

Leading article

Ileal pouch–anal anastomosis for Crohn’s disease

Over the past 10 years ileal pouch–anal anastomosis has become the operation of choice for most patients with ulcerative colitis. Although pouch surgery in ulcerative colitis does have a moderate complication rate, so do the alternatives of proctocolectomy and ileostomy.¹ The very real advantage of avoiding a stoma along with the inherent curability of ulcerative colitis by excisional surgery help to explain the attractiveness of this operation.

In Crohn’s disease the situation is notably different as the condition is not curable by surgery, and all operations in Crohn’s disease are followed by a higher complication rate and fairly frequent recurrence. Indeed, recurrence is often seen when a permanent stoma is avoided and an anastomosis constructed.

Patients with Crohn’s disease are just as averse to a stoma as those with ulcerative colitis, and so for very good reasons stomas are often avoided even though both patient and doctor are well aware that this puts the patient at increased risk of recurrence and further surgery. Thus, it would be standard practice to offer a patient with terminal ileal Crohn’s disease right hemicolectomy and some patients with large bowel Crohn’s disease colectomy and ileorectal anastomosis. As a consequence of restorative surgery, clinical recurrence is seen within 10 years in 50–80% of these patients.^{2,3} Figure 1 makes the point quite dramatically: the upper curve represents recurrence rates after colectomy and ileorectal anastomosis, whereas the lower shows how infrequent it can be when a permanent stoma is used instead of an anastomosis. Yet despite this high rate of recurrence, restorative surgery in these circumstances is generally accepted by the surgical and medical community. Does such a policy result in undue loss of small intestine? One study of 82 patients who underwent colectomy and ileorectal anastomosis found that 46 (56%) subsequently underwent revisional surgery with an average cumulative loss of small intestine of 44 cm in the fixed state.⁴ Although these losses at first glance might seem to be quite high, short bowel syndrome is an uncommon problem in patients with Crohn’s disease and there is as yet no sign of waning enthusiasm for either right hemicolectomy or colectomy and ileorectal anastomosis because of this anxiety.

Ileal pouch–anal anastomosis has, for some time, been considered to be quite inappropriate in patients with Crohn’s disease. To some extent this has arisen owing to poor results when compared with pouches in ulcerative colitis and familial adenomatous polyposis, but to some extent it has also arisen because of a tendency to compare apples with oranges.

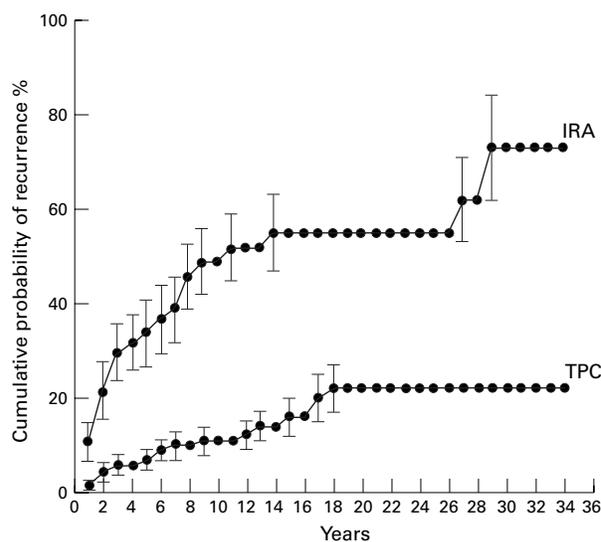


Figure 1 Cumulative recurrence rate after total proctocolectomy (TPC) or colectomy and ileorectal anastomosis (IRA) for Crohn’s disease at St Mark’s Hospital 1947–87.³ Reproduced with permission.

Kock pouches were originally constructed for both Crohn’s disease and ulcerative colitis. Nils Kock selected patients with disease limited to the colon, in many of whom the preoperative diagnosis had in fact been ulcerative colitis but who later turned out to have Crohn’s disease.⁵ Of the 280 patients treated with Koch pouches, 49 had Crohn’s disease. One patient died postoperatively and 27% developed complications as inpatients. In eight (16%) the pouch had to be removed some time later, in four because of recurrent disease. Of the remaining 40 patients, another 17 developed recurrent disease, six in the ileal segment proximal to the reservoir, five in the reservoir alone and six at both sites. Fourteen of these patients had surgical removal of their recurrent Crohn’s disease. Overall, 37 of these 40 patients had continent ileostomies and only three needed to wear an ileostomy appliance.

For restorative operations in patients with Crohn’s disease these results were really very good. But Kock, comparing apples with oranges, was worried because the in-hospital complication rate was double that for patients with colitis and excision of the pouch had been necessary in 16% compared with only 2% in ulcerative colitis. He concluded that, “this procedure should be performed in patients with Crohn’s disease only exceptionally”.

In another report⁶ 15 of the 168 patients studied had Crohn's disease, eight (53%) of whom subsequently had to have their pouch removed. However, 11 of the 15 patients had been referred after proctocolectomy or construction of a continent ileostomy which had been performed elsewhere, so there may well have been a selection bias for those patients with more severe disease. The authors⁶ were generally against construction of Kock pouches in Crohn's disease, particularly in small bowel Crohn's disease, but did "concede that it may have a role in selected patients with colonic Crohn's disease, under appropriately controlled conditions".

Three papers in the early 1990s described a combined experience of 44 patients who had undergone ileo-anal pouch surgery for Crohn's disease.⁷⁻⁹ These patients represented about 6% of the total number performed in those institutions over the previous two to 10 year period. Fifteen (34%) subsequently had their pouch excised or permanently defunctioned.

All of these papers report some cases diagnosed as having Crohn's disease at the time or shortly after surgery and others being diagnosed some time later. These late diagnoses almost always represent a biased group selected because of complications, as may also have been the case in Fazio and Church's study.⁶ Deutsch *et al* described five patients diagnosed with Crohn's disease immediately after surgery on the basis of examination of the resected rectum. Three of the patients had a continuing functional pouch. Of a further four diagnosed, on average two and a half years later, two had the pouch excised, one had a pouch in situ with a pouch-vaginal fistula, and another had problematic anal fissures. Clearly, this latter group represents patients with late Crohn's disease with serious clinical problems and ignores a potential group of unknown size with unsuspected Crohn's disease who did not have problems.

It is against this background that the paper by Panis *et al* in the *Lancet* should be considered.¹⁰ This described 31 patients apparently with Crohn's disease who had undergone pouch surgery with comparable short and longer term results to a group of 71 patients with ulcerative colitis similarly operated upon over the same period. The authors were at particular pains to point out that the patients selected had neither anoperineal nor small bowel Crohn's disease, and concluded that pouch surgery could be recommended in some patients with Crohn's disease.

The key issue is whether the patients really did have Crohn's disease, or whether some of them had what other authors term indeterminate colitis, where results for pouch surgery have been shown to be equivalent to those for ulcerative colitis.¹¹ Only 18 of their patients were considered preoperatively to have Crohn's disease, whereas 13 were at that time classified as having indeterminate colitis, only being reclassified as Crohn's disease after resection. Overall, only eight (26%) patients had epithelioid granulomas, two had "chronic ileitis" and the remaining 21 patients were classified as having Crohn's disease because they had at least four of the following features: skip segments on the resected bowel (n=20), lymphoid aggregates (n=19), crypt abscesses (n=19), fissuring ulceration (n=4), submucosal fibrosis (n=21), and mucus

secretion (n=17). Were some of these cases really cases of indeterminate colitis? The authors must have known that their paper would stir up considerable controversy, so it was a missed opportunity not to have had an external panel of pathologists agree that these really were all cases of Crohn's disease.

As it is, we really do not know the place of pouch surgery in Crohn's disease. We do know, however, that operating on patients with Crohn's disease is not the same as operating on patients with ulcerative colitis as complications and recurrence are frequent, especially when an anastomosis is used. Nevertheless, restorative operations such as right hemicolectomy and colectomy and ileorectal anastomosis are part of accepted surgical practice in patients with Crohn's disease, short bowel syndrome is uncommon and lengths of small bowel lost through this policy are not that different to those used to construct an ileo-anal pouch. The results of pouch surgery do not seem any worse than for any other restorative operation in Crohn's disease. There are fears that inordinate lengths of small bowel might be lost if pouches were used more frequently in these patients. But pouches, like stricturoplasty sites, may just as likely be less prone to Crohn's disease than the afferent limb of neo-terminal ileum after right hemicolectomy or colectomy and ileorectal anastomosis. If Kock's experience is anything to go by, then six of 17 recurrences were completely outside the pouch and 14 were able to have their diseased gut removed and the pouch preserved.⁵

We should stop comparing pouch surgery in Crohn's disease with pouch surgery in completely different conditions, such as ulcerative colitis or familial adenomatous polyposis. Rather, we should consider it in the context of other restorative operations in Crohn's disease: something not to be dismissed out of hand in those few patients without small bowel or anal disease, so long as they have an experienced colorectal surgeon on hand.

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Leading article

Sphincter of Oddi dysfunction and acute pancreatitis

Introduction

Fifty years ago Lium *et al* stated that... "Acute pancreatitis is the result of ductal obstruction in an actively secreting pancreas". A number of mechanisms for pancreatic ductal obstruction were reviewed and the role of the sphincter of Oddi (SO) in producing "obstruction" was discussed.¹ The studies by Archibald were reported and suggested a possible role of SO "spasm" in producing ductal obstruction. It was suggested that the cause of biliary pancreatitis in patients with gallstones who did not have a stone impacted at the ampulla may be secondary to SO "spasm" and oedema.

Sphincter of Oddi dysfunction

Normal human SO motility has been characterised by a number of studies and normal manometric parameters have been established using standardised manometry, as has SO dysfunction. The clinical presentation of patients with SO dysfunction may be divided into two groups: biliary SO dysfunction presenting with biliary type pain; and recurrent pancreatitis.² In 1995, the following definition of SO dysfunction was developed: "partial obstruction of the SO biliary segment giving rise to intermittent, episodic upper abdominal pain, deranged liver function tests, dilatation or delayed drainage of injected contrast from the common bile duct. Likewise, similar condition of the pancreatic segment can give rise to pancreatitis or episodic pain suggesting a pancreatic origin".³ The main consequence of SO dysfunction is impedance of bile and

pancreatic juice flow, either through a structural stenosis or functional stenosis from hypertonia. In some instances, however, hypotonia as a result of dyskinesia may also occur and reflect SO dysfunction.

The term SO dysfunction includes structural stenosis of the SO and functional stenosis secondary to hypertonia.⁴ It also encompasses dysmotility which may lead to intermittent or transient impedance of bile or pancreatic juice flow. The frequency of SO dysfunction in the community is not known. It is also uncertain whether transient SO dysfunction secondary to food, drugs or systemic infection is common. The definition of SO dysfunction to date has not included the dimension of time. It is uncertain whether transient SO dysfunction occurs and whether it results in symptoms or biochemical abnormality.

Biliary sphincter of Oddi dysfunction

Much of the initial understanding of SO dysfunction was related to patients presenting with recurrent biliary type pain following cholecystectomy. In a series of studies reported in the 1980s, manometric abnormalities have been defined and assessed in determining which patients will respond to treatment by sphincterotomy. We have subdivided the patients with biliary SO dysfunction into two groups according to SO manometry: patients with manometric SO stenosis and patients with SO dyskinesia.⁴

Patients with SO stenosis characteristically have an abnormally increased SO basal pressure (>40 mm Hg) recorded on manometry (fig 1). This manometric

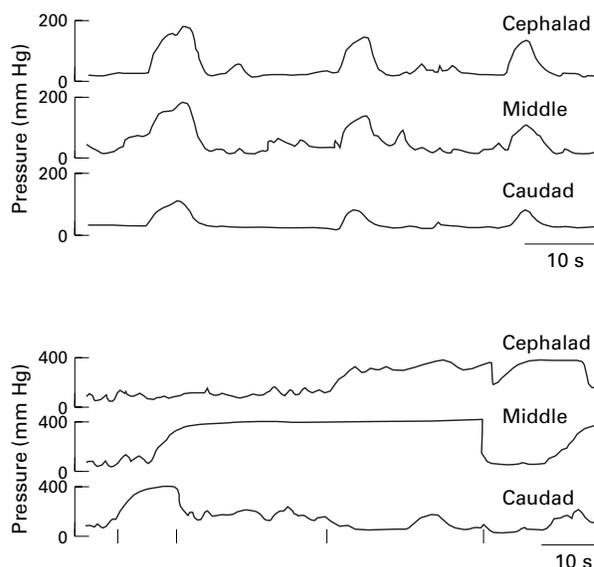
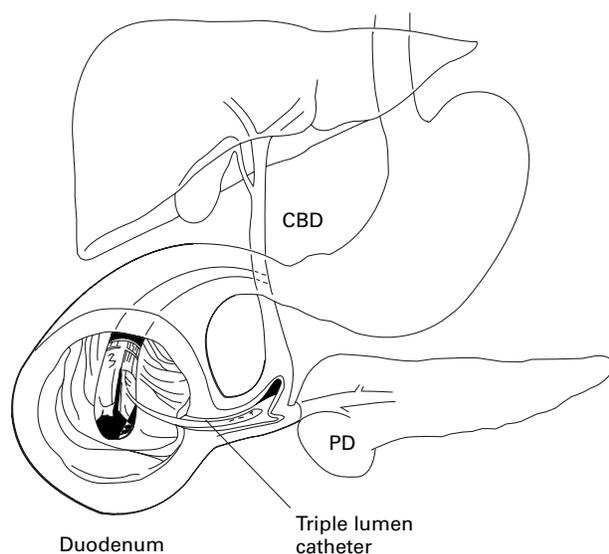


Figure 1 Sphincter of Oddi manometry is recorded using a triple lumen catheter introduced via the biopsy channel of a duodenoscope. A normal pressure profile is illustrated in the upper tracing, whereas the lower tracing illustrates a recording from a patient with sphincter of Oddi stenosis. CBD, common bile duct; PD, pancreatic duct.

Table 1 Sphincter of Oddi pressures

| | Normal (median (range)) | Abnormal |
|------------------------|----------------------------|-----------|
| Basal pressure (mm Hg) | 15 (3–35) | >40 |
| Amplitude (mm Hg) | 135 (95–195) | >300 |
| Frequency (number/min) | 4 (2–6) | >7 |
| Sequence | | |
| %Antegrade | 80 (12–100) | |
| %Simultaneous | 13 (0–50) | |
| %Retrograde | 9 (0–50) | >50 |
| CCK (20 ng/kg) | Inhibits | Contracts |

abnormality is reproducible, and does not relax with administered pharmacological agents.⁴ A prospective randomised study which evaluated the relation between manometry, SO dysfunction and clinical outcome following endoscopic sphincterotomy has shown that this group of patients will respond well to sphincterotomy and experience long term cure or a noticeable reduction in their symptoms.⁵ Other non-invasive investigations do not correlate as well as manometry with a successful treatment outcome, consequently manometric diagnosis remains the gold standard in selecting patients for treatment (table 1).

Patients with SO dyskinesia are characterised by a number of manometric findings: an excess of retrograde contractions (>50%), rapid contraction frequency (>7/min) and a paradoxical response to administration of cholecystokinin-octapeptide (CCK-8).^{4, 5} These manometric findings are not reproduced well by repeated study and may reflect the intermittent nature and the methodological difficulty of SO manometry in that it only “samples” a short period of SO motility. Treatment of this group of patients by either sphincterotomy or pharmaceuticals has not been associated with lasting good results, and thus awaits further investigation.

Acute pancreatitis

The most common causes of acute pancreatitis are gallstones and alcohol. Other causes are less frequent and include hypercalcaemia, hyperlipidaemia, viral infections, drugs, and the more exotic aetiologies such as scorpion envenomisation and organophosphate poisoning. Recent studies suggest that the SO may be involved in the development of pancreatitis. However, the underlying mechanisms have not been defined. Recently reported clinical studies suggest that SO dysfunction may be an aetiological factor in recurrent pancreatitis, hence strengthening the hypothesis that SO motility is involved in its pathogenesis.⁵

The sphincter of Oddi and pancreatitis

Ever since Opie first described the association of impacted gallstones with acute pancreatitis in 1901, the trigger mechanism remains a matter for debate.⁶ It is accepted that passage of gallstones causes acute pancreatitis and that obstruction is the likely trigger. SO “spasm” resulting in pancreatic duct obstruction in gallstone pancreatitis was first suggested by Archibald in 1913.¹ However, it is not known why “spasm” occurs in some patients whereas in others, stones may pass without causing ill effects.

In one study, unlike in the controls, the sphincter of Oddi of patients with biliary pancreatitis did not relax following injection of the CCK analogue, ceruletide. It was postulated that this group of patients had SO dysfunction predisposing them to gallstone pancreatitis.⁷ In another study, T tube cholangiography revealed SO stenosis/obstruction in patients with biliary pancreatitis in the

absence of common bile duct stones, suggesting that oedema or SO dysfunction may be contributing to biliary pancreatitis.⁸

Idiopathic recurrent acute pancreatitis

Evidence that the SO is involved in the aetiology of human pancreatitis is lacking. However, indirect evidence of an association between SO dysfunction and pancreatitis is increasing. In patients undergoing surgery for idiopathic recurrent pancreatitis, surgeons have shown using small probes that the SO narrows at the opening of the pancreatic duct.⁹ The morphine prostigmine test has been used to show an association between SO dysfunction and abdominal pain associated with pancreatitis.¹⁰ Nardi and Acosta postulated that there is an association between SO motor abnormalities and the development of pancreatitis.¹¹

In a manometric study, we showed an association between SO dysfunction and a proportion of patients with idiopathic recurrent pancreatitis.⁵ In this series of 28 patients, one or several SO manometric disorders were detected in 25, the most common of which was an abnormally raised SO basal pressure, reflecting SO stenosis. However, in addition, the patients also had SO dyskinesia, characterised by excessive retrograde contractions, rapid contraction frequency and paradoxical response to CCK-8. The manometric findings in patients with idiopathic recurrent pancreatitis suggested that impedance of flow of pancreatic secretions may produce pancreatitis.

Real time ultrasonographic studies of the diameter of the pancreatic duct after induction of pancreatic secretion by secretin support this observation.¹² After infusion of secretin (1 unit/kg), the diameter of the pancreatic duct was monitored: 83% of patients with SO stenosis and 72% with stenosis of the accessory papilla showed pancreatic duct dilatation of ≥ 1 mm compared with controls. This dilatation response was abolished after surgical sphincteroplasty. A positive secretin test was associated with good operative outcome in 90% of patients and was thought to be of good predictive value.

The results of these studies suggesting pancreatic SO stenosis have led to treatment aimed at relieving obstruction. Surgical division of the SO by transduodenal sphincteroplasty and septoplasty has been reported.^{9, 13} Early studies were associated with mixed results mainly as a result of the types of patients selected for treatment. Although some patients were cured after sphincter division, a high proportion continued to have symptoms and episodes of pancreatitis. These treatment failures were largely attributed to the inhomogeneity of the patient population, which included patients with alcoholic pancreatitis and those who were heavy narcotic users. In a more recent study which used SO manometry to select patients for treatment, those without a history of alcohol or narcotic drug addiction and manometric SO stenosis were treated by open sphincteroplasty and septoplasty.³ Medium to long term follow up has shown that in over 90% of these patients, episodes of recurrent pancreatitis have stopped. This finding led to the conclusion that transduodenal sphincteroplasty and septoplasty should be offered to patients with recurrent idiopathic pancreatitis if SO manometry reveals manometric stenosis.

Similar results have been found in patients with the congenital anomaly of pancreas divisum. The real time ultrasound investigation of pancreatic duct size was used to select patients for surgical treatment. A high correlation was found between an abnormal investigation and clinical outcome.¹⁴

Endoscopic stenting of the pancreatic duct has also been used either to treat or to select patients for surgical

treatment.^{15 16} Results of long term outcome are not available. It has been suggested that complete division of the SO may be achieved via an endoscopic rather than an open surgical approach. The potential difficulty of the endoscopic approach is the safety of an adequate sphincterotomy. In open surgery, in order to achieve successful ablation of the pancreatic SO, division is extended beyond the duodenal wall. This opening is subsequently closed by suture apposition, hence avoiding the complication of "duodenal perforation". In order to achieve a similarly effective sphincteroplasty and septoplasty via the endoscope approach, one would need to determine how perforation can be avoided.

Endoscopic retrograde cholangiopancreatography (ERCP) and SO manometry have been associated with production of acute pancreatitis. In many instances, iatrogenic or technical factors such as excessive injection of contrast medium or oedema produced by multiple attempted cannulations are the cause of pancreatitis. However, in some patients pancreatitis seems to relate to a susceptibility to production of SO "spasm" or dysmotility. This conclusion is supported by circumstantial evidence which shows a higher incidence of pancreatitis in patients with idiopathic recurrent pancreatitis undergoing either ERCP or SO manometry.¹⁷

SO dysfunction has been implicated as a possible factor in chronic pancreatitis with several studies showing increased SO basal and pancreatic duct pressure in patients with this condition. There is no evidence to suggest whether these SO manometric abnormalities were a cause or result of chronic pancreatitis. The results of sphincterotomy to correct these abnormal SO pressures have been mixed.

Cholinergic stimulation of the pancreas and the SO results in both increased pancreatic secretion and increased SO activity in animal models.¹⁸ It has been shown that excessive cholinergic stimulation using an acetylcholine agonist can result in acute pancreatitis. Organophosphate (Diazinon) used as an insecticide irreversibly inhibits cholinesterase resulting in delayed breakdown of synaptic acetylcholine and has been noted to cause acute pancreatitis in humans.¹⁹ In animal models Diazinon results in acute pancreatitis associated with raised pancreatic duct pressure.²⁰ This is thought to be secondary to "obstruction" at the SO level coupled with cholinergic stimulation of pancreatic secretion.

Scorpion venomisation is a known cause of acute pancreatitis.²¹ Evidence suggests that scorpion toxin releases acetylcholine from cholinergic nerves, leading to stimulation of the pancreas and SO, resulting in a secretion-obstruction block similar to organophosphate poisoning.²² SO dysfunction secondary to excessive cholinergic stimulation is likely to impede increased pancreatic secretion, thereby causing acute pancreatitis.

Hypercalcaemia has been shown to stimulate pancreatic secretion in animal models²³ and is also a well known cause of acute pancreatitis. The pathophysiological mechanism underlying hypercalcaemia induced pancreatitis is not known. The presence of high extracellular calcium has been shown to stimulate smooth muscle and it is possible that abnormal calcium regulation in SO smooth muscle may play a role in this type of acute pancreatitis.

Ocreotide, a somatostatin analogue, is used in various pancreatic disorders to shut down pancreatic exocrine secretion. Recently, the effect of ocreotide on SO activity has been studied in both humans and animals. This has shown a stimulatory effect resulting in increased SO motility and impaired pancreatic flow into the duodenum.²⁴ Indeed, cases of acute pancreatitis following ocreotide administra-

tion have been reported and these are postulated to be secondary to SO dysfunction caused by ocreotide.^{25 26}

Hyperlipidaemia is thought to be associated with acute pancreatitis. However, the role of the SO has not been studied. A recent case report suggests a possible association with hyperlipidaemia and the nitric oxide pathway causing SO dysfunction and pancreatitis.²⁷ This is supported by a study showing failure of SO relaxation in hypercholesterolaemic rabbits.²⁸

Conclusions

The role of the SO in the production of pancreatitis is supported by some direct evidence, but mainly by a large body of circumstantial evidence. Abnormal motility of SO (SO dysfunction), either as a primary event or secondary to triggering factors, seems to be the mechanism underlying the production of obstruction-secretion induced pancreatitis and theoretically if repeated over a number of years, may result in permanent dysfunction of the sphincter. Manometric studies can be used to identify patients who will respond to treatment requiring total ablation of the SO. Division of the SO via transduodenal sphincteroplasty and septoplasty is associated with excellent results in patients with recurrent pancreatitis who have been shown to have SO manometric stenosis and no evidence of alcoholic pancreatitis or addiction to opiates. Laboratory and human studies, currently underway, may determine the underlying mechanism for SO dysfunction and may lead to treatment which can influence the induction of pancreatitis.

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