunders JH, Varma JS, King PM. Laparoscopic cholecystectomy as a safe and effective treatment for severe acute cholecystitis. *BMJ* 1992; **305**: 394-6.

118 Wolfe BM, Gardiner BN, Leary BF, Frey CF. Endoscopic cholecystectomy: an analysis of complications. *Arch Surg* 1991; **126**: 1192-8.

119 Berci G, Sackier JM. The Los Angeles experience with laparoscopic cholecystectomy. *Am J Surg* 1991; **161**: 382-4.

120 Brown E, Hawasli A, Lloyd L. Laparoscopic cholecystectomy: morbidity and mortality in a community teahing institution. *J Laparoendosc Surg* 1993; **3**: 13-8.

121 Clair DG, Carr-Locke DL, Becker JM, Brooks DC. Routine cholangiography is not warranted during laparoscopic cholecystectomy. *Arch Surg* 1993; **128**: 551-5.

122 Davis CJ, Arregui ME, Nagan RF, Shaar C. Laparoscopic cholecystectomy: the St. Vincent experience. *Surgical Laparoscopy and Endoscopy* 1992; **2**: 64-8.

123 Lane GE, Lathrop JC. Comparison of results of KTP/532 laser versus monopolar electrosurgical dissection in laparoscopic cholecystectomy. *J Laparoendosc Surg* 1993; **3**: 209-14.

124 Soper NJ, Stockmann PT, Dunnegan DL, Ashley SW. Laparoscopic cholecystectomy: the new "gold standard"? *Arch Surg* 1992; **127**: 917-23.

125 Baird DR, Wilson JP, Mason EM, et al. An early review of 800 laparoscopic cholecystectomies at a university-affiliated community teaching hospital. *Am Surg* 1992; **58**: 206-10.

126 Graffis R. Laparoscopic cholecystectomy: the Methodist Hospital experience. *Surgical Laparoscopy and Endoscopy* 1992; **2**: 69-73.

127 McGee JM, Randel MA, Morgan RM, et al. Laparoscopic cholecystectomy: an initial community experience. *J Laparoendosc Surg* 1992; **2**: 293-302.

128 Taniguchi Y, Ido K, Kimura K, et al. Introduction of a "safety zone" for the safety of laparoscopic cholecystectomy. *Am J Gastroenterol* 1993; **88**: 1258-61.

129 Kozarek R, Gannan R, Baerg R, Wagonfeld J, Ball T. Bile leak after laparoscopic cholecystectomy: Diagnostic and therapeutic application of endoscopic retrograde cholangiopancreatography. *Arch Intern Med* 1992; **152**: 1040-3.

130 Litwin DE, Girotti MJ, Poulin EC, Mamazza J, Nagy AG. Laparoscopic cholecystectomy: trans-Canada experience with 2201 cases. *Can J Surg* 1992; **35**: 291-6.

131 Airan M, Appel M, Berci G, et al. Retrospective and prospective multi-institutional laparoscopic cholecystectomy study organized by the Society of American Gastrointestinal Endoscopic Surgeons. *Surg Endosc* 1992; **6**: 169-76.

132 Deveney K. The early experience with laparoscopic cholecystectomy in Oregon. *Arch Surg* 1992; **128**: 627-32.

133 Macintyre IMC, Wilson RG. Laparoscopic cholecystectomy. *Br J Surg* 1993; **80**: 552-9.

134 Deziel DJ, Millikan KW, Economou SG, Doolas A, Sung-Tao K, Airan MC. Complications of laparoscopic cholecystectomy: a national survey of 4,292 hospitals and an analysis of 77,604 cases. *Am J Surg* 1993; **165**: 9-14.

135 Fullarton GM, Bell G, and the West of Scotland Laparoscopic Cholecystectomy Study Group . A prospective audit of the introduction of laparoscopic cholecystectomy in the West of Scotland. *Gut* 1993; **34**: S69.

136 Suc B, Fontes Dislaire I, Fourtanier G, Escat J. 3606 cholecystectomies sous coelioscopie: registre de la Societe Francaise de Chirurgie Digestive. *Ann Chir* 1992; **46**: 219-26.

137 Go PM, Schol F, Gouma DG. Laparoscopic cholecystectomy in the Netherlands. *Br J Surg* 1993; **80**: 1180-3.

138 McQuillan T, Manolas SG, Hayman JA, Kune GA. Surgical significance of the bile duct of Luschka. *Br J Surg* 1989; **76**: 696-8.

139 Hobsley M. Intra-hepatic anatomy: a surgical evaluation. *Br J Surg* 1958; **45**: 635-44.

140 Foster JH, Wayson EE. Surgical significance of aberrant bile ducts. *Am J Surg* 1962; **104**: 14-9.

141 HEaley JE, Schroy PC. Anatomy of the biliary ducts within the human liver. *Arch Surg* 1953; **66**: 599-616.

142 Pickleman J, Gonzalez RP. The improving results of cholecystectomy. *Arch Surg* 1986; **121**: 930-4.

143 Walker AT, Shapiro AW, Brooks DC, Braver JM, Tumeh SS. Bile duct disruption and biloma after laparoscopic cholecystectomy: imaging evaluation. *Am J Roentgenol* 1992; **158**: 785-9.

144 Nelson MT, Nakashima M. How secure are laparoscopically placed clips? *Arch Surg* 1992; **127**: 718-20.

145 Nathanson LK, Shimi S, Cuschieri A. Laparoscopic cholecystectomy: the Dundee technique. *Br J Surg* 1991; **78**: 155-9.

146 Mintz M. Risk and prophylaxis in laparoscopy: a survey of 100,000 cases. *J Reprod Med* 1977; **18**: 269-72.

147 Peterson H, Greenspan J, Ory H. Death following puncture of the aorta during laparoscopic sterilisation. *Obstet Gynecol* 1982; **59**: 133-4.

148 Riedell HH, Lehmann-Willenbrock E, Mecke H, Semm K. The frequency distribution of various pelviscopic (laparoscopic) operations, including complication rates statistic of the Federal Republic of Germany in the years 1983-1985. *Zentralbl Gynakol* 1989; **111**: 78-91.

149 Dunn DC, Watson CJE. Disposable guarded trocar and cannula in laparoscopic surgery: a caveat. *Br J Surg* 1992; **79**: 927.

150 Nenner RP, Imperato PJ, Alcorn CM. Serious complications of laparoscopic cholecystectomy in New York State. *N Y State J Med* 1992; **92**: 179-81.

151 Penfield AJ. How to prevent complications of open lapararoscopy. *J Reprod Med* 1985; **30**: 660-3.

152 Loffer FD, Pent D. Indications, contraindications, and complications of laparoscopy. *Obstet Gynecol Surv* 1975; **30**: 407-27.

153 Bruhl W. Complications of laparoscopy and liver biopsy under vision: the results of a survey. *German Med Monthly* 1967; **12**: 31-2.

154 Phillips J, Keith D, Hulka B, Keith L. Gynaecologic laparoscopy in 1975. *J Reprod Med* 1976; **16**: 105-17.

155 Chamberlain, G. and Carron-Brown, J. *The report of the working party of the Confidential Enquiry into Gynaecological Laparoscopy.*The Royal College of Obstetricians and Gynaecologists, 1978; 116-7.

156 Greville AC, Clements EA, Erwin DC, McMillan DL, Wellwood JM. Pulmonary air embolism during laparoscopic laser cholecystectomy. *Anaesthesia* 1991; **46**: 113-4.

157 Whiston RJ, Eggers KA, Morris RW, Stamatakis JD. Tension pneumothorax during laparoscopic cholecystectomy. *Br J Surg* 1991; **78**: 1325.

158 Herzog U, Kocher T, Ackermann C, Schuppisser JP, Looser C, Tondelli P. Die laparoskopische Cholezystektomie -Erfahrungen und Ergebnisse mit einer neuen Operationstechnik. *Schweiz Med Wschr* 1992; **122**: 659-62.

159 Mealy K, Hyland J. Small bowel obstruction following laparoscopic cholecystectomy. Case report. *Eur J Surg* 1991; **157**: 675-6.

160 Ballem RV, Kenny R, Giuliano M. Small bowel obstruction following laser laparoscopic cholecystectomy: a case study. *J Laparoendosc Surg* 1993; **3**: 313-4.

161 Boyce DE, Wheeler MH, Fugelstone LJ. An unusual complication of laparoscopic cholecystecomy. *Ann R Coll Surg Engl* 1992; **74**: 254-5.

162 Bredesen J, Jorgensen T, Andersen TF, et al. Early postoperative mortality following cholecystectomy in the entire female population of Denmark, 1977-1981. *World J Surg* 1992; **16**: 530-5.

163 McSherry CK. Cholecystectomy: the gold standard. *Am J Surg* 1989; **158**: 174-8.

164 Nottle PD. Laparoscopic cholecystectomy: an Australian view. *Aust N Z J Surg* 1992; **62**: 150.

165 Fitzgibbons RJ, Schmid S, Santoscoy R, et al. Open laparoscopy for laparoscopic cholecystectomy. *Surgical Laparoscopy and Endoscopy* 1991; **1**: 216-2.

166 Barkun JS, Fried GM, Barkun AN, et al. Cholecystectomy without operative cholangiography: implications for common bile duct injury and retained common bile duct stones. *Ann Surg* 1993; **218**: 371-9.

167 Perissat J, Collet D, Belliard R, Desplantez J, Magne E. Laparoscopic cholecystectomy: the state of the art - a report on 700 consecutive cases. *World J Surg* 1992; **16**: 1074-82.

168 Martin IG, Curley P, McMahon MJ. Minimally invasive treatment for common bile duct stones. *Br J Surg* 1993; **80**: 103-6.

169 Berci G, Sackier JM, Paz Partlow M. Routine or selected intraoperative cholangiography during laparoscopic cholecystectomy? *Am J Surg* 1991; **161**: 355-60.

170 Flowers JL, Zucker KA, Graham SM, Scovill WA, Imbembo AL, Bailey RW. Laparoscopic cholangiography. Results and indications. *Ann Surg* 1992; **215**: 209-16.

171 Schirmer BD, Edge SB, Dix J, Hyser MJ, Hanks JB, Jones RS. Laparoscopic cholecystectomy. Treatment of choice for symptomatic cholelithiasis. *Ann Surg* 1991; **213**: 665-76.

172 Macintyre IMC, Wilson RG. Impact of laparoscopic cholecystectomy in the UK: a survey of consultants. *Br J Surg* 1993; **80**: 346.

173 Joyce WP, Keane R, Burke GJ, et al. Identification of bile duct stones in patients undergoing laparoscopic cholecystectomy. *Br J Surg* 1991; **78**: 1174-6.

174 Hall C, Ganas P, Tyrell PNM, Li JKW, Dorricott NJ. Investigation and management of the bile duct before laparoscopic cholecystectomy. *Gut* 1992; **331**: S27.

175 Shapiro SJ, Gordon LA, Daykhovsky L, Grundfest W. Laparoscopic exploration of the common bile duct: experience in 16 selected patients. *J Laparoendosc Surg* 1992; **1**: 333-41.

176 Hunter JG. Laparoscopic transcystic common bile duct exploration. *Am J Surg* 1992; **163**: 53-6.

177 Ferzli GS, Massaad A, Ozuner G, Worth MH. Laparoscopic exploration of the common bile duct. *Surg Gynecol Obstet* 1992; **174**: 419-21.

178 Metcalf AM, Ephgrave KS, Dean TR, Maher JW. Preoperative screening with ultrasonography for laparoscopic cholecystectomy: an alternative to routine intraoperative cholangiography. *Surgery* 1992; **112**: 813-7.

179 Leitman IM, Fisher ML, McKinley MJ, et al. The evaluation and mangement of known or suspected stones of the common bile duct in the era of minimal access surgery. *Surg Gynecol Obstet* 1993; **176**: 527-33.

180 Cotton PB. Endoscopic management of bile duct stones; (apples and oranges). *Gut* 1984; **25**: 587-97.

181 Viceconte G, Viceconte GW, Pietropaolo V, Montori A. Endoscopic sphincterotomy: indications and results. *Br J Surg* 1981; **68**: 376-80.

182 Leese T, Neoptolemos JP, Carr-Locke DL. Successes, failures, early complications and their management following endoscopic sphincterotomy: results in 394 consecutive patients from a single centre. *Br J Surg* 1985; **72**: 215-9.

183 Heinerman PM, Boeckl O, Pimpl W. Selective ERCP and preoperative stone removal in bile duct surgery. *Ann Surg* 1989; **209**: 267-72.

184 Neoptolemos JP, Carr Locke DL, Fossard DP. Prospective randomised trial of pre-operative endoscopic sphincterotomy versus surgery alone for common bile duct stones. *BMJ* 1987; **294**: 470-4.

185 Cuschieri RJ, Morran CG, Howie JC, McArdle CS. Postoperative pain and pulmonary complications: comparison of three analgesic regimens. *Br J Surg* 1985; **72**: 495-8.

186 Frank ED, McKay W, Rocco A, Gallo JP. Interpleural bupivacaine for postoperative analgesia following cholecystectomy: a randomized prospective study. *Reg Anesth* 1990; **15**: 26-30.

187 VadeBoncouer TR, Riegler FX, Gautt RS, Weinberg GL. A randomized, double-blind comparison of the effects of interpleural bupivacaine and saline on morphine requirements and pulmonary function after cholecystectomy. *Anesthesiology* 1989; **71**: 339-43.

188 Hendolin H, Lahtinen J, Lansimies E, Tuppurainen T, Partanen K. The effect of thoracic epidural analgesia on respiratory function after cholecystectomy. *Acta Anaesthesiol Scand* 1987; **31**: 645-51.

189 Dureuil B, Viires N, Cantineau JP, Aubier M, Desmonts JM. Diaphragmatic contractility after upper abdominal surgery. *J Appl Physiol* 1986; **61**: 1775-80.

190 Duggan J, Drummond GB. Activity of lower intercostal and abdominal muscle after upper abdominal surgery. *Anesth Analg* 1987; **66**: 852-5.

191 Simonneau G, Vivien A, Sarten R, et al . Diaphragm dysfunction induced by upper abdominal surgery. *Am Rev Respir Dis* 1983; **128**: 899-903.

192 Alexander JI, Spence AA, Parikh RK, Stuart B. The role of airway closure in postoperative hypoxaemia. *Br J Anaesth* 1973; **45**: 34-40.

193 Arunasalam K, Davenport HT, Painter S, Jones JG. Ventilatory responses to morphine in young and old subjects. *Anaesthesia* 1983; **38**: 529-33.

194 Catley DM, Thornton C, Jordan C, Lehane JR, Royston D, Jones JG. Pronounced, episodic oxygen desaturation in the postoperative period: its association with ventilatory pattern and analgesic regimen. *Anesthesiology* 1985; **63**: 20-28.

195 Coelho JC, de Araujo RP, Marchesini JB, Coelho IC, De Araujo LR. Pulmonary function after cholecystectomy performed through kocher's incision, a mini-incision, and laparoscopy. *World J Surg* 1993; **17**: 544-6.

196 Buanes T, Raeder MG. Introduction of laparoscopic techniques in gastrointestinal surgery: experience at a Norwegian university hospital as revealed by prospective comparative studies. *Surgical Laparoscopy and Endoscopy* 1993; **3**: 21-8.

197 Attwood SEA, Mealy K, Hill ADK, Stephens RB. A prospective comparison of laparoscopic versus open cholecystectomy. *Ann R Coll Surg Engl* 1992; **74**: 397-400.

198 Rademaker BM, Ringers J, Odoom JA, De Wit LT, Kalkman CJ, Oosting J. Pulmonary function and stress response after laparoscopic cholecystectomy: comparison with subcostalincision and influence of thoracic epidural analgesia. *Anesth Analg* 1992; **75**: 381-5.

199 Schauer PR, Luna J, Ghiatas AA, Glen ME, Warren JM, Sirinek KR. Pulmonary function after laparoscopic cholecystectomy. *Surgery* 1993; **114**: 389-99.

200 Frazee RC, Roberts JW, Okeson GC, et al. Open versus laparoscopic cholecystectomy. A comparison of postoperative pulmonary function. *Ann Surg* 1991; **213**: 651-3.

201 Joris J, Cigarini I, Legrand M. Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy. *Br J Anaesth* 1992; **69**: 341-5.

202 Mealy K, Gallagher H, Barry M, Lennon F, Traynor O, Hyland J. Physiological and metabolic responses to open and laparoscopic cholecystectomy. *Br J Surg* 1992; **79**: 1061-4.

203 Soper NJ, Barteau JA, Clayman RV, Ashley SW, Dunnegan DL. Comparison of early postoperative results for laparoscopic versus standard open cholecystectomy. *Surg Gynecol Obstet* 1992; **174**: 114-8.

204 Bradbury AW, Stonebridge PA, Wallace IWJ, MacLeod DAD, Rainey JB. Open biliary surgery and the use of routine inpatient audit. *J R Coll Surg Edinb* 1993; **38**: 86-8.

205 Stoker ME, Vose J, O'Mara P, Maini BS. Laparoscopic cholecystectomy: a clinical and financial analysis of 280 operations. *Arch Surg* 1992; **127**: 589-95.

206 Hall RC. Short surgical stay: two hospital days for cholecystectomy. *Am J Surg* 1987; **154**: 510-5.

207 Saltzstein EC, Mercer LC, Peacock JB, Dougherty SH. Outpatient open cholecystectomy. *Surg Gynecol Obstet* 1992; **174**: 173-5.

208 Al-Tameem MM. Minilaparotomy cholecystectomy. *J R Coll Surg Edinb* 1993; **38**: 154-7.

209 Grace PA, Quereshi A, Coleman J, et al. Reduced postoperative hospitalization after laparoscopic cholecystectomy. *Br J Surg* 1991; **78**: 160-2.

210 Vitale GC, Collet D, Larson GM, Cheadle WG, Miller FB, Perissat J. Interruption of professional and home activity after laparoscopic cholecystectomy among French and American patients. *Am J Surg* 1991; **161**: 396-8.

211 Cuckow PM. Cost can and must be a component of surgical audit. *Ann R Coll Surg Engl* 1992; **74**: 406-11.

212 Kurzawinski T, Hayter B, Tate J, Davidson B, Hobbs KEF. The cost implications of laparoscopic vs open cholecystectomy (abstract). *Gut* 1992; **33**: S64.

213 Fullarton GM, Darling K, McMillan R, Bell G. Evaluation of the cost of laparoscopic and open cholecystectomy. *Gut* 1992; **33**: S27.

214 Jordan AM. Hospital charges for laparoscopic and open cholecystectomy. *JAMA* 1991; **266**: 3425-6.

215 Grundfest W. Laparoscopic surgery: the need for self-control. *J Laparoendosc Surg* 1992; **2**: 131-2.

216 Neuhaus H, Feussner H, Ungeheuer A, Hoffmann W, Siewert JR, Classen M. Prospective evaluation of the use of endoscopic retrograde cholangiography prior to laparoscopc cholecystectomy. *Endoscopy* 1992; **24**: 745-9.

217 Graham SM, Flowers JL, Bailey RW, Zucker KA, Imbembo AL. Utility of planned perioperative endoscopic retrograde cholangiopancreatography and sphincterotomy in the era of laparoscopic cholecystectomy. *Endoscopy* 1992; **24**: 788-9.

218 Dashow L, Friedman I, Kempner R, Rudick J, McSherry C. Initial experience with laparoscopic cholecystectomy at the Beth Israel Medical Center. *Surg Gynecol Obstet* 1992; **175**: 25-30.

219 The epistemology of surgery. *Lancet* 1986; **1**: 656-7.

220 Medical Research Council . Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948; **2**: 769-82.

221 Goligher JC, Pulvertaft CN, Watkinson G. Controlled trial of vagotomy and gastroenterostomy, vagotomy and antrectomy and subtotal gastrectomy in elective treatment of duodenal ulcer - Interim report. *BMJ* 1964; **i**: 455-60.

222 Pollock AV. The rise and fall of the random controlled trial in surgery. *Theor Surg* 1989; **4**: 163-70.

223 Halsted WS. The results of radical operations for the cure of carcinoma of the breast. *Ann Surg* 1907; **46**: 1-19.

224 Salzman EW. Is surgery worthwhile? . *Arch Surg* 1985; **120**: 771-6.

225 Fielding LP, Phillips RKS, Fry JS, Hitlinger R. The prediction of outcome after curative resection for large bowel cancer. *Lancet* 1986; **2**: 904-7.

226 McArdle CS, Hole D. Impact of variability among surgeons on postoperative morbidity and mortality and ultimate survival. *BMJ* 1991; **302**: 1501-5.

227 Chalmers TC. Randomization of the first patient. *Med Clin North Am* 1975; **59**: 1035-8.

228 van der Linden W. Pitfalls in randomized surgical trials. *Surgery* 1980; **87**: 258-62.

229 Murphy ML, Hultgren HN, Detre K, Thomsen J, Takaro T, and participatants of the Veterans Administration Cooperative Study . A preliminary report of survival data of the randomized Veterans Administration Cooperative Study. *N Engl J Med* 1977; **297**: 621-7.

230 Passamani E. Clinical trials - are they ethical? *N Engl J Med* 1991; **324**: 1589-92.

231 Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987; **317**: 141-5.

232 McMahon AJ, O'Dwyer PJ, Russell IT, Baxter JN. Laparoscopic versus mini-cholecystectomy. *Lancet* 1993; **341**: 249.

233 Nicholl JP, Brazier JE. Laparoscopic versus mini-incision cholecystectomy. *Lancet* 1993; **341**: 47.

234 Schwartz, D., Flamant, R. and Lellouch, J. *Clinical trials*. London: Academic Press, 1980.

235 Hunt, S., McKenna, S.P. and McEwen, J. *The Nottingham health profile user's manual*.Manchester: Galen Research and Consultancy, 1989.

236 Lahat N, Zlotnick AY, Shtiller R, Bar I, Merin G. Serum levels of IL-1, IL-6 and tumour necrosis factors in patients undergoing coronary artery bypass grafts or cholecystectomy. *Clin Exp Immunol* 1992; **89**: 255-60.

237 Shenkin A, Fraser WD, Series J, et al. The serum interleukin 6 response to elective surgery. *Lymphokine Res* 1989; **8**: 123-7.

238 Colley CM, Fleck A, Goode AW, Muller BR, Myers MA. Early time course of the acute phase protein response in man. *J Clin Pathol* 1983; **36**: 203-7.

239 Klingstedt C, Giesecke K, Hamberger B, Jarnberg PO. High- and low-dose fentanyl anaesthesia: circulatory and plasma catecholamine responses during cholecystectomy. *Br J Anaesth* 1987; **59**: 184-8.

240 Giesecke K, Hamberger B, Jarnberg PO, Klingstedt C, Persson B. High- and low-dose fentanyl anaesthesia: hormonal and metabolic responses during cholecystectomy. *Br J Anaesth* 1988; **61**: 575-82.

241 Petersson B, Wernerman J, Waller SO, von der Decken A, Vinnars E. Elective abdominal surgery depresses muscle protein synthesis and increases subjective fatigue: effects lasting more than 30 days. *Br J Surg* 1990; **77**: 796-800.

242 Fleck A, Raines G, Hawker F, et al . Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. *Lancet* 1985; **1**: 781-4.

243 Salo M, Eskola J. Immunosuppression after cholecystectomy. *Acta Anaesthesiol Scand* 1977; **21**: 509-16.

244 Madsbad S, Buschard K, Siemssen O, Ropke C. Changes in T-lymphocyte subsets after elective surgery. *Acta Chir Scand* 1986; **152**: 81-84.

245 Lennard TWJ, Shenton BK, Borzotta A, et al. The influence of surgical operations on components of the human immune system. *Br J Surg* 1992; **72**: 771-6.

246 Cooper GM, Scoggins AM, Ward ID, Murphy D. Laparoscopy - a stressful procedure. *Anaesthesia* 1982; **37**: 266-9.

247 Alexander GD, Brown EM. Physiologic alterations during pelvic laparoscopy. *Am J Obstet Gynecol* 1969; **105**: 1078-81.

248 Seed RF, Shakespeare TF, Muldoon MJ. Carbon dioxide homeostasis during anaesthesia for laparoscopy. *Anaesthesia* 1970; **25**: 223-31.

249 El-Minawi MF, Wahbi O, El-Bagouri IS, Sharawi M, El-Mallah SY. Physiologic changes during carbon dioxide and nitrous oxide pneumoperitoneum in diagnostic laparoscopy. *J Reprod Med* 1981; **26**: 338-46.

250 Kelman GR, Swapp GH, Smith I, Benzie RJ, Gordon NLM. Cardiac output and arterial blood-gas tension during laparoscopy. *Br J Anaesth* 1972; **44**: 1155-61.

251 Brown DR, Fishburn JI, Robertson VO, Hulka JF. Ventilatory and blood gas changes during laparoscopy with local anaesthesia. *Am J Obstet Gynecol* 1976; **124**: 741-5.

252 Puri GD, Singh H. Ventilatory effects of laparoscopy under general anaesthesia. *Br J Anaesth* 1992; **68**: 211-3.

253 Hodgson C, McClellan RMA, Newton JR. Some effects of the peritoneal insufflation of carbon dioxide at laparoscopy. *Anaesthesia* 1970; **25**: 382-90.

254 Motew M, Ivankovich AD, Albrecht RF, Zahed B, Scommegna A. Cardiovascular effects and acid-base and blood gas changes during laparoscopy. *Am J Obstet Gynecol* 1973; **115**: 1002-12.

255 Raemer DB, Francis D, Philip JH, Gabel RA. Variation in carbon dioxide tension between arterial blood and peak expired gas during anesthesia. *Anesth Analg* 1983; **62**: 1065-9.

256 Fitzgerald SD, Andrus CH, Baudendistel LJ, Dahms TE, Kaminski DL. Hypercarbia during carbon dioxide pneumoperitoneum. *Am J Surg* 1992; **163**: 186-90.

257 Levitt MD, Bond JM. Volume, composition and source of intestinal gas. *Gastroenterology* 1970; **59**: 921-9.

258 Beattie, I.R. *Mellor's comprehensive treatise on inorganic and theoretical chemistry.*London: Longmans, 1967; vol 8, 209-215.

259 Drummond LJ. Shock induced reaction of methane with nitrous and nitric oxides. *Bulletin of the Chemical Society of Japan* 1969; **42**: 285-9.

260 Uhlich GA. Laparoscopy: the question of the proper gas. *Gastrointest Endosc* 1982; **28**: 212-213.

261 Sharp J, Pierson W, Brady C. Comparison of carbon dioxide and nitrous oxide induced discomfort during peritoneoscopy under local anaesthesia. *Gastroenterology* 1982; **82**: 453-6.

262 Mianoli G, Terruzzi V, Spinzi GC, Benvenuti C, Rossini A. The influence of carbon dioxide and nitrous oxide on pain during laparoscopy: a double blind, controlled trial. *Gastrointest Endosc* 1982; **28**: 173-5.

263 Robinson JS, Thompson JM, Wood AW. Laparoscopy explosion hazards with nitrous oxide. *BMJ* 1975; **3**: 764-5.

264 Bongard FS, Pianim N, Liu SY, Lippmann M, Davis I, Klein S. Using helium for insufflation during laparoscopy. *JAMA* 1991; **266**: 3131.

265 Fleming MD, Weigelt JA, Brewer V, McIntire D. Effect of helium and oxygen on airflow in a narrowed airway. *Surg Forum* 1992; **42**: 485-7.

266 Leighton TA, Liu SY, Bongard FS. Comparative cardiopulmonary effects of carbion dioxide versus helium pneumoperitoneum. *Surgery* 1992; **113**: 527-35.

267 Stirrat GM, Farndon J, Farrow SC, Dwyer N. The challenge of evaluating surgical procedures. *Ann R Coll Surg Engl* 1992; **74**: 80-4.

268 Neugebauer E, Troidl H, Spangenberger W, Dietrich A, Lefering R. Conventional versus laparoscopic cholecystectomy and the randomized controlled trial. *Br J Surg* 1991; **78**: 150-4.

269 Russell RC. Laparoscopic cholecystectomy (letter) *Lancet* 1991; **338**: 1074-5.

270 Baadsgaard SE, Billek S, Egeblad K. Major vascular injury during gynecologic laparoscopy. *Acta Obstet Gynecol Scand* 1989; **68**: 283-5.

271 Wermeling DP, Foster TS, Rapp RP, Kenady DE. Evaluation of a disposable, non-electronic, patient-controlled-analgesia device for post-operative pain. *Clin Pharm* 1992; **6**: 307-14.

272 Davidson JAH, Dryden CM, Smith DD. Laboratory assessment of the Baxter disposable patient-controlled analgesia system. *Anaesthesia* 1993; **48**: 243-6.

273 Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. *Anaesthesia* 1976; **31**: 1191-8.

274 Jenkins SC, Barnes NC, Moxham J. Evaluation of a hand-held spirometer, the respiradyne, for the measurement of FEV1, FVC, and PEFR. *Br J Dis Chest* 1988; **82**: 70-5.

275 Moller JT, Jensen PF, Johannessen NW, Espersen K. Hypoxaemia is reduced by pulse oximetry monitoring in the operating theatre and in the recovery room. *Br J Anaesth* 1992; **68**: 146-50.

276 Brazier JE, Harper R, Jones NMB, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992; **305**: 160-4.

277 Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russell IT. The SF 36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? *BMJ* 1993; **306**: 1440-4.

278 Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; **67**: 361-70.

279 Altman, D.G. How large a sample? In: Altman DG , Gore SM. eds.*Statistics in Practice*.London: British Medical Association, 1982; 6-8.

280 Schwartz D, Lellauch J. Explanatory and pragmatic attitudes in clinical trials. *J Chronic Dis* 1967; **20**: 637-48.

281 Cuschieri, A. Preoperative, operative and postoperative care. In: Cuschieri A, Giles GR , Moossa AR. eds.*Essential Surgical Practice*.2nd ed. London: Wright, 1988;150-72.

282 Wilson P, Leese T, Morgan WP, Kelly JF, Brigg JK. Elective laparoscopic cholecystectomy for "all-comers" . *Lancet* 1991; **338**: 795-7.

283 McIntyre RC,Jr., Zoeter MA, Weil KC, Cohen MM. A comparison of outcome and cost of open vs. laparoscopic cholecystectomy. *J Laparoendosc Surg* 1992; **2**: 143-8.

284 Schulze S, Roikjaer O, Hasselstrom L, Jensen NH, Kehlet H. Epidural bupivacaine and morphine plus systemic indomethacin eliminates pain but not systemic response and convalescence after cholecystectomy. *Surgery* 1988; **103**: 321-7.

285 Rutberg H, Hakanson E, Anderberg B, Jorfeldt L, Martensson J, Schildt B. Effects of the extradural administration of morphine, or bupivacaine, on the endocrine response to upper abdominal surgery. *Br J Anaesth* 1984; **56**: 233-8.

286 Scott NB, Mogensen T, Bigler D, Kehlet H. Comparison of the effects of continuous intrapleural vs epidural administration of 0.5% bupivacaine on pain, metabolic response and pulmonary function following cholecystectomy. *Acta Anaesthesiol Scand* 1989; **33**: 535-9.

287 Lerno G, Slaats G, Coenen E, Herregods L, Rolly G. Anaesthetic management of systemic mastocytosis. *Br J Anaesth* 1990; **65**: 254-257.

288 Coulie PG, Cayphas S, Vink A, Uyttenhove C, Van Snick J. Interleukin-HPI-related hybridoma and plasmacytoma growth factors induced by lipopolysaccharide in vivo. *Eur J Immunol* 1987; **17**: 1217-20.

289 Mosmann T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J Immunol Methods* 1983; **65**: 55-61.

290 Brakenhoff JP, De Groot ER, Evers RF, Pannekoek H, Aarden LA. Molecular cloning and expression of hybridoma growth factor in *E. coli.*. *J Immunol* 1987; **139**: 4116-21.

291 Thompson NW, Demers ML, Lundy E. Pancreatic cystocholedochostomy. First report of a case. *Arch Surg* 1989; **124**: 1343-1346.

292 Weissmann G, Zurier RB, Hoffstein S. Leukocytic proteases and the immunologic release of lysozomal enzymes. *Am J Pathol* 1972; **68**: 539-59.

293 Long CL, Birkhahn RH, Geiger JW, Betts JE, Schiller WR, Blakemore WS. Urinary excretion of 3-methylhistidine: an assessment of muscle protein catabolism in adult normal subjects and during malnutrition, sepsis, and skeletal trauma. *Metabolism* 1981; **30**: 765-76.

294 Davidson DF, Fitzpatrick J. A simple, optimised and rapid assay for urinary free catecholamines by HPLC with electrochemical detection. *Ann Clin Biochem* 1985; **22**: 297-303.

295 Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *BMJ* 1990; **300**: 230-5.

296 Di Padova F, Pozzi C, Tondre MJ, Tritapepe R. Selective and early increase of IL-1 inhibitors, IL-6 and cortisol after elective surgery. *Clin Exp Immunol* 1991; **85**: 137-42.

297 Simpson PJ, Radford SG, Lockyer JA. The influence of anaesthesia on the acute phase protein response to surgery. *Anaesthesia* 1987; **42**: 690-696.

298 Fraser WD, Taggart DP, Fell GS, et al. Changes in iron, zinc, and copper concentrations in serum and in their binding to transport proteins after cholecystectomy and cardiac surgery. *Clin Chem* 1989; **35**: 2243-2247.

299 Dominioni A, Benevento A, Carcano G, Chiappa A, Dionigi R. Acute phase response after laparoscopic and open cholecystectomy (abstract). *Br J Surg* 1993; **80**: S44.

300 Jakeways MSR, Mitchell V, Hashim A, et al. Metabolic and inflammatory changes following laparoscopic cholecystectomy (abstract). *Proceedings of the Nutrition Society* 2nd and 3rd December, 1992; p25.

301 Tanaka H, Sugimoto H, Yoshioka T. Role of granulocyte elastase in tissue injury in patients with septic shock complicated by multiple-organ failure. *Ann Surg* 1991; **213**: 81-5.

302 Terebuh PD, Otterness IG, Strieter RM, et al . Biologic and immunohistochemical analysis of interleukin-6 expression in vivo: constitutive and induced expression in murine polymorphonuclear and mononuclear phagocytes. *Am J Pathol* 1992; **140**: 649-57.

303 Nunn JF, Hill DW. Respiratory dead space and arterial to end-tidal carbon dioxide tension difference in anaesthetized man. *J Appl Physiol* 1960; **15**: 383-9.

304 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307-10.

305 Bongard FS, Pianim NA, Leighton TA, et al. Helium insufflation for laparoscopic operation. *Surg Gynecol Obstet* 1993; **177**: 140-6.

306 Scott DB, Julian DG. Observations on cardiac arrhythmias during laparoscopy. *BMJ* 1972; **1**: 411-3.

307 Nunn JF. Predictors for oxygen and carbon dioxide levels during anaesthesia. *Anaesthesia* 1962; **17**: 182-94.

308 Graff TD, Arbegast NR, Phillips OC, Harris LC, Frazier TM. Gas embolism: a comparative study of air and carbon dioxide as embolic agents in the systemic venous system. *Am J Obstet Gynecol* 1959; **78**: 259-65.