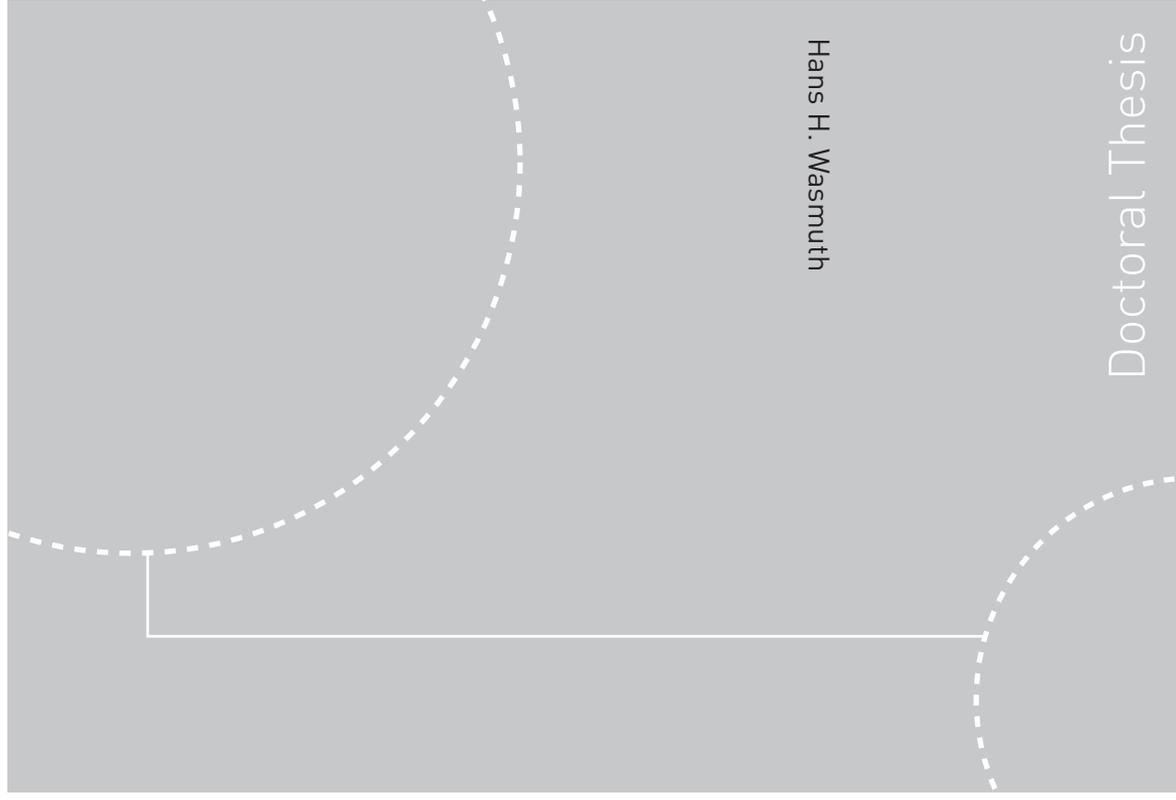


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Hans H. Wasmuth  
**Ileal Pouches**

**NTNU**  
Norwegian University of  
Science and Technology  
Thesis for the degree of  
philosophiae doctor  
Department of Cancer Research and Molecular Medicine  
Faculty of Medicine

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Hans H. Wasmuth

# Ileal Pouches

Thesis for the degree of Doctor Philosophiae

Trondheim, January 2012

Norwegian University of  
Science and Technology  
Faculty of Medicine  
Department of Cancer Research and Molecular Medicine



**NTNU**

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## **List of papers**

### **Paper I**

**Wasmuth HH, Tranø G, Endreseth B, Rydning A, Wibe A, Myrvold HE.  
Long-term surgical load in patients with ileal pouch-anal anastomosis.  
Colorectal Dis 2009;11:711-718.**

### **Paper II**

**Wasmuth HH, Tranø G, Midtgård TM, Wibe A, Endreseth BH, Myrvold HE.  
Long-term functional outcome in patients with IPAA - Functional outcome does not  
deteriorate with time. Colorectal Dis 2010;12: e283-e290.**

### **Paper III**

**Wasmuth HH, Svinsås M, Tranø G, Rydning A, Endreseth BH, Wibe A, Myrvold  
HE. Surgical load and long-term outcomes for patients with Kock continent  
ileostomy. Colorectal Dis 2007;9:713-717.**

### **Paper IV**

**Wasmuth HH, Tranø G, Wibe A, Endreseth BH, Rydning A, Myrvold HE.  
Failed pelvic pouch substituted by continent ileostomy. Colorectal Dis 2010;12:e109-  
e113.**

### **Paper V**

**Wasmuth HH, Myrvold HE. Durability of Ileal Pouch-Anal Anastomosis and  
Continent Ileostomy. Dis Colon Rectum 2009;52:1285-1289.**

### **Paper VI.**

**Wasmuth HH, Tranø G, Endreseth BH, Wibe A, Rydning A, Myrvold HE.  
Primary Sclerosing Cholangitis and Extraintestinal Manifestations in Patients with  
Ulcerative Colitis and Ileal Pouch-Anal Anastomosis. J Gastrointest Surg  
2010;14:1099-1104.**



## **Summary**

### **Background**

The conventional ileostomy can be avoided. Many attempts have been performed. The first successful solution was the continent ileostomy- Kock pouch. The high rate of complications and revisions some experienced forced surgeon to try to restore the continence by the mechanism of the anus involving an ileal pouch. Both procedures afterwards documented excellent functional outcome, but the complication rates were not negligible and the long-term failure rate were increasing. Different surgical refinements were done and the risk factors for complications and failures were investigated as experience and materials increased.

Restoring of the integrity of anal function and the success of the ileal pouch-anal anastomosis shadowed the practise of the forerunner: the continent ileostomy reservoir. This latter procedure was more demanding and seemed in the first year of ileal pouch-anal anastomosis era to have significant more complications and revisional surgery. The worldwide adoption of the pelvic pouch decreased the need for the continent ileostomy and a vicious circle evolved. Today only few centres perform the procedure. Patients who are not suitable for ileal anal-pouch anastomosis are seldom offered the possibility of having a continent ileostomy.

### **Aims**

The aims of the study was to investigate surgical load, complications and long-term functional outcome and to define factors which affect these subjects in patients operated with ileal pouch-anal anastomosis, continent ileostomy or both in one single surgical

department during the same period and without any institutional learning curve, and furthermore, to compare and contrast the two options.

### **Material and methods**

From 1984 to 2005(7) 304 (315) patients were operated with IPAA at St. Olavs Hospital (earlier: Regional Hospital of Trondheim). From 1983 to 2002(7) 50 (65) patients had a continent ileostomy constructed.

This was an observational study in the scope of surveillance and quality assurance. All patients were offered a planned regularly annual outpatient clinic follow up programme including a prospective standardised interview on clinical outcome. This was a supplement to clinical investigation with endoscopy and consecutive documentation of complications and other factors affecting the patients' health. Data were recorded in the medical chart. In this system, all patients had recorded dataset. However, the intervals between data recordings differ and the intervals increased by time. All inpatients data were included.

Standard descriptive statistical analysis and simple associations were undertaken. Handling longitudinal data with limited cases, varying time intervals was done in a Times Series Cross Sectional data model, analysed, and adjusted for several factors affecting functional outcome. Multivariable analysis was done.

### **Results**

The estimated failure rate at 20 years was 11.4% for ileal pouch-anal anastomosis and 11.6% for continent ileostomy. Salvage procedures rates were 31% vs. 38%, respectively ( $p=0.06$ ). The salvage procedures in IPAA included local procedures and redoes with

laparotomy. Salvage procedures in CI were related to the function of the nipple valve, mainly nipple valve sliding and less frequent stenosis or fistulas.

Complications rates were high. In pelvic pouch surgery, half of the patients would need re-operations in 20 years. Ten percentages had early anastomotic separation without septic complications. Four percentages had early pelvic septic complications. Fistulas and sepsis at the anastomotic site were the main severe complications, often leading to pouch failure. Closing of the loop ileostomy was accompanied with complications in six percentages. In the patients (48) who did not have a covering stoma the overall complications rate did not differ from those with a loop ileostomy, although nine needed a secondary stoma. Covering stoma seems to postpone anastomotic complications. Hand-sewn anastomosis had more strictures, but otherwise the complications rates were similar to stapled anastomosis. Patients having the diagnosis changed to Crohn`s diseases had more complications and higher failure rate. Early anastomotic complications were associated with long-term complications.

In patients with continent ileostomy the nipple valve sliding is the main cause of revision. One third needed revision once or several times. At 20 years follow-up, half of the patients would need surgery due to complications. Although many patients with CI need several revisions, all patients were continent at the last follow up with a stable intubation frequency of 3 – 5 per 24 hour.

The failure of the pelvic pouch is the end of severe complications. Two third of the failures had the pouch excision or permanent ileostomy with the pouch in situ. One third underwent a conversion to CI, with equal surgical and functional outcome as other patients with CI.

In IPAA, bowel movements at day were between 5-6 at day and 0-1 at night. The rates of more or less frequent incontinence were about 10%, and 41% and 55% had reported soiling at day and night respectively. The long-term functional outcome did not deteriorate with time: *ie.* observational time, as an independent factor did not influence outcome. Factors influencing the outcome were found but the impact of gender, age, protective stoma, hand-sewn anastomosis and early complications were negligible. Pouchitis did significantly influence functional outcome negatively, but did not create deterioration over time.

Estimated pouchitis rate in IPAA was 43% for more than 20 years. The onset of the first pouchitis appears mostly in the 5-6 first years after surgery. The crude rate was 35% and 6% of the patients had chronic pouchitis. Severe/chronic pouchitis was associated with primary sclerosing cholangitis, but not with pyoderma gangrenosum or diagnosed joint affections. Idiopathic pouchitis were absent among patients with familial adenomatous polyposis. In continent ileostomy the rate of pouchitis was 26%.

### **Conclusion**

The complications in both the pelvic pouch surgery and the surgery of continent ileostomy are considerable. Although not similar the surgical load are in the same order of magnitude. For the continent ileostomy revisional surgery are to be expected. The failure rate of both procedures are high and in long-term similar. The long-term functional outcome are however stabile and excellent. The failed pelvic pouch can be converted to a continent ileostomy in selected and motivated patients. The entity of pouchitis is conflicting and has to be divided into several different entities both on

clinical, constitutional and other differentiating features. Patients with PSC should be informed of a possible higher risk of severe and chronic pouchitis after IPAA.

**Key words**

Ulcerative colitis, Familial adenomatous polyposis, Crohn`s disease, Indeterminate colitis, Ileal pouch-anal anastomosis, Continent ileostomy, Kock pouch, Pouch failure, Surgical load, Salvage procedure, Conversion procedure, Long-term outcomes, Pouchitis, Primary sclerosing cholangitis, Extraintestinal manifestations

## Abbreviations

IPAA:	Ileal Pouch-Anal Anastomosis
RPC:	Restorative Proctocolectomy
CI:	Continent Ileostomy (Continent ileal reservoir)
IRA:	Ileorectal Anastomosis
TME:	Total Mesorectal Excision
UC:	Ulcerative Colitis
IC:	Indeterminate Colitis
CD:	Crohn`s Disease (Mb. Crohn)
PSC:	Primary Sclerosing Cholangitis
EIM:	Extraintestinal Manifestation
BWI:	Back-Wash Ileitis
ATZ:	Anal Transitional Zone: The mean of a 0.45 cm zone above the dentate line containing both squamous and columnar epithelium
BM:	Bowel Movements
QoL:	Quality of Life
HRQoL:	Health Related Quality of Life
HS:	Health Status
NSAID:	Non Steroidal Anti-Inflammatory Drug
BMI:	Body Mass Index (kg/m <sup>2</sup> )
ET:	Enterostoma Therapist
RCT:	Randomised Control Trial
ci:	Confidence interval
OR:	Odds ratio
TSCS:	Times Series Cross Section
SD:	Standard deviation
p:	The likelihood that the statistical difference found is statistically arbitrary

## **1.0 Introduction**

During the late part of the 20th century ileal pouch surgery evolved as an alternative to the conventional ileostomy after proctocolectomy for ulcerative colitis (UC) and familial adenomatous polyposis (FAP). Although proctocolectomy and conventional ileostomy was, and still is, a safe and convenient operation, the prospect of a permanent protruding ileostomy with external appliances for collecting feces was unpalatable for many patients. The development of the continent ileal reservoir (CI) and later the ileal pouch-anal anastomosis (IPAA) (restorative proctocolectomy- RP) offer the patients a life without the inconvenience of an ileostomy. Pouches have now become the preferred alternatives after proctocolectomy for UC and FAP. However, both CI and IPAA challenge normal anatomy and physiology and have its adverse effects and a fair number of complications. The benefit of functional surgery has to outweigh the disadvantage and complications of the procedures. Clinical assessment and surgical performance must be optimal. Follow-up after IPAA and CI is necessary to confirm safe and acceptable treatments for these patients. The results from the studies of IPAA and CI add to the body of knowledge of pouch surgery. The aims of this study were to evaluate the outcomes in IPAA and CI patients at St. Olavs Hospital since 1983.

### **1.1 History**

In 1967, Nils G. Kock used a double-folded U-shaped low-pressure profile reservoir to construct a continent ileostomy (Kock 1969). The basic principle of the continent ileostomy is the construction of a reservoir that can be filled with 400 – 600 ml without increasing the intraluminal pressure, thus providing the prerequisite for continence. A

corner of the reservoir was left open and sutured to the skin allowing intubation of the reservoir. It soon became obvious that the outlet had to be improved to prevent leakage. Attempts were made by interposition of iso-peristaltic- and anti-peristaltic segments for the outlet. Further improvements of continence were achieved by intussusception of the outlet segment into the reservoir, thus creating a biological valve - the nipple valve, which is effective in providing continence (Kock 1977, Kock 1980) (Figure 1). These effort to improve continence was requested because of the patients penance and problems with the continuous emptying of the conventional ileostomy into collecting devices. Although Bryan Brooke's refinement was a major leap forward (Brooke 1952), a the considerable number of documented clinical problems with the conventional ileostomy were reported (Leong 1994). The CI therefore gained support in the early seventies, but the reported revision and complication rates were high, although varied considerable (Goligher 1975, Beahrs 1976). The enthusiasm declined at several institutions.

In 1955 Valiente and Bacon (Valiente 1955) had already discovered that adding a reservoir to an ileoanal anastomosis in dogs controlled the bowel frequency. In 1968, Kock sutured the reservoir to the anus, preserving the anal sphincter and achieving continence. The reservoir had to be emptied by intubation. This was not pursued due to improved construction of the nipple valve and because it was considered more convenient to intubate through the abdominal wall than by the perineal route (Kock 1980). In 1971 Peck created a reservoir added to an ileoanal anastomosis in a two-stage operation (Peck 1971).

The modern era of the IPAA began in 1978 with the report by Sir Alan G. Parks and R.J. Nicholls. It was based on the experience of five patients operated with a triple

loop side-to-side ileal pouch (S-reservoir) sutured to the anus, end-to-end (Parks 1978). Four patients needed intubation and one had spontaneous evacuation without incontinence. The original anatomical route of evacuation was restored with a functional reservoir just proximal to the anus.

Both the CI and the IPAA procedures evolved in many directions, which seem to be the “law” in functional surgery – and many into “valuable” dead ends.

In CI construction, stabilizing the nipple valve was the main concern. The intussusception has a natural tendency to desussusception. The introduction of stapling techniques and fixation of nipple to the pouch wall introduced by Kock and co-workers reduced the problem of sliding of the nipple valve. It did not solve all nipple related problems, and revision rates are still high (Kock 1980\*, Fazio 1992, Lepistö 2003).

Different types of pelvic pouches have been designed (Nicholls 1987). The long efferent loop in the S-pouch was shortened or omitted. These measures preserved continence without the need of intubation (Nicholls 1987, Pescatori 1988). A side-to-end anal anastomosis using the apex of the pouch replaced the end-to-end anastomosis, which was used initially. In 1980, J. Utsunomiya reported favourable results with the J-pouch with the apex to the pouch-anal anastomosis (Utsunomiya 1980). Although the S-pouch is preferred in some centres, the J-pouch is easier to perform and this procedure dominates contemporary pelvic pouch surgery (Figure 2).

In Norway, the first pelvic pouch was performed in 1980 by K. E. Giercksky and A. Revhaug in Tromsø using the lateral ileal reservoir, designed by Fonkalsrud in 1979 (Fonkalsrud 1981), but after some years they preferred the J-pouch.

The history of attempts to solve the problems of the different complications and dysfunctions in pouch surgery are well documented in many reviews (Kock 1977, Hultén 1998, Parc 1999) together with reviews of persisting controversies (Bach 2007).

Experience with complications and conflicting results of the CI accumulated during a decade before the IPAA provided new developments. This time lag in favour of the IPAA promoted the pelvic pouch development. The enthusiasm and the successes in pelvic pouch surgery, which have offered thousands of patients a life without ileostomy and preserving the natural route of defecation, may have shadowed the possibility of offering a continence solution to patients not suitable for IPAA or for patients with failed IPAA (Vernava 1988, Fazio 1988). The demanding procedure of CI, the revision rates and patient preference has contributed to the decline of the CI. Only a few centres perform the procedure today. These, together with fewer patients being referred to CI-centres have perpetuated a vicious circle - and CI does not seem to be an option for many GI-surgeons at all, and is almost excommunicated in the society.

Functional surgery is continuously improving and the rate of publications dealing with different aspects of IPAA is significant and seems to be the most published issue in GI-surgery. In CI surgery the situation is the reverse.

In pouch surgery, several issues are conflicting and the handling and prevention of failure and complications are still problematic. No definite consensus has been established for several aspects of pouch surgery: such as its indications, performance and interpretation of results.

## **1.2 A Short Review of IPAA and CI**

### **1.2.1 Indications for IPAA**

#### **Ulcerative colitis**

“Restorative proctocolectomy with an ileal pouch-anal anastomosis (IPAA) has become the surgical therapy for choice for ulcerative colitis and most patients with familial adenomatous polyposis” (Kiran 2010). This statement, which is repeatedly the opening sentence in most of the literature about IPAA, is only valid when proctocolectomy is necessary, and the aim is to avoid a permanent ileostomy. The incidence of UC is increasing in the Western world (Shivananda 1996, Vind 2006), and in the Nordic countries the incidence may be as high as 24/100 000 inhabitants. In Norway, the incidence was estimated to be about 13/100.000 inhabitants in the early 90-ties (Moum 1997). A risk of colorectal cancer may not be increased in UC, if at all, as suggested previously (Eaden 2001, Winther 2004, Jess 2006, Rutter 2006). Subsequently the indication of preventive proctocolectomy has decreased. In the Ibsen study from Norway (Solberg 2009) including 519 UC the risk of CRC was almost absent as indication for surgery. In addition, the medical treatment of UC may have improved due to more exact diagnostic and treatment algorithms and new efficient medical agents. The incidence of emergency surgery in UC varies between countries and may be declining (Shivananda 1996). Although the incidence of UC has increased, the rate of IPAA has declined substantially in Norway (Table 1). This seems to be a general tendency. In the same time the average age at the time of pelvic pouch surgery has increased (Hahnloser 2007).

Many patients prefer conventional ileostomy (Jimmo 1998, Seidel 2000). About half the patients with a stoma have complications, as documented in numerous reports (Nastro 2010). Although ileostomy appliances have improved considerably, conventional

ileostomy is still incontinent and inconvenient. The capability of stoma handling and acceptance varies between individuals and cultures. A renaissance of the ileorectal anastomosis (IRA) for UC has been proposed (Lepistö 2005, Börjesson 2006, da Luz Moreiera 2010).

Approximately 10-30% of patients with UC will at some point need surgery (Dhillon 2005, Vind 2006, Jess 2007, Solberg 2009). Half the patients who need surgery for UC are likely to have an IPAA (Høie 2007). The incidence of UC, proctocolectomies and the rate of IPAA differ between countries and counties. In Ontario, Canada, two patients of 100 000 inhabitants undergo IPAA. Out of 1000 patients with UC, 170 have an IPAA per year (Kennedy 2006). In Norway, between 50- 60 primary IPAA's (2009: n=49) are performed each year at about 16 hospitals. The Norwegian annual rate of IPAA is thus 1.1 patient per 100 000 (Table 1). Primary CI is performed in only two Norwegian institutions.

Pouch surgery is demanding and the handling of the complications even more so. Concerns about the high numbers of sporadic IPAA surgery, the issue of low volume and high volume institutions and the surgeon's caseload are now placed on the international agenda by the results from the UK (Burns 2011). Mowat (2011) recommend an institutional rate of IPAA of 10 primary cases annually as a minimum.

IPAA as the treatment of choice has been challenged, particularly when quality of life (QoL) is the ultimate endpoint of treatment (Jimmo 1998, Seidel 2000). Conventional ileostomy is an alternative. The assessment of QoL is hampered by many difficulties (Heikens 2010). The results and conclusion drawn from studies on QoL in IPAA, CI, IRA and ileostomy varies considerable, including long-term changes in QoL (Köhler 1991,

McLoad 1991, Martin 1998, Fazio 1999, Berndtsson 2002, Weinryb 2003, Hoekstra 2009, Lovegrove 2010, Tulchinsky 2010, da Luz Moreira 2010). Altogether the choice of pouch surgery in UC seems not to be what it looks like.

#### **Familial adenomatous polyposis and the indication for IPAA**

Nearly all patients with FAP would be proctocolectomized, many of whom prior to the age of 25-30 years. An interval with IRA and close surveillance of the rectum has recently again gained support in selected patients. To proceed to a necessary proctectomy and IPAA at a later stage is an option. This option is but controversial due to the risk of malignancy in the rectum and a reduced possibility of constructing of IPAA at a later stage (Penna 1993\*, Soravia 1999, Bjørk 2001). Reduced fecundity after IPAA (Olsen 2003) is also an issue that has to be kept in mind in decision making for females in need for surgery for FAP. Desmoids formation is promoted of the surgical trauma and the tumour itself impairs ileal pouch formation (Penna 1993\*). The risk of abdominal desmoids is associated to the different mutations in the APC gene. These issues, such as a familial history of desmoids have to be considered when deciding on surgical strategy in FAP. Erkek (2007) found decreased bowel movements (BM) among patients young at surgery compared to older patients, favouring early pelvic pouch surgery when timing is discussed.

The meta-analysis of observational studies (Aziz 2006) could not draw any definitive conclusion regarding whether to perform IRA or IPAA. Only huge database can provide enough patients to assess the risk factor profile for both options and comparing advantages and disadvantages.

The prevalence of IPAA in Norway among FAP patients is about 1/3. Sixty-one patients have had IPAA among the FAP patients (n=187) included in the Norwegian Polyposis Registry. In a study by Tulchinsky (2005), 41 out of 50 patients with FAP had IPAA. The Norwegian rate seems low considering the fact that the rate of complications and long-term functional outcome of IPAA significantly favours FAP patients when compared to patients with UC (Dozois 1989, Lovegrove 2006\*). In addition, the IPAA can be an option for diseases in need of preventive proctocolectomy.

Other indications are rare, colorectal cancer (CRC) being one of them (Radice 1998, Meagher 1998, Burns 2011). Kollmorgen (1996) found it safe to do IPAA in CRC, but the stadium and prognosis had to be taken into consideration along with the principals of oncological surgery. Colonic dysfunction and various congenital disturbances of the colon and anus have been reported as possible indication for IPAA (Fazio 1995).

### **Crohn`s disease**

Patients with known colonic Crohn`s disease are not considered to be suitable for pelvic pouch surgery (Forbes 2009, Mowat 2011). This consensus is based on documented significantly increased complication and failure rates in patients operated on for UC or indeterminate colitis (IC) who were diagnosed with Crohn`s disease at a later stage (Brown 2005, Hahnloser 2007, Reese 2007). The rate of delayed CD varies from 2-10% (Hahnloser 2007). The criteria for the diagnosis of Crohn`s colitis varies and may interfere with the diagnosis of IC. The diagnostics criterion for delayed CD is not established.

The failure rate in patients with CD from Cleveland Clinic was 12% (Hartley 2004). Peyregne (2000) reported that half of the patients who turned out to have CD at follow-up had pouch failure, supporting the above-suggested opinion. The failure rate from St Marks Hospital was 50% (Tekkis 2005\*) and 29% in a study by Braveman (2004) also reported a crude rate of 50% of pouchitis in CD.

Evidence on CD and IPAA is not easy to establish. The retrospective conclusions of CD is based on manifested complications and do not include other silent Crohn's disease who's indications for IPAA was considered to be UC. If complications revealed CD, it is a logical fallacy to conclude that CD leads to complications.

Some studies have reported similar results among patients with known Crohn's colitis compared to UC patients (Regimbeau 2001, de Oca 2003). A recent and small study (Grucela 2009) reported excellent results in 13 patients with Crohn's colitis. Failure occurred in two patients compared to none in the matched group of patients with UC. Diagnosing colitis into different entities can be difficult. A case mix of different IBD may contribute to reports of excellent results in studies on this issue.

A recent study from the Cleveland Clinic (Melton 2008) included 204 patients with CD and IPAA. Twenty patients had a pre-operative diagnose of CD, and in 97 patients (47%) the colonic specimen showed incidental CD. The remaining 87 patients (43%) had a delayed diagnosis of CD. This diagnosis was based on histopathology in 37%, whereas the rest were based on clinical assessments. Patients with delayed diagnosis had significantly worse outcome compared to the former two groups, which had outcomes similar to UC patients. The cumulate failure rate in the delayed group was

63% in 20 years. Abdominopelvic sepsis and pouch-vaginal fistulas were the main risk factors for loss of the pouch.

These reports have not provided sufficient evidence for a consensus of selection criteria for patients with known Crohn's colitis. It is very challenging to predict failure in IBD patients with delayed CD. Pouch surgery in itself already has high rates of complications among relatively uncomplicated UC patients, and to introduce CD is complex and controversial.

### **Indeterminate colitis**

The term IC evolved after the inflammatory bowel disease was divided into the two more distinct entities of UC and CD. IC can be classified into three different forms: UC like, CD like and a third form in between. This distinction was based on prognostic factors for different rates of complications, but failure was not included in the classification strategy (Gramlich 2003).

Pouch failure increased in patients with IC reported in the studies by Atkinson (1994) and by McIntyre (1995). The rate of complications and functional outcomes differs between studies and there is conflicting evidence on the importance of IC in clinical decision-making (Hahnloser 2007). The risk of postoperative complications is however higher than in UC patients (Atkinson 1994). In a study from Cleveland Clinic (Delaney 2002) the results among 230 patients with preoperative diagnosis of IC were equivalent to a comparable group of patients with UC; in particular the failure rate was similar. Delayed CD was more frequent among patients with IC (4.3%) than UC (0.4%).

According to current knowledge, the consensus is that IC and UC patients tolerate pouch surgery equally well.

### **1.2.2 Indications for continent ileostomy**

Those diseases, which finally can end up with a pelvic pouch, are diseases where CI also can be an option.

Continent ileostomy is also an option for motivated patients with a malfunctioning conventional ileostomy. Many patients experience psychological and functional problems, including sexual difficulties related to the ileostomy and external appliance. These were the main reasons for CI in the study of Cohen (1982). In the study by Sjödaahl (1990) 45 among 55 patients had a conventional ileostomy converted to CI. The QoL was “dramatically” improved after the conversion.

Patients with UC and FAP not suitable for IPAA due to diseases in the pelvis, the pelvic floor or in the anal canal can be offered CI. It is feasible to convert a failed pelvic pouch to CI. This was introduced by the group of Utsunomiya (Kusunaki 1990) and by Hultén (1992), when the failures of IPAA emerged in the eighties (Figure 3). In selected patients, the CI can be a second strategy if the construction of IPAA fails during the operation (Fazio 1988).

### **Limitations for CI**

In FAP, patient abdominal desmoids involving the mesentery may interfere with pouch construction. A family history of abdominal desmoids formation may also indicate a

hesitation in offering patients pouch surgery (Church 1991). Computed tomography scan will draw attention to possible desmoids that may interfere with the construction.

Kock (1981) included patients with colorectal Crohn's disease with acceptable results. Offering these patients CI is controversial (Handelsman 1993, Delaini 2005). The unpredictable biology and complications of CD adds to the hesitation to offer CI to patients with CD. Fazio (1988) found that CD was associated with high rates of complications in CI surgery. Patients with CD in the small intestine are not candidates for any kind of pouch surgery. Bloom (1981) claimed that CI might be considered when CD is confined to the colon and with no small bowel involvement for at least five years of observation and with no perineal disease. Strictures and a low threshold for fistula formation in CD threaten the function of CI. Handelsman (1993) stated that CD was a contraindication to Kock pouch. In his study all patients (8) with CD or IC from a series of 100 patients suffered serious complications and all needed excision.

### **Pelvic pouch redoes and conversion to continent ileostomy**

In failed pelvic pouches, the possibility of salvage is dependent on several factors. The cause of failure and a patient's desire for further surgery, the prediction of success, and preferences and experience of the surgical team will determine the type of surgical treatments for the failed pelvic pouch. The patients with IPAA might be highly motivated to avoid the conventional ileostomy option.

Major salvage procedures in pelvic pouch failure are demanding but highly experienced centres achieve success rates of 20-80% (Saltzberg 1991, Sagar 1996, Tulchinsky 2003, Baixauli 2004, Mathis 2009, Shawaki 2009). After salvage procedure

the failure rate (27%) is three times the primary rate. Tekkis (2010) estimated the long-term rate of secondary failure to be 41%. At the Mayo Clinic, the second failure rate was 11% in five years and CD was the cause in 75% of the cases (Mathis 2009). The rate of complications after salvage surgery is high and repeated surgical interventions are often needed. It should be mention that the rate of major salvage is low, and few centres have performed more than 100.

Excision of the pelvic pouch or exclusion with creating a permanent diverting loop or end-ileostomy may result in a loss of at least 40 cm of the distal ileum. This may imply a risk of water and salt depletion and malabsorption of vitamins and fat (Phillipsson 1978, Delin 1984). Conversion to CI preserves length of the intestine. Excellent functional results after conversion have been reported to be similar to primary CI (Börjesson 2004, Lian 2009). Conflicting experiences has been reported and Karoui (2004) from St. Mark's Hospital found that all of seven patients who had a conversion needed the CI later excised. Other, Ecker (1996), reported success in four out of five conversions, adding four new conversions published in 1999. In the series form Paris (Parc 2011) none of the five CI after failed IPAA was later removed.

Many claim that the surgical burden after ordinary CI is unacceptable high (Cima and Palmerton's comments to: Lian 2009), and to add further surgical load and possible complication to the patients in need of surgery after pelvic pouch failure should be avoided. The surgical burden before and after redoing pelvic pouch surgery, including months or years with diverting ileostomy is, however, also very high. There is controversy about the conversion procedure.

The horizon of complications and revisions in CI seems to be more clearly predictable than the salvage of pelvic pouches after pelvic sepsis or other complications. After pelvic pouch failure the assessment of what a motivated patient can sustain to maintain the preferred function is not easy, regardless of which procedure chosen. The worst-case scenario is the loss of the pouch with a permanent ileostomy. Whether to create a new pelvic pouch as a salvage procedure or to make a new CI after pelvic pouch excision one has to acknowledge that the new pouch may also fail. This serious complication may impair the absorptive function of small intestine.

An additional problem after excision of the pelvic pouch is that the risk of a persistent perineal sinus is high (40%), with its own morbidity (Karoui 2004, Lohsiriwat 2008). Permanent ileostomy, leaving the failed pouch in situ and creating a proximal end-ileostomy is an option (Bengtsson 2007\*). This excludes the distal ileum and absorption may be impaired.

### **1.2.3 Restrictions in indications to pouch surgery**

#### **Age**

Patient's age at IPAA construction seems to influence the rate of complications and to increase failure rate (Carmon 2003, Delaney 2003, Hahnloser 2004, Chapman 2005, Wibmer 2010, Burns 2011). From a series of 17 patients older than 70 years at surgery Ho (2004) indicated that the procedure was feasible and safe. Another study reported that the failure rate among patients older than 60 years at surgery was significantly increased (Wibmer 2010). Several studies have indicated that age at surgery also affects long-term

functional outcome, although reports on this issue are conflicting (Delaney 2002\*, Chapman 2005, Bengtsson 2007).

Age limits in CI construction are not empirically challenged or established. A practical consensus is not to offer patients older than 60 years at surgery the option of CI, taking the expected long-term revision rate of 30-40% into consideration (Lepistö 2003).

With absences of risk factors and especially factor following increased age, the nominal age may not be a high a risk factor for complications and failures in pouch surgery. According to the literature the age limits seem to be increased both for IPAA and CI.

### **Obesity**

Body weight (body mass index (BMI)) has an impact on surgical and functional outcome (Kiran 2008, Efron 2001), but the cut- off BMI is not well established. In some studies patients with BMI>30 had increased rates of early septic complications (Kiran 2010) and anastomotic leakage (Kirat 2010, Nisar 2011), while other studies did not find any differences between obese and normal weight patients (Canedo 2010).

When constructing the nipple valve in CI as much as possible of the fat of the mesentery is stripped off, taking great care in not compromising the blood supply. This is done in order to reduce the mass inside the nipple. A bulky fat mesentery within the nipple valve make the nipple valve less stable facilitating nipple valve sliding with resulting incontinence of the pouch. High BMI may be a risk for nipple valve sliding in CI. Females have less valve complications than males, which may be related to the less fatty mesentery in females (Schrock 1979). In the long-term follow up, weight gaining

can be regarded as a risk factor for nipple valve sliding and nipple valve sliding is not restricted to the early post operative period (Denoya 2008).

### **Agents**

Corticosteroids (>20 mg daily) have been documented to increase surgical complications in IPAA (Heuschen 2002). The new immunomodulating agents have also been suggested to be a risk factor for septic complications (Schluender 2007).

### **Fecundity**

In the meta-analysis by Waljee (2006), the conclusion was that the infertility was threefold increased after IPAA. Young women may be advised to postpone the definitive surgery with proctectomy and pelvic pouch construction if planning to get pregnant (Olsen 2002, 2003, Johnson 2004). On the other hand, the practice may be different; in the study by Lepistö (2007) the fulfilling of the child-wish was not much reduced compared to patients that had undergone appendectomy. The introduction of in vitro fertilization have offered patients an increased chance of being pregnant. In Norway patients with IPAA do have priority to this option.

### **Other risk factors**

The large amount of empirical documentation in ruling out risk factors to establish selection criteria or predictors in pelvic pouch surgery is still an issue (Fazio 2003, Wibmer 2010). General co-morbidity and psychological status has not been studied in detail, possibly because those patients with severe co-morbidity or psychiatric

disturbance have not been offered pouch surgery, and that the patients are generally young with little co-morbidity. Patients with symptomatic (elevated liver test) primary sclerosing cholangitis (PSC) run a higher risk of chronic/severe pouchitis and malignancy, and these patients should be properly informed and offered surveillance both for the liver disease and the IPAA (Penna 1996, Lepistö 2008). The occurrence of EIM is however not regarded a contraindications to pouch surgery.

In CI surgery the considerations and the selection criteria are handled in the same manner as in IPAA surgery, although the indications for CI include other conditions; i.e. such as dysfunctional ileostomies, conversion of conventional stomas, failed pelvic pouches and other conditions not suitable for pelvic pouch treatment. Contraindications to CI are CD of the small bowel and inability to handle intubations. CI should probably not be considered done in very obese patients, in patients with known portal hypertension causing possible serious bleedings from stoma varicose (Mathis 2011) or when abdominal desmoids are present. The patient psychological status and capability to handle the CI has to be taken into considering when offering CI (Gelernt 1997).

#### **1.2.4 Surgical options**

##### **Stages of the procedures**

Performing IPAA and CI in patients with acute fulminating colitis is never an option. An emergency operation is performed to save the patient, not to restore continence at the risk of complications and re-operations. A two-stage procedure at least, is recommended in order to have the patient in good medical condition for the definitive pouch procedure.

Healthy patients in need of proctocolectomy can have the pouch construction in the same operation. One-stage procedure, proctocolectomy and IPAA, are reported to be safe in patients in otherwise good health (Järvinen 1993, McGuire 2007, Raval 2007). Construction of CI is usually a one-stage procedure, depending on the indications. The controversy in IPAA is the need of temporary diverting stoma in IPAA.

#### **Temporary diverting stoma: divert or not divert?**

Without a diverting stoma, the patient is spared a surgical intervention in order to close the stoma, thus reducing the hospital stay, the costs and the well documented and not negligible complications related to the closing procedure (Gunnarsson 2004, Chow 2009, Giannakopoulos 2009).

The intention of a diverting stoma is to protect the fragile ileal pouch-anal anastomosis and diminish the septic consequences of early separations of the anastomosis, which may diminish functional outcome (Grobler 1992). The benefits of the possible reduction of complications of the pouch-anal anastomosis due to protection should outweigh the complications of the diverting procedures.

In the recent study by Mennigen (2011) anastomotic separation, leakage and pelvic sepsis was significantly reduced from 18.2% to 5.6%, in favour of the loop ileostomy. The total rate of emergency laparotomies was significantly lower in the loop ileostomy group 30.3% vs. 13.5%). More strictures (24.7%) were seen in the group with ileostomy, but the strictures were easily treated. In the meta-analysis by Weston-Petrides (2008) anastomotic strictures were less frequent when diversion was omitted. A recent report by Kirat (2010) did not support this finding. The meta-analysis (Weston-Petrides

2008) also concluded that the rate of bowel obstruction did not differ between the groups, but the risk of pouch anal anastomotic leakage was higher when the ileostomy was omitted.

Bowel obstructions, anastomotic leakages, abscesses are documented in numerous reports together with a high overall rate of complications (10%-30%) of both diverting stoma formation and its closing (Carlsen 1999, Gunnarsson 2004, Koruda 2009, Scarpa 2011). Other complications include wound infections, enterocutaneous fistulas, stoma retractions, prolapses and parastomal hernias. The disadvantages of high output, skin irritation and leakages are well documented (Scarpa 2011). Among 1504 patients at the Cleveland Clinic the overall complications rate was 11%; bowel obstructions were reported in 6.5% and wound infections in 1.5% (Wong 2005). This rate was concluded to be acceptable considering the intention of diverting.

One randomized controlled study in 1992 did not find any differences in septic complications (Grobler 1992) and two randomized trials from 1990 did not find any differences and could not conclude in favour of using a covering stoma (Everett 1990, Matikainen 1990). The Cleveland Clinic study (Kiran 2010) reported similar rates of septic complications (6.2%) irrespective of the use of the loop ileostomy. The patients were not randomised, but were selected for omitting the diverting. Tulchinsky (2003) found more pouch failures among non-diverted patients than those diverted. After more than 20 years of debate it is generally advised to perform a diverting stoma (Meager 1998, Wong 2005, Lovegrove 2008, Weston-Petrides 2008, Friel 2009). These guidelines are also supported by the parallel in many reports on anastomotic leakages of low rectal anastomosis in rectal cancer surgery (Mala 2008). Rottoli (2011) suggested that the

consequences of anastomotic separation after IPAA are reduced when having a loop ileostomy.

#### **Selections criteria for omitting loop ileostomy**

Most authors state that diverting ileostomy can be omitted in carefully selected patients. (Remzi 2006, Lovegrove 2008). However, the criteria for omitting the covering stoma are not quite established. Male gender, malnutrition, the usage of steroids, proctocolectomy with IPAA (single-stage procedure), low anastomosis/hand-sewn anastomosis, high BMI and demanding intra-operative difficulties are all factors that seem to require a diverting ileostomy. Patients, who are healthy, young, female, non-IBD, and with no steroid medication, can omit a loop ileostomy particularly when the anastomosis is stapled and good blood supply is achieved without any tension of the anastomosis (Tekkis 2006, Joyce 2010, Lovegrove 2011). Sugerman (2000) recommend omitting the loop ileostomy in obese patients because the length of the mesentery needed for stoma creation can make tension on the anastomosis. The rate of omitting a loop ileostomy from Cleveland Clinics was reported to 10% (Rottoli 2011).

Although, most patients certainly would like to avoid a temporary ileostomy, Tjandra (1993) suggested that patients who have had an ileostomy might have a psychological benefit before the change to IPAA.

In CI, there are no arguments about creating a diverting proximal protective stoma, although it was performed for a short period in the beginning of the CI era (Fasth 1987). The dilatation procedure of the pouch can start early, after three weeks of a protective decompression period using a catheter. Once the healing process is almost

complete the risk of leakage from the suture lines is small (Kock 1977). The procedure to increase the volume by increasing the interval of intubation is described in detail by Kock and colleagues (Kock 1977).

### **Pouch types**

In restorative proctocolectomy (RPC) the many folding-limbs of the intestine from J (twofold) to S (three) to W (four) have been performed. Several other variants of pouches have been created. The J-pouch, as the least demanding procedure, provides the patients with almost the same outcomes as the S-and W-pouches, which initially has a greater volume. In the meta-analysis of Lovegrove (2007) who compared the J, W and S-pouches, the overall outcomes were almost equal. The S-pouch was associated with evacuation difficulties and an increased need of intubation and the W-pouch was associated with decreased bowel movements (BM). The W-pouch is technically a more demanding and a longer procedure than the J-pouch. The side-to-end anastomosis is superior to the more anatomical end-to-end anastomosis.

The debate seems ended in the favour of the J-pouch (Tekkis 2010), but a spherical pelvic pouch (K-pouch) was proposed to have beneficial outcomes due to the peristalsis patterns in the pouch and a greater initially volume (Kock 1989, Öresland 1990). The K-pouch, with a stapled pouch-anal anastomosis, had a significantly better functional score than the J pouch reported by Block (2009) and the soiling at night was less in the K-pouch group. The K-pouch had a larger volume and less BM than J-pouch in a randomized study by Hallgren (1990). The K-pouch has, however, not gained wide acceptance.

The length of the limb in the J-pouch can vary between 10-18-20 cm and the effects have not been systematically evaluated. The volume of the pouch will gradually expand within the first years after surgery, independent of the pouch design, to an adapted volume in the pelvis that gives almost similar functional outcome of the different types of reservoir after one year. Similar initially pouch dilatation is observed and is a promoted procedure in CI.

The K-pouch is preferred in CI procedures. However, when a failed IPAA is converted from CI the dilated pelvic pouch can be used irrespectively of the pelvic pouch design. The main problem in CI surgery is the stability of the nipple valve. Barnett (1984) modified the K-pouch, but the use of this construction is limited to few centres. The T-pouch design without intussusception has a promising nipple valve construction (Kaiser 2002).

#### **Anastomotic techniques - mucosal proctectomy – hand-sewn vs. stapled anastomosis**

The intention of mucosal proctectomy is to remove all diseased rectal mucosa. Leaving a cuff of rectal mucosa in UC patients constitute a risk of recurrent inflammation (cuffitis) or development of dysplasia. In FAP neoplasia and CRC may develop. After mucosal proctectomy, however, residual islands of rectal mucosa may be present (Reilly 1997). Rectal mucosa seems not regenerate after mucosectomy (O'Connell 1987). All patients at risk of malignancy, defined by the underlying disease, need surveillance if the intention is to prevent malignant transformation.

The ATZ is on average 0.45 cm in length above the dentate line (Thompson-Fawcett 1998). It is important to distinguish the ATZ from the rectal mucosa remnant,

which is called the columnar cuff after stapling procedure. The cuff can be of varying length depending of surgical procedure chosen.

Cancer at the anastomotic site is anecdotal in UC. The definition of the anastomotic site is not established, but seems to include the ATZ, rectal cuff and the anastomosis area. In a review by Das (2007), nine patients developed adenocarcinoma in the residual anorectal mucosa and seven in the pouch. All cancers were recruited from case reports. In the Helsinki study (Vento 2009), one patient developed adenocarcinoma in the anal canal after mucosectomy for chronic pouchitis. Kariv (2010\*) found eleven adenocarcinomas in the IPAA for patients with UC in the database from Cleveland Clinic. Eight were only in the ATZ/cuff, and one only in the pouch. Two cases were both in the cuff and in the pouch. The study summed up 30 other reported malignancy; 18 at the ATZ and eight located in the pouch, four were without known origin. The report from (Al-Sukhni 2010) supported the distribution in localisation. O'Riordan (2011) added two new cases, and in this report the poor prognosis of pouch malignancy in UC was documented. The total number of adenocarcinoma reported in IPAA after UC seems then to be 43 cases.

The total prevalence of dysplasia is 1.13% according to the meta-analysis of Scarpa (2007), equally distributed between the pouch and the cuff. This favours the stapling technique in UC patients (Remzi 2003). When dysplasia or cancer is the indication for restorative proctocolectomy, it is mandatory to perform mucosectomy (Ziv 1994, O'Riordain 2000), as low-grade dysplasia has been detected in the rectal cuff after stapled anastomosis. Kariv (2010\*) also found increasing pouch neoplasia after RP when the indication was UC with neoplasia, both cancer and dysplasia, supporting the

mucosectomy technique. This is contrary to a recent study by Kupier (2011) and a study from Toronto (Al-Sukhni 2010): after hand-sewn anastomosis (n=22), one patient developed unresectable adenocarcinoma and one developed dysplasia. After stapled anastomosis (n=59) no patients had such events.

Mucosectomy seem not to prevent the rare development of cancer in the pouch in UC patients, but obviously will be a precaution to reduce the incidence of dysplasia at the anastomotic site. In patients with UC and no neoplasia surveillance for neoplasia after stapled anastomosis is unnecessary and the need of surveillance was strongly doubted after mucosectomy for UC in the study of Börjesson (2004\*).

In selected patients with diseases all the way down to the dentate line, mucosectomy may be considered (Chambers 2007). Silvestri (2008) in Chicago compared patients with inflammatory signs at the ATZ who had a stapled anastomosis with UC patients having a hand-sewn anastomosis. In spite of inflammation in the cuff, the patients with a stapled anastomosis had better functional outcomes, less incontinence and better QoL than those with hand-sewn anastomosis.

Patients with PSC generally have a higher risk of dysplasia and CRC (Soetikno 2002) could be offered mucosectomy. However, only two cancers seem to have been reported in pouches of PSC patients (Walker 2006). Kariv (2010\*) found that among 117 patients with PSC, no one had cancer in their pouches and only one had dysplasia.

The concern about dysplasia and cancer after IPAA is small. In CI, it is almost absent (Hultén 2002).

### **Mucosectomy and familial adenomatous polyposis**

The need for mucosectomy in FAP patients is unclear (Remzi 2001). In general, it is strongly recommended to do mucosal proctectomy (Kartheuser 1996, Möslein 2003), although all patients are recommended regular endoscopy (Nyam 1997, Ooi 2003). No matter how good a screening programme is it could not compensate fully for the phenomenon of interval incidents and for overlooking abnormalities.

In a study by Ooi (2003), at the Cleveland Clinic, none of 146 FAP patients developed cancer after mucosectomy. The rate of precancerous adenomas after mucosectomy was reported to be 6 out of 42 vs. 21 out of 76 stapled anastomoses (Remzi 2001). The report concluded the necessity of removing as much of the potentially pre-malignant epithelium of the rectum and ATZ as possible in FAP patients. In the literature Tajika (2009) found a total of 19 malignancies in IPAA, eight of which arose from the pouch epithelium. The latest report from St. Mark's Hospital (von Roon 2011) demonstrated significantly more dysplasia in the ATZ/cuff after stapled anastomosis. The recommendation was to perform mucosectomy in particular when lower part of the rectum had adenomas. Despite a reduction of neoplasia after mucosectomy, the risk for the development of adenoma or cancer was however not significantly reduced. The advantage of mucosectomy has to be balanced against possible worse functional outcomes compared to the stapling technique and the patients' compliance to the necessary surveillance program. There is no general agreement on this subject, but several reports recommend mucosectomy, but all patients had to participate in a surveillance program.

### Complications and functions in different anastomotic techniques

Ziv (1996) reported that the stapling technique had fewer complications than the hand-sewn method. No differences in abscess or fistula formation were found between the two methods in a study from the Mayo Clinic (Gecim 2000); the septic complications were related to the experience of the surgeon. In a study from Chicago (Fichera 2007), the preservation of the ATZ/cuff was safe and with no development of dysplasia. Even inflammation of the ATZ and the cuff did not alter the functional outcome.

Several studies comparing stapled vs. hand-sewn anastomosis (Hallgren 1995, Lovegrove 2006) report less incontinence to liquid stools and less seepage at night after the stapled anastomosis technique. A recent study of Rink (2009) reported excellent results after hand-sewn anastomosis; the anastomotic leakage rate was one out of 131 anastomoses. The preservation of the ATZ and the cuff maintains the nerves and smooth muscle, which may facilitate a better function (continence) due to the reflexes in the anal canal and innervations that discriminate between solid and liquid stools and gas. On the other hand, if this cuff above the dentate line exceeds more than 2 – 2.5 cm after ileal-pouch anastomosis the function is worse compared to lower anastomosis (Annibaldi 1994, Tulchinsky 2001). In fact the IPAA is then an ileal pouch-rectal anastomosis.

Three randomized studies have been conducted comparing hand-sewn and stapled anastomosis. In the study from the Mayo Clinic (Reilly 1997), the differences between the methods were minor and non-significant. No significant differences were found in two other studies either (Seow-Choen 1991, Luukkonen 1993). In the study of Mennigen (2011) mucosectomy was associated with the use of ileostomy, but “complications,

second laparotomies, or pouch-related septic complications” were not increased compared to stapled anastomosis.

In a study from the Cleveland Clinic (Lian 2009) pouch failures due to anastomotic leakages were significantly higher in hand-sewn anastomosis than in stapled anastomosis; 35.3% vs. 16.6%. Complication and functional outcome was similar apart from the incontinence rate in the follow up was higher in hand-sewn anastomosis, otherwise.

In a comprehensive review from Oxford by Chambers (2007) concluded that mucosectomy impair functional outcome significantly and therefore should be avoided. It should only be performed in patients with high risk of severe disease in the rectal cuff, because it seems that these patients would benefit. The last statements did not reach significance. The success of treatments after septic complications were higher after stapled anastomosis than after hand-sewn (Sagap 2006) indicating that anastomotic complications after hand-sewn anastomosis may be more difficult to treat than complications after stapled anastomosis.

A hand-sewn anastomosis at the dentate line requires a longer mesentery than is required for stapled anastomosis in order to avoid tension in the anastomosis and without compromising the blood supply. Tension is an important risk factor for anastomotic complications (Heuschen 2002\*). This might explain the contradictory complication rates and outcomes in different reports. It is possible to optimize mesenteric length and reduce anastomotic tension (Goes 1995, Martel 2002, Uraiqat 2007).

The level of anastomosis above the dentate line is not measured in most studies. In a study by Kiran (2010), the mean level above the dentate line was 1.5 cm. Rectal

remnants of more than 2-3 cm are probably not uncommon (Seow-Choen 1991, Reilly 1997, Anderson 2009). Intubation may be necessary and correction procedure is often needed (Baixauli 2004). The tension on the anastomosis is a minor problem with a long rectal cuff.

A risk associated with mucosectomy may be damage to the anal canal muscle layers and thereby compromise function (Tuckson 1991, Becker 1997). The mucosectomy may be regarded as a more demanding procedure than the stapled technique. The learning curve for suturing an anastomosis is twice the learning curve for the stapling technique (23 procedures) (Tekkis 2005). Since the anastomosis is the Achilles' heel of the procedure an impact of the surgeon is likely. In the study of Kiran (2010) the surgeon was a significant independent variable for septic complications.

The diameter of the stapling devices differs. A study of more than 2000 patients did not find any difference between the diameter of the stapler used (28-29 and 31-33mm) and the frequency of strictures or anastomotic leakages (Kirat 2010), although the report by Senapati (1996) showed more strictures after small size diameter.

When stapling device fails, in most cases the pouch-anal anastomosis can only be completed by suturing the anastomosis. Misfiring or an incomplete donut is a rare event – in 0.7% of cases (Kiran 2010). Most redoes require hand-sewn anastomosis and success in these procedures is dependent on the surgeon's skill (Tulchinsky 2001) and experience with the procedure (Ziv 1996, Kennedy 2006). In some patients (FAP, CRC and dysplasia) mucosal proctectomy is indicated. There are, however reports on stapling of the anastomosis in these patients (Kirat 2010).

The practical consensus seems to advocate stapled anastomosis of the J-pouch and hand-sewn anastomosis when required.

### **Preservation of the mesorectum**

The proctectomy can be done by a close rectal wall dissection leaving the mesorectum in situ. Some prefer total mesorectal excision (TME) (Michelassi 2000). The risk of autonomic nerve damage with mesorectal excision is documented. Complications related to sexual and urinary functions are almost absent after dissection close to the rectal wall (Karthuser 1996, Nyam 1997). Lindsey (2001) did not find any differences between the two methods regarding erectile dysfunction in male. In an institutional consecutive series (Rink 2009), the surgical technique with preservation of the mesorectum demonstrated favourable outcomes and very low septic complication rates (1.5%). The preservation of mesorectum was the suggested explanation to a very low rate of pelvic sepsis (2%) in a study from Denmark (Walker 2008). Pelvic drainage after low rectal cancer surgery is recommended to reduce fluid collection and lower the risk of pelvic abscesses, and hence drainage after IPAA may be favourable.

### **Laparoscopic access**

Laparoscopic proctocolectomy and IPAA construction with or without a diverting stoma doubles the operation time (Schmitt 1994). All partial procedures, colectomy, proctectomy and ileal-pouch anal anastomosis are feasible for laparoscopy. When the techniques improve, the laparoscopic approach may be common (Larson 2006, Lefevre 2009). At present, the benefit is the cosmetic avoidance of a long midline incision scar,

which for some patients is of importance for their body image. Body image has certainly been one of the arguments for the pelvic pouch option in patients in need of proctocolectomy avoiding an ileostomy. Other benefits such as minimised adhesion formations have been documented (Indar 2009). Less bowel obstructions and hernias after laparoscopy are not clearly documented. This access is demanding and time consuming, which has put the caseload and learning curve on the agenda, again, but the laparoscopic assisted approach is rapidly gaining popularity.

### **1.2.5 Complications**

#### **IPAA**

Overall, surgical complication rates in long-term follow-up affect more than 50% of the patients undergoing IPAA (Marcello 1993, Fazio 1995, 2003, Røkke 2011). The mortality rate is generally very low, 0.4% (McGuire 2007), although Ikeuchi (2010) reported a mortality rate of 2%. In functional surgery perioperative mortality has been extremely seldom. From the Mayo Clinic Kollmorgen (1996) reported a mortality rate of 0.2% and an overall mortality rate of 2% after IPAA in long-term follow-up. The late deaths were not related to the IPAA procedure. Malignancy was the main cause of late deaths.

#### **Failure**

Failure of IPAA may be defined by a permanent diversion of the IPAA with or without excision of the pouch. Diversion may be a conventional or a continent ileostomy. Failure

could also be attributed to poor outcome. It is not commonly included in the reported failure rate otherwise it ends with diversion.

The long-term failure rate in IPAA, for exclusion or excision of the pouch will reach 16% (8-20%) after 10 years (Tulchinsky 2003, Leowardi 2009, Tekkis 2010, Ikeuchi 2010, Wibmer 2010, Burns 2011). Thus, failure may thus occur in one out of six patients with IPAA. The often cited review by Hueting (2005) estimated after including 9,317 patients an overall failure rate of 8.5% after a mean of five years of follow-up (range from 4-5% to 20-25%). Increased follow up time will increase the failure rate in IPAA (Wibmer 2010) and a rate of 10 -20% is reported in long time follow up series with more than 15 years of observation (Tekkis 2010). Among patients having had the pouch for more than 15 years the annual failure rate was still more than 2% (Kiran 2011). The increasing failure rate is of concern in IPAA.

Pouch failure is the end of a shorter or longer period of suffering from a malfunctioning IPAA and repeated salvage attempts. Incontinence and pain are common problems. Failures are due to septic complications and fistulas not suitable for salvage or after unsuccessful salvage procedure (Tulchinsky 2003, Forbes 2009, Meagher 1998, Heuschen 2002\*, 2002\*\*). Heuschen (2000\*\*) reported that the risk of failure due to pelvic sepsis was higher when the origin of sepsis was related to the pouch or to the anastomosis than to the rectal cuff area.

In a recent multivariate analysis from Mount Sinai, Toronto (Forbes 2009), CD and septic complications (46%) were found to predict failure. Out of 1554 patients, the causes for failure other than sepsis were: pouchitis (17%), increased frequency/incontinence (8%), evacuation difficulties (3%), functional problems after

sepsis (6%), perineal complications (8%), strictures (2%) and dysplasia/malignancies (2%). Meagher (1998) reported similar figures, but very low figures on pouchitis as a cause of failure. In the study by Ståhlberg (1996) pouchitis was the cause of failure in only 1.3% of the failures. Mechanical causes, poor function and perineal soreness were a major group of causes of failure. The failure rate in underdiagnosed CD is more than 50% as reported by Brown (2005) from the same clinic. This is supported by other reports (Tekkis 2005\*, Melton 2008). A failure rate of 80% in CD after 20 years was estimated in a study from Japan (Ikeuchi 2010).

In the multivariate analysis from Cleveland Clinic (Fazio 2003) the significant risk factors for failures were fistulas, pelvic sepsis, symptomatic strictures, anastomotic separation ( $p < 0.001$ ). Other risk factors were pre-operative low anal sphincter manometry pressure, CD and co-morbidity ( $p < 0.05$ ). In a hazard ratio model the dominant risk factor for failures were vaginal fistula and two or more episodes of pelvic sepsis. In the recent study from the Cleveland Clinic failures among 3407 patients perioperative pelvic sepsis, 30 days postoperative haemorrhage and female gender were the most prevalent risk factor (Rottoli 2011).

Prudhomme (2006) found that pelvic sepsis, chronic pouchitis and CD of the pouch were the common cause of failure. In the classical study by Meagher (1998) poor function including incontinence, obstruction and frequent BM was the second most common cause of failure.

The failure rate is high after IPAA. Whether an increasing repertoire and experience in major salvage operations could compensate for the high failure rate is questionable (Tekkis 2010). The optimistic era concerning low failure rate has ended, in

spite of improved results compared to the early period of pouch surgery (Tulchinsky 2003).

### **Continent ileostomy: failure and complications**

In CI surgery the overall complications rates are equal to IPAA ( $\approx 50\%$ ). Long-term failure rate varies between  $<10\%$  (Dozois 1980, Kock 1986, Ecker 1999, Hoekstra 2009) and 10-30% (Halvorsen 1978, Litle 1999, Lepistö 2003, Nessar 2005). The recent study from Paris (Parc 2011) reported five excisions among 49 patients with mean observational time of 20 years. Two of the excisions were done despite normal functional pouch, two had undiagnosed CD and one had recurring fistulas.

Failure is due to incontinence or intubation problems. Nipple valve sliding is the dominant cause of incontinence. Risk factors are previous ileostomies, elderly and male gender (Dozois 1981).

About 30- 40% of the patients need revision due to nipple valve sliding one or several times (Fazio 1988, Lepistö 2003). The success rate of revision is high (90%) (Kock 1986). Fistulas are reported in up to 25% (Nessar 2005, Castillio 2005), but re-operations are even successful (Fazio 1988). The later long-term follow-up study from Cleveland Clinic (Nessar 2005) concluded despite high revision rates that CI offers patients whose only alternative is an ileostomy encouraging long-term result and with excellent QoL.

In a recent study by Denoya (2008) late revision was successful in 31 patients after almost 20 years of good pouch function, also after several revisions. Only two patients needed excision of the CI. The revision procedures were not regarded more

challenging than the primary construction. Parc (2011) reported that 35% of the patients needed early postoperative surgical interventions. Half the patients had 50 reoperations due to late complications. The performed Kock pouch in 27 patients and the Barnett modified J-pouch continent ileostomy in 22 patients.

An association between the number of revisions and the rate of conversion to conventional ileostomy has been suggested, but controversies exist regarding the relationship between revision rate and the rate of low or a high failure rates (Litle 1999, Lepistö 2002, 2003). Järvinen (1986) reported a very high complications rate (66%), but only 4 of 76 patients had the CI excised. Handelsman (1993) showed a low rate of complications (20%). Seventeen patients out of 87 patients with UC needed correction of which six cases were minor and easily treated. The patients with CI must accept the possibility of necessary re-constructions. Almost all studies reporting complications and revision procedures in CI, conclude that patients prefer further revisions rather than to have a conventional ileostomy. In CI the burden of repeated revisions is out-weighted by the advantage of the CI compared to conventional ileostomy, experienced by the patients.

**List of complications of continent ileostomy:**

- Nipple valve sliding
- Pouch loosening from the abdominal wall
- Nipple stenosis/ischemic stricture
- Fistulas: Pouch to nipple; pouch to skin; nipple to skin; intestine to pouch
- Prolapse of the nipple
- Volvulus of the pouch
- Stoma hernia/Para-stomal hernia
- Stoma skin stricture
- Pouch/ nipple bleeding
- Stoma varicose due to portal hypertension, especially in PSC
- Intubation difficulties
- Pouchitis

The complication rates after CI from several reports are given in Table 2.

### **Pelvic pouch related complications**

In IPAA, the most significant complications are related to the anastomosis. Separation and leakage of the anastomosis, followed by septic complications, is the main causes of troublesome treatments and subsequent failure (Fazio 1995). The frequency of anastomotic leaks and their related complications has been reported to be between 6% and 37% (Mikkola 1995, Tan 1997, Heuschen 2002\*\*, Lim 2007, Kirat 2010). In the meta-analysis of Weston-Petrides (2008) the anastomotic leakages rate was 7.1% and the pouch related sepsis was 10.3%.

Anastomotic leakage was found more frequently in patients with increased BMI and in males (Kirat 2010, Lian 2010). These results were explained by technical more demanding operative conditions in a narrow pelvis. The overall leakage rate was 5.2 %, and anastomotic separation was more frequent in males than among females (Rottoli 2011).

In Table 3 the results on complication rates in IPAA from several reports are shown.

### **Pelvic sepsis**

Overall, septic complications affect more than 10 % of the patients (Heuschen 2002\*, Forbes 2009, Tekkis 2010). In a small study by Selvaggi (2010) patients with septic complications had reduced functional outcome after five years. Other author suggesting an aggressive management of septic complications (Chessin 2008) and perineal complications (Breen 1998) and did not find any association between septic

complications and long-term functional outcome or QoL. In a study by Heuschen (2002\*\*), 131 of 706 patients with a J-pouch had septic complications (18.6%), 107 of whom needed surgical treatments with an average of 2.2 procedures. The failure rate after these complications was high (30%) and mainly related to complications at the anastomotic site. Patients with pelvic sepsis had a five times higher risk for failure after ten years compared to patients without pelvic sepsis reported by Tekkis (2006). Pelvic sepsis can appear at any time in the follow up period.

From the UK national pouch registry Tekkis (2010) reported an estimated failure rate of 41% at 10 years after salvage procedure in IPAA. Salvage was associated with worse functional outcome with increased BM, rate of seepage at day and urgency and not only in the first years after salvage. The success of salvage is related to the cause of failure. Septic causes have worse outcomes than non-septic (Baixauli 2004).

Minor complications and simple fistulas may be treated with success, but more severe pathologies and the need of redo-surgery by laparotomy have a worse fate, as suggested by Chessin (2008). In a study by Sagap (2006) from the Cleveland Clinic, the failure to manage septic complications was related to the need of laparotomy and a secondary diversion. It was also associated with delayed closure of the protecting ileostomy and the need of trans-anal drainage of the septic area. Percutaneous drainage was associated with success. These strategies were related to the severity of the septic complications. Fistulas and hand-sewn anastomosis and hypertension were other independent co-factors for failure after septic complications. Pelvic sepsis was associated with anastomotic leakage in 34% and with fistulas in 25% of the patients. The crude success rate in the management of pelvic sepsis was 75%. The Mount Sinai (Toronto)

experience (Forbes 2009) reported improved anastomotic leakage rates and less morbidity due to improved surgical handling of complications together with improved complication rates over time.

Impaired blood supply and tension has to be avoided in all intestinal anastomoses and is a risk factor for failure in IPAA (MacRae 1997, Heuschen 2002\*). The ileal pouch-anal anastomosis is also fragile due to its closeness to the influence and traction from striated muscles of the anal sphincter and the pelvic floor.

Anastomotic separation/leakages may not always lead to septic complications, as they can heal spontaneously or result in sinuses or fissures. Recently the risk factors for septic complications from anastomotic leaks was analysed among more than 3000 patients from the Cleveland Clinic (Kiran 2010). The rate of septic complications within 3 months of a functioning pouch was 6.2%. BMI >30, a definite diagnosis of ulcerative/indeterminate colitis, Crohn`s disease and intra- and postoperative transfusions were risk factors for septic complications. Surgical factors; pouch design and anastomotic techniques, technical problems with the stapling procedure, proximal diversion, level of anastomosis above the dentate line, laparoscopic technique and lysis of adhesion had no impact, but the individual surgeon as a factor had impact on septic complications (Kiran 2010).

In patients with FAP the risk of septic complications is less compared to patients with IBD (Kartheuser 1996, Korsgen 1997, Nyam 1997, Heuschen 2002\*) indicating that IBD is a risk factor for septic complications.

## **Fistula**

Fistulas can appear at any time in the follow-up of pelvic pouch, and the rate of fistulas after more than 15 years was 15% in the cohort study by Hahnloser (2004). Fistulas can be classified in early and late appearance in the follow-up, or in CD associated or not. Fistulas due to CD often appear later than fistulas due to anastomotic complications. The location is mostly at the anastomotic site, but fistulas and sinuses can also appear along the stapled line in the pouch wall or at the tip of J-pouch. The leak from this tip is rare and it can be difficult to diagnose. The surgical treatment is often successful as documented in a report of 27 cases (Kirat 2011).

The rate of fistulas, especially the vaginal fistulas, is not negligible, often leading to severe morbidity and failure. The rate of vaginal fistula varies between 3.3% and 16% (O`Kelly 1994, Shah 2003, Lolohea 2005, Tekkis 2005\*). Approx 50% of the vaginal fistulas may be of cryptoglandular origin whereas the rest originates from the anastomotic site (Burke 2001). The latter may be due to leaks, strictures and damage to the posterior wall of vagina during the stapling of the anastomosis (O`Kelly 1994). CD should be suspected in complicated and late occurring fistulas.

In a study by Tekkis (2005\*) of 144 patients with fistulas among 1965 patients with pelvic pouch, the main risk factor for fistulas was found to be CD and IC. Other contributing factors were prior abscesses/fistulas and pelvic sepsis, female gender more so than male and abnormal anal manometry. Rottoli (2011) found more fistulas in females and vaginal fistulas constituted 47% of the fistulas. A suggestion of a more aggressive underlying disease of UC and delayed CD in females was put forward. This was also based on the fact that females are younger at surgery.

Another recent report from the Cleveland Clinic found that late pouch fistulas was associated with CD, and early fistulas with BMI > 30 kg/m<sup>2</sup> and postoperative leakages. In a multivariate model failure due to fistulas was associated with delayed CD, completion proctectomy, hand sewn anastomosis, anastomotic leakage, BMI > 30 kg/m<sup>2</sup> and severe fistulas (Nisar 2011).

### **Stricture**

Anastomotic stricture in IPAA is common (5%-38 %) (Fazio 1995, Prudhomme 2003). The Mayo Clinic (Prudhomme 2003) reported significantly fewer strictures after stapled anastomosis than after hand-sewn anastomosis. The meta-analysis of Lovegrove (2006) and the randomized study by Reilly (1997) did not support this. Kirat (2010) found 4-6% strictures after stapled anastomosis not related to the size of the stapler in contrast to the report by Senapati (1996). Females have more strictures after stapled anastomosis whereas males experience more incontinence (Kirat 2010). Prudhomme (2003) differentiated between fibrotic (14%) and non-fibrotic (86%) strictures. The former was associated with anastomotic complications. The latter was easily treated by one or more dilatations. Asymptomatic web-like strictures were excluded from the analysis. Lohola (2005) differentiated between fibrotic and inflammatory strictures. Kirat (2010) did not find any association between anastomotic leakages and stricture, which is in contrast to a prior study by Lewis (1994). Different definitions of stricture complicate the comparison between studies. An anastomotic stricture may be caused by impaired anastomotic technique, ischemia and Crohn's disease.

A list of complications after IPAA can be made in many different ways, one among many:

**List of ileal pouch-anal anastomosis complications:**

- Anastomotic leak and separation
- Pouch leakages
- Abscess: Pelvic sepsis
  - Pelvic abscesses with or without later fistulisation
  - Perineal abscess with or without fistulisation
- Fistulas: Anastomotic fistula
  - Pouch fistulas
  - Internal fistulas (intestinal to pouch fistulas)
  - Vaginal fistulas (pouch-vaginal, anastomotic-vaginal)
  - Cryptoglandular abscess and fistula formation
- Sinusoid: Anastomotic/peri-pouch
- Stricture: Fibrotic, stenotic, inflammatory, web like stricture.
- Fissure/ulcer in the anastomotic area. Cuffitis.
- Perineal eczema/soreness/irritation/itching
- Pouch necrosis/ischemia
- Bleeding from the pouch
- Twisted pouch
- Pouch prolapse
- Mid-pouch stricture, pouch-bridges
- Inlet obstruction, inlet stricture
- Pouchitis (idiopathic, acute, episodic, relapsing, chronic, secondary)
- Dysplasia

**Some other complications**

The overall non-pouch related complications, like small bowel obstructions hernias or other general postoperative complications were reported in a rate of 13.3% in the review of Hueting (2005). One fourth will be resubmitted to hospital care with symptoms of intestinal obstruction, and half of these patients will undergo surgical treatments.

Obstruction was found to be due to adhesions (Åberg 2007), and occurred mostly in patients who had had a diverting stoma. Other causes can be anastomotic complications after closure of the diverting stoma or the stoma itself and volvulus. From Toronto

McLean (2002) reported a cumulative rate of bowel obstruction of 31% after 10 years, mainly distributed between the pelvis (32%) and ileostomy closure site (21%).

The afferent limb syndrome has been described as a particular partial small bowel obstruction at the inlet of the pouch, due to angulations, prolapse or intussusception (Read 1997, Kirat 2010\*).

It is worth to mention that particularly young men seem to be exposed to the serious complication of lower limb compartment syndrome (Michelassi 2000, Walker 2008), which can be prevented proper stockings, protective position on the table and regular movements of the extremities during the stay on the operating table. IBD is associated with thrombotic complications and an increased risk of portal vein thrombi have been described after IPAA (Remzi 2002).

#### **Complications, outcomes and learning curves**

Meagher (1998) reported fewer complications with increased experience in the period from the early eighties to the nineties, with a drop from 7% to 3% at the Mayo Clinic. The Cleveland Clinic found differences in complications rates between surgeons, and between each surgeon's caseloads. Surgeons who had performed more than 150 procedures did significantly better (Kiran 2010). The learning curves at Cleveland Clinic according to failure rate were 23 procedures for the stapled anastomosis and 40 for the hand-sewn anastomosis (Tekkis 2005).

Experience from Toronto (Kennedy 2006, Raval 2007, Forbes 2009) supported an association between volume and results (quality), and improved results with centralization and institutional learning curves. A study by Burns (2011) using the

Hospital Episode Statistics in UK found that the caseload of the surgeon did not influence failure, but low institutional volume did. The other findings were the very low caseload among most of the surgeons; 80% of the surgeons performed less than 10 procedures in 12 years and only 5% did more than 29 pelvic pouches, and none had done more than 134 procedures. In contrast the caseload at the Cleveland Clinic was 3407 procedures done by 19 surgeons (Rottoli 2011).

Small volume-series from Scandinavia with excellent results however challenges the volume-quality discussion. (Mikkola 1995, Johnson 2001, Berndtsson 2007, Walker 2008, Stornes 2010). The results can be explained by case selection, which in fact excludes patients who eventually could have been offered IPAA. To achieve superior results by strict selection is not fully compatible with the idea of equality in health services.

### **1.2.6 Pouchitis**

The aetiology of pouchitis is unknown. Pouchitis is the third most common intestinal inflammation in the IBD entity. This idiopathic and “iatrogenic” inflammation is a separate and distinct form of IBD and could be suggested as a novel manifestation of a colitis-like syndrome (Stoechi 2001).

Suggested factors in a possible aetiology is dominated by the idea of stagnant material (de Silva 1991) with a subsequent relative bacterial overgrowth (Yamamoto 2005), which undergoes a shift towards an anaerobic microbiology (Nasmyth 1989) and a reduction in bacterial diversity (McLaughlin 2010). In particular, sulphate-reducing bacteria may play a distinct role in the pathogenesis. The bacteria seem to colonize in UC

patients only (Ohge 2005). Degrading toxic agents, fermentation and ischemia have been proposed as contributing factors. Lipman (2011) found an association between pulmonary disease and pouchitis, suggesting a hypoxic influence. All these factors may disturb the mucosal barrier, triggering an abnormal immunological response, or the response in an abnormal way, which in turn can be influenced or aggravated by the underlying IBD-constitution (Sandborn 1994). The low frequency of pouchitis in FAP patients (Penna 1993, Tjandra 1993, Fazio 1995, Lovegrove 2006\*, Ganschow 2010) and the absence of pouchitis in FAP patients with CI (Bonello 1981, Fazio 1988), indicate the importance of a systemic aetiological component. Whether or not pouchitis actually occurs in FAP has been questioned (Kartheuser 1996, Lipman 2011). Salemans (1992) found nil pouchitis among patients with FAP.

The colonic extent of UC is a risk factor for pouchitis, and supports the idea of a gradual systemic effect of the disease (Schmidt 1998, Lipman 2011).

The intestinal mucosa undergoes several changes including villous atrophy, which resembles colonic metaplasia (de Silva 1991). The debate about adaptive mucosal change and its definition is an ongoing issue (Fruin 2003). The mucosal changes may be interpreted as a structural defence to the altered content and bacterial changes.

Achkar (2005) assessed risk factors for pouchitis. The extent of colonic disease and EIM were associated with both acute and chronic pouchitis, NSAID with chronic pouchitis. Fulminate acute colitis as indication for surgery seem to prevent chronic pouchitis, but not acute.

There are controversies in the definition of pouchitis and hence the diagnosis and diagnostics. Diagnosis based on symptoms, endoscopic inflammatory changes and

histopathology has been recommended. The necessity of histological confirmation of acute inflammation is debatable (Shen 2003, White 2010). The microscopic inflammatory changes can be scattered and thus absent in parts of the pouch and the inflammation can occur in the suture lines without true pouchitis. Granulomas can be found in suture lines. Royston (2010) found that biopsies were to a large extent not representative and the accuracy of histopathology was low. Biopsy may be necessary to exclude CD, viral inclusion body seen in CMV infections, dysplasia or other conditions that may trigger or cause secondary pouchitis (Shen 2005, McGuire 2007). The symptoms of pouchitis (urgency, incontinence, increased frequency, rectal bleeding, liquidity combined with cramps, abdominal pain and nausea, vomiting, malaise and low-grade fever) together with mucosal changes at endoscopy (oedema, granularity, friability, ulceration, loss of vascular patterns and mucus exudates) establish the diagnosis of pouchitis. This duo-diagnosis approach is often used and Shen (2003\*) demonstrated a high sensitivity and specificity score when creating a modified pouchitis disease activity index based only on symptoms and endoscopic appearance compared to diagnosis based on adding the result from histopathology. Successful antibiotic treatment of symptoms associated with pouchitis, as diagnostic for pouchitis may be fallible; the symptoms may have other causes. The problem of establishing an accurate and universal definition of pouchitis can partly explain the diversity of different reports on pouchitis. In addition, the symptoms of pouchitis are overlapping with different sequelae of IPAA such as cuffitis, CD of the pouch and irritable pouch syndrome (Shen 2005).

The definition of acute *vs.* chronic pouchitis varies. Chronic pouchitis has been defined by symptoms lasting for more than four weeks (Shen 2003\*). This limited

definition excludes frequencies/relapses of episodes of pouchitis and the effects of treatments. Some authors use cut-off points for chronic pouchitis usually more than three episodes (Hoda 2008, Vento 2009). Others define chronic pouchitis by effects of treatment and the duration of treatment. Continuous use of antibiotics or a refractory state is the strictest definition of chronic pouchitis (Fleshner 2007, White 2010). The finding of pyloric gland metaplasia in biopsies from pouchitis seems to be indicative of chronic pouchitis, but also to CD (Kariv 2010).

It is generally agreed that a distinct difference between an acute form and a chronic form of idiopathic pouchitis should be made (Abdelrazeq 2005, 2008, Achakar 2005, Fleshner 2007, White 2010). In the excluded pouch after IPAA failure due to chronic pouchitis, the pouchitis continues (Tulchinsky 2003). This finding supports the idea of a distinctive chronic form of pouchitis.

Anastomotic complications are risk factors for chronic pouchitis (Hoda 2008). In the follow up fistulas and sinuses may be revealed as the cause of refractory secondary pouchitis. In the study by Lipman (2011) both strictures and fistulas were associated with pouchitis. Stricture was a risk factor for pouchitis (Banasiewicz 2011) and supports the “stagnant theory”.

Classification of pouchitis can also be divided in antibiotic-respondent, antibiotic-dependent and antibiotic-refractory pouchitis (Shen 2003). A distinction between acute/episodic and chronic pouchitis also seems mandatory when investigating the impact on functional outcome and the association with EIM (Abdelrazeq 2005).

Scorings systems have been constructed to diagnose pouchitis, to meet the demand for comparative purposes and to assess the effect of treatments. The pouch

disease activity index (PDAI) (Sandborn 1994), the St. Mark's Hospital criteria (Moskowitz 1986) and the Heidelberg criteria (Heuschen 2002) are the most commonly used criteria. The many index systems do reflect a problem of definition and seems not to be in universal use or correctly performed (Shen 2003, Heuschen 2010, Roysten 2010). The criteria are aimed to diagnose acute pouchitis and do not discriminate between acute or chronic pouchitis.

### **Incidence of pouchitis**

In the long-term, about 40%-50% of the IPAA patients are expected to have one or more episodes of pouchitis (Shepard 1989, Svaninger 1993, Farouk 2000, Heuschen 2001, Hahnloser 2004, Ferrante 2008). A 59% rate of pouchitis has been reported (Simchuk 2000). The estimated cumulative rate of pouchitis in UC from the Mayo Clinic (Hahnloser 2007) reached 70% at 20 years. The diagnosis was based on symptoms and the indicative of successful treatment with antibiotics. The first onset of pouchitis occurs in the first few years, most before the fifth year (Ståhlberg 1996, Abdelrazeq 2008). Several studies have reported low rates of pouchitis, as low as 10–20% (Heuting 2005). This may be due to short observational times and different definitions and study designs.

The rate of chronic pouchitis varies substantially between studies. In long-term studies 5-20% has been reported (Heuschen 2001). Even with a strict definition of chronic pouchitis it is reported to affect 11% of the patients (White 2010). Ståhlberg (1996) reported a rate of chronic severe pouchitis of 9.4% and totally 21.5% had a chronic form.

The high rate of pouchitis in IPAA is a considerable contribution to morbidity, even if antibiotics easily treat most cases. The impact on long-term function is negligible in antibiotic responding pouchitis, but chronic pouchitis affect the function negatively (Keränen 1997). In a recent study by Kariv (2010\*) the concern of cancer formation due to chronic pouchitis was not supported

In CI the rate of long-term pouchitis is generally reported to be lower than in IPAA although one third of the patients may experience pouchitis (Järvinen 1986, Fazio 1988, Svaninger 1993). Idiopathic chronic pouchitis in CI seems rare.

### **Treatments of pouchitis**

The treatment of acute and sporadic pouchitis is well established and most of the patients respond to antibiotics. Treatment with anti-IBD agent adds to the treatment algorithm of pouchitis. The treatment of chronic pouchitis is more difficult and in few cases exclusion or removal of the pouch is the only option. In a recent study by Leowardi (2009), as much as 35 % of the pouch failure was due to chronic pouchitis.

The different probiotic treatments interfering with the bacterial theory have not been successful. The VSL#3 probiotic may have been suggested for prevention of pouchitis (Gionchetti 2003, 2007). The few species in VSL#3 may not enhance the diversity to induce remission. Other miscellaneous treatments of chronic pouchitis acting on suggested aetiology has been disappointing, like the use of octreotide (D'Hoore 2009). The continuous use of antibiotics is still the most effective treatment.

### **Crohn`s disease and pouchitis**

Pouchitis in CD patients can be a separate type of pouchitis – de novo CD. Pouchitis in CD reach a rate of 83% in 10 years in a study by Hahnloser (2007). Biopsies cannot always confirm CD in the pouch by showing granulomas. Pyloric gland metaplasia can indicate CD (Kariv 2010). Strictures in the follow up period, stricture and ulcers at the pouch inlet or distal in the pouch, and cuffitis refractory to treatments, are associated with CD. The diagnosis and successful treatment algorithms of CD of the pouch are not easily established.

### **Secondary pouchitis**

Secondary pouchitis (Navaneethan 2010) are due to identified agents, ischemia, therapeutic agents (NSAID-induced pouchitis), autoimmune disorders, viral agents or surgical complications including fistulas and peri-pouch sinuses. Radiotherapy can induce pouchitis. Other rare entities have been identified, such as collagen pouchitis (Shen 2006\*).

Cuffitis due to persistent IBD inflammation of the rectal mucosa in the ATZ (strip proctitis) or the rectal cuff is a distinct entity other than inflammation due to anastomotic complications. The symptoms of cuffitis are similar to pouchitis, but contrary to pouchitis almost all cuffitis have bloody BM (Shen 2004). Topical mesalamine or systemic agents can be effective in treatment of cuffitis, but in refractory cases mucosectomy with the pouch advancement is an option (Fazio 1994).

### **Back-wash ileitis and pouchitis in the continent ileostomy**

Because pouchitis does exist in CI, it supports the idea of bacterial change and overgrowth as an important factor in the aetiology due to obstruction. Pouchitis in CI may also support a theory of an initial pathology in the ileum as a predisposition for pouchitis in ileal pouches. This is supported by the reportedly higher risk of pouchitis in patients with “back-wash ileitis” (BWI) in IPAA (Schmidt 1998, Abdelrazeq 2005\*, Ferrante 2008). Abdelrazeq (2005\*) reported that both acute and chronic pouchitis was associated with BWI in a multivariate analysis. BWI was found in 22% of patients with UC and IPAA. However, a recent report (White 2010) performing a multivariate analysis did not find any significant association between BWI and acute or chronic pouchitis. There was however a tendency towards more cases of chronic pouchitis in patients with BWI. An association between BWI and primary sclerosing cholangitis (PSC) was also found.

The definition of BWI is not established. Some similarities with CD are found, but BWI is regarded as an entity exclusively included in UC (Goldstein 2006). The term reactive “back-wash ileitis” may thus be misleading (Abdelrazeq 2005\*).

### **Pouchitis and extraintestinal manifestation**

The rate of PSC in UC patients having IPAA varies between 3 – 12% depending of criteria and diagnosing of PSC. From Cleveland Clinics Rottoli (2011) reported rates of PSC among UC patients having IPAA. In female it was 3.7% and for male 4.9%. UC patients who undergo surgery have a higher rate of PSC than UC patient who do not need colonic surgery, indicating a relationship between the severity of UC and PSC. After

liver-transplantation the severity of colonic inflammation decreased and an association between PSC and UC was likely (Jørgensen 2011).

PSC affect the rate and severity of pouchitis (Fleshner 2007, White 2010). Penna (1996) found that the severity of PSC did not influence the seriousness of pouchitis. PSC was associated with chronic pouchitis in the study by Aitola (1998). In the study of Ståhlberg (1996) all patients with PSC had pouchitis and the frequency of pouchitis in all EIM was 21.2 compared to 8.4 in UC patients without PSC or other EIM.

An underlying common aetiology in PSC and pouchitis may explain the increased frequency of severe pouchitis in PSC patients (Lepistö 2008). Mathis (2008) showed that the severity of pouchitis did not improve after liver transplantation. These results support the assumption that chronic/severe pouchitis in PSC patients is a separate clinical entity (Faubion 2001, Shen 2010). Other studies, however have not found associations between PSC and pouchitis (Gorgun 2005, Hoda 2008). Conflicting results add to the problem of understand the aetiology of different forms of pouchitis and its relationship to PSC

A recent study from the Mayo Clinic investigating patients with PSC at surgery for IPAA documented a crude high rate of pouchitis (64%), dominated with recurrent acute pouchitis (40%) and chronic (16%). Age at surgery was mean 42 years. The follow up was 5.9 years (median) (Mathis 2011). The study, which is the largest series of IPAA patients with PSC, was not aimed to compare the rates of pouchitis. The authors were therefore reluctant to conclude on any association between IPAA and PSC and the risk of pouchitis. They conclude that IPAA could safely be performed in patients with known PSC without compromising long-term functional outcome. Patients undergone liver transplant should not be excluded. In a previous study by Mathis (2008) the pouchitis was

unaffected of the presence of PSC, a result that make these relationship extraordinary difficult to investigate.

Other EIM have been reported to be associated with pouchitis, but these associations are questionable and are not conclusive (Penna 1996, Ståhlberg 1996, Abdelrazeq 2008). In the study of Lipman (2011), preoperative manifestation of rheumatic extraintestinal disease was associated with pouchitis. PSC was not evaluated in that study possibly because it seem that most of PSC are diagnosed in the follow-up after IPAA. Shen (2006) found in a multivariate risk factor analysis that arthralgias was associated with cuffitis, but not with pouchitis.

Other risk factors for pouchitis have been investigated. Several genetic and biological factors have been found to be associated with pouchitis. The use of NSAID aggravates pouchitis, as it influences IBD negatively (Fleshner 2007, Shen 2006). The pre-operative use of steroids, smoking, different biological markers among others have been identified, but these factors do not fit easily into the understanding of pouchitis. Shen (2006) documented that dysplasia in UC was significantly associated with pouchitis indicating that the severity of the underlying factors for UC may play a role in the aetiology of pouchitis.

Irritable pouch syndrome (IPS) emerged from the problems with the definition of pouchitis and its symptoms, when no endoscopic signs of inflammation or histological confirmation of pouchitis could be found (Shen 2002). Shen (2006) have demonstrated an association between IPS and the use of antidepressant and anti-anxiety agents.

An entity of prepouch ileitis has also been reported. Pouchitis was not a precondition for the disease and no association to CD was found in the study by Bell

(2006). The study by McLaughlin (2009) showed that the prepouch ileitis occurred in 5.7% of patients with UC/IC and was seen in 13% of the patients with pouchitis, and was associated with pouch inflammation. The prepouch ileitis has been reported to be associated with PSC and different autoimmune diseases (Shen 2010). Ulcers in the afferent limb were found to predict CD or were an effect of the use of NSAID (Wolf 2004).

Pouchitis is a frequent complication and affects functional outcome. The incidence and definitions of pouchitis vary considerably; it is thus a troublesome factor interfering in the analysis of outcomes in IPAA and CI surgery.

### **1.2.7 Functional outcome**

#### **Functional outcomes in IPAA**

The deterioration in functional outcome in long-term follow-up has been confirmed in many studies and reviews (Bullard 2002, Bengtsson 2007, ECCO 2009, Tekkis 2010, Lovegrove 2010). The incontinence rates tend to increase, but deterioration of other functional outcomes varies in different studies (Hahnloser 2004, Lovegrove 2010, Tulchinsky 2010). The experience from the Mayo Clinic (Meagher 1998) was that functional outcomes were stable. This was the main conclusion in the follow-up study of Hahnloser (2007). Michelassi (2003) and Penna (1993) (FAP patients) concluded with improvement in long-term functional outcome. Results from several publications on functional outcomes are listed in Table 4.

### **Bowel movements**

Frequencies of bowel movements between 5- 6 during the daytime and 0-1 at night is classified as excellent in many reports on this subject (Tekkis 2010). BMs of more than 10 per 24 hour could be considered a failure. The recent study by Genschow (2010) demonstrated that QoL decreases significantly when BM rates exceed seven during day and/or two at night. This was supported by a study by Leowardi (2009) and from the Norwegian study by Røkke (2011). Lovegorve (2010) found that the BM exceeding 6-8 per 24 h and more than one BM at night affected QoL negatively. The rate did not deteriorate over in 20 years. A Norwegian study (Anderson 2011) reported seven BM (median) during the day and two at night with a corresponding lower QoL compared to the general population. In general, QoL, HRQoL and HS after IPAA are reported to be similar to the general population (Tiainen 1999, Carmon 2003, Berndtsson 2007, Heikens 2010). Hahnloser (2004) found stable QoL with a small, but significant increase in the rate of BM at 1 and 15 years (5.5 -6.1 at day and 1.1- 2.0 at night, respectively). The study concluded with stability in the long-term follow-up, both in function and QoL because the increase was small and it seemed not to be of clinical importance. The UK national registry (Tekkis 2010) found stable BM (5 per 24h and 0-1 at night). Michelassi (2003) reported an almost stable BM in long-term follow-up.

### **Incontinence, seepage and soiling**

The definition of incontinence and seepage/soiling is subjected to substantial variations between studies. The study by Hahnloser (2004) reported a diurnal incontinence rate of 19% after five years increasing to 45% after 10/15 years of observation. The nocturnal

rates were 53% to 76%, respectively. Other studies report incontinence rates below 20% (Chapman 2005). These substantial differences may be due to different definitions of incontinence.

Different rates between incontinence and seepage were reported in the often-cited study from the Cleveland Clinic (Fazio 1995). The incontinence rate was low, 1.9%. The seepage rate at night was 29%. The seepage rates from the UK study (Tekkis 2010) increased from 8% at one year to 15.4% after 20 years.

The aggregated results on function and QoL recently published from the Cleveland Clinic and from the Imperial College London (Lovegrove 2010) included more than 4000 patients. After 20 years of observation 98 patients were evaluated. Function (urgency, incontinence, seepage and the use of pads) was concluded to deteriorate over time and was reported to be associated with decrease in QoL. The median BM was 6 at day and 1 at night and this did not deteriorate over time. Incontinence and a 24 h frequency of BMs of more than 8 had major impact on QoL (Cleveland Global Quality of Life Score). Incontinence affected 32% at one year and 65% at 20 years, whereas minor incontinence (seepage/soiling) affected 16% and 24% of the patients during the day and 29% and 45% at night, respectively. This was a significant increase using a time dependent statistical analyses (Lovegrove 2010): A “model development was performed using dependent linear regression. Length of follow-up from PRC was used as time-dependent variable, with individual patients at each time point being designated by unique identifier”. Interestingly, the use of antidiarrhoeals decreased. Another study from Cleveland Clinic (Kiran 2011) included patients having had the pouch for more than 15 years. The rate of patients who never experienced incontinence was almost halved in all

age groups in the interval from 5 to 15 years. The QoL was stable. In the study of Holubar, (2003) the alterations in incontinence after IPAA compared to patients having laparoscopic cholecystectomy seemed not to affect QoL. QoL was similar between the groups.

Michelassi (2003) reported that the incontinence improved in long-term follow-up. The incontinence rate was 8.7% among patients with stapled anastomosis (116) at five years after surgery and 3.6 % of the patients suffered total incontinence. The conclusion was that the incontinence decreased during the long-term, which was based also on the reduced use of pads and the decrease of perineal skin complications. An improved result over time was also reported in a study of Penna (1993) evaluating the outcome in FAP patients.

Although incontinence, minor incontinence and seepage can be defined and recorded in many different ways, the incontinence constitutes a major functional annoyance and leads to failure.

### **Urgency**

Urgency is not being able to defer evacuation for more than 15 minutes. The UK national ileal pouch registry reported an increase in urgency from 5.1% to 9.1% after one and 15 years of follow-up, respectively (Tekkis 2009). The long-term change was significant. In contrast the urgency rate in the study by Hahnloser (2004) was stable. In the study by Lovegrove (2010), the increase was significant. In a separate study from the Cleveland Clinic (Kirat 2010), the urgency rate was below 10%, but the rate “improved over continued follow-up” of 15 years.

### **Other functional outcomes**

Pads are used for several reasons, ranging from total incontinence to the feeling of moisture or from the fear of urine incontinence. The rate of pad usage varies. Meagher (1998) found decrease in the use of pads from 25% to 15% after 10 years. Hahnloser (2004) reported an increase in the use of pads from 30% to 50% from 5 years to 15 years of observation. Bengtsson (2007) reported a decrease in the use of pad during night and an increase at daytime.

Perineal eczema/soreness/inflammation/skin-irritation is experienced by many of the patients. Meagher (1998) reported a rate about 50%, which was stable throughout the follow-up time.

The ability to control and distinguish between gas and stool is often a part of functional outcome assessments. Meagher (1998) reported that in 70- 87% of the patients and this ability significantly improved over time. Hahnloser (2007) found that three quarters of the patients maintained this ability.

Medications to control several of these functions are used by more than half the patients. Half the patients never had used medication to regulate the stool consistency and BM (Hahnloser 2007). It is a paradox that regulating agents decreases over time when adverse function increases (Lovegrove 2010).

### **Risk factors for worse outcomes**

The risk factor profile for reduced functional outcome has been evaluated in several reports. Pouchitis, which is defined by deteriorated function, certainly have this effect. Delayed CD is a strong predictor for decreased function and failure, because CD in fact is

revealed by these complications. Many risk factors have been reported of which many are controversial: indeterminate colitis, pelvic sepsis, fistulas, age at pouch construction, female gender, hand-sewn anastomosis, increased BMI, BWI, PSC and other extra intestinal manifestations.

### **Stability in functional outcomes?**

In a study by Tulchinsky (2010), the functional outcome was stable in more than 11 years. The Mayo Clinic experience reported stable long-term (10 years) functional outcome (BM and incontinence) (Meagher 1998, Hahnloser 2007). The Cleveland Clinics latest report (Kirat 2010) concluded with a stable long-term functional outcome after 15 years of observations. The earlier study by Fazio (1995) concluded with stable QoL. The functional outcome was stable and few patients experienced incontinence always. In the Norwegian study by Røkke (2011), functional outcome was stable after mean eleven years and the QoL (SF-36) was similar to the general population.

One may question the reason for reduced function after years, reported by many. Why should the function deteriorate in otherwise healthy people, who have good living conditions in wealthy societies and who were young at surgery (20-40 years) and who now are not older than 60-70 years? Hahnloser (2004) proposed a weakening of the anal sphincter strength over time, which could explain the change in incontinence rates. Possible damage to the anal sphincter muscles during vaginal delivery was proposed and that “irritable bowel syndrome becomes more common with age”. All these supposed factors may be absent or they are at least controversial for explaining the proposed functional deterioration in the long-term follow-up after IPAA (Pretlove 2006).

In a critical review by Lichtenstein (2006) including eleven studies, the QoL after IPAA was analysed. The authors concluded that surgery in a substantial number of patients did not restore QoL to normal levels in the general population. The bowel functions are considerably different compared to individuals without IPAA and surgery can have extra disadvantages or complications such as reduced sexual function and fecundity.

Ko (2000) studied the relationship between functional outcomes and HRQoL. He compared IPAA and IRA among FAP patients. A worse functional outcome in IPAA compared to IRA was not reflected in reduced HRQoL in IPAA patients, the HRQoL was similar. The issue of different QoL assessment and results is not resolved.

In Table 4 functional outcomes and QoL from several reports over the long-term are given.

### **Elderly patients**

Most studies report that patients who are old at surgery face a risk of more complications, higher failure rates (Wibmer 2010, Burns 2011) and reduced functional outcome (Chapman 2005, Hahnloser 2007, Bengtsson 2007). In contrast, other studies, which investigated this issue, have reported excellent results in highly motivated and selected old patients (Delaney 2002, Ho 2005). Old patients with no co-morbidity, normal anal function without signs of diseases and with normal BMI may be good candidates for IPAA.

### **IPAA in familial adenomatous polyposis**

The reported percentages of FAP patients among the total of IPAA cases vary from 5% – 23.8% (Kiran 2010, Wibmer 2010). In contrast to IBD patients FAP patients are generally young and otherwise healthy at surgery and do not have any local or systemic pathologies, which IBD patients may have. They have not been exposed to medical treatments with possible adverse effects. It is thus possible to assess the more pure effect of pelvic pouch surgical procedures without the impact of IBD. In a study of FAP patients the complication rate was lower compared to IBD patients (Lovegrove 2006). The risk for septic complications was lower for FAP patients than patients with IBD (Kiran 2010). Erkek (2007) found a tendency of increased BM with increased age at surgery. Other functional outcomes and QoL-score were stable and almost similar between the age groups after five years of observation. The older (>40 years) had a tendency of worse outcome and more work restrictions.

Lovegrove (2010) reported that the QoL in patients with FAP was equal compared with patients with UC after IPAA. Preventive RP, however, do have a deteriorative impact on bodily function among otherwise preoperatively asymptomatic patients, as the opposite is the consequence for UC patients (Lichtenstein 2006).

### **Continent ileostomy and long-term functional outcome**

Intubations, which varies between 3 – 5 times per 24 hours is the method of evacuation. Incontinence due to nipple valve sliding or fistulas is failures, which needs surgical corrections. The definite failure is incontinence, which leads to continuous use of collection devices or the need of removal of the CI replaced with conventional ileostomy.

Complications such as intubations problems, which are minor complication, occasionally occur due to nipple stenosis. Nipple stenosis can be a consequence of ischemia or wearing from the repeated intubation procedures. Deterioration in function is not a subject of analysis due to the fact that the incontinence is by definition failure of CI. Brevinge (1992) reported that the frequency of intubation seems to be stable with time. The study revealed that the intubations rate did not increase when output increased. The reason for increased output was unknown. The compensatory mechanism was the expanding of the reservoir.

Complications can occur at any time after surgery (Denoya 2008), but most revisions due to nipple valve sliding are reported to appear during the first years after construction (Nessar 2006).

The Mayo Clinic reported better QoL results among IPAA patients than for CI and conventional ileostomy patients (IPAA>CI> Ileostomy) (Køhler 1991). The QoL improved after conversion of a conventional ileostomy to CI in the study of Sjødahl (1990). This was supported by the studies by Gerber (1980, 1984) favouring CI compared to ileostomy, although ~~of~~ several revisions of CI were necessary. A report from the Netherlands (Hoekstra 2009) did not find inferior results in CI patients compared to IPAA patients and patients with conventional ileostomy. The long-term study from Gothenburg (Berndtsson 2004) demonstrated that QoL was in a range similar to the general population, although many patients have had several revision procedures and problems with evacuation of faeces.

### **1.2.8 The durability of IPAA and CI**

The durability of IPAA and CI has been investigated in the long-term study from Helsinki (Lepistö 2002, 2003). The conclusion from this single institution in Helsinki with a very low failure rate in IPAA (5.3%), favoured the IPAA compared to an estimated failure rate of 29% among CI patients at 29 years of follow-up. Because failure rate in CI differs considerable between studies it complicates comparison between IPAA and CI. Problems related to selection bias and lag in time of observation add to the complexity of interpretation of the results from different studies in comparing IPAA and CI.

Considering the failure rate of 15% in IPAA after 15 years and similar rates for CI it may be premature to exclude potential candidates for CI. The ECCO statement (2009) concludes that CI in highly selected patient offers an excellent outcome when operated at dedicated centres.

## **2.0 Aims of the study**

To investigate surgical load, complications and long-term functional outcome in patients operated with ileal pouch-anal anastomosis, continent ileostomy or both in one single surgical unit, and to define factors which affect these subjects.

To assess the results after conversion of a failed pelvic pouch to continent ileostomy.

To compare IPAA and CI according to complication rates, functional outcomes and long-term failure rate.

To evaluate the impact of PSC and other EIM on the rates of pouchitis and functional outcomes in UC patients.

### **3.0 Material and Methods**

The material consists of patients operated at a single institution, which is a referral hospital for IPAA and continent ileostomy. The study design is a prospective observational study including all patients operated since 1983. A standardized interview, which has not been changed during the period, was conducted at every outpatient visit for IPAA patients. A total of 1802 charts were completed for 315 IPAA patients. These data were included in the medical records in standardized form. At every contact a documentation including clinical status, clinical investigations, pouch endoscopy, complications, other medical issues, or any problem related to function of the pouch were recorded.

All patients were invited and encouraged to participate in the regular annually outpatient visits, regardless the presence or absence of pouch surgery-related or other medical problems. These outpatient visits were higher than the planned annual visits for some patients, depending on their needs and wishes. For other patients the interval was increased as an agreement between the patient and the surgeon. The patients were also offered to contact the outpatient clinic beyond the planned visits whenever they had any problem related to their reservoir. These contacts were received by a consultant surgeon or senior registrar and/or an enterostoma therapist (ET). The National Health Service met all costs related to the visits, including long-distance travel costs to St. Olavs Hospital. Any visit, admittance and medical needs of the patients were free of charge for all Norwegian citizens, regardless where they lived in Norway. Thus, the follow up of IPAA patients and CI patients was not influenced by their financial status.

The education of skilled ETs started in Norway in the early 1980s. All patients included in this study were offered a visit to one of the hospitals ETs.

CI patients were offered the same follow-up program, but the standardized interview and the information obtained were not included in a questionnaire, but all relevant information was collected. Functional outcome was based on the number of intubations during 24 hours, and any problems related to intubations; i.e. stenosis, angulations. Incontinence and leaks were recorded and the use of pad or collecting device. Incontinence is failure of the CI. All data concerning function and complications were recorded in the medical records.

Additional retrospective data were obtained from medical records and previous audits of pouch patients during the years after the introduction of IPAA and CI at St. Olavs Hospital. To include all patients with IPAA and CI more than 800 patients diagnosed with IBD, FAP and patients who had undergone proctocolectomy were identified. This was done to reveal any missing patients. A few patients (8) younger than 17 years were operated at the department of paediatric surgery without any of the IPAA surgeon participating. These patients were not included in the material.

A personal request was made to many of the medical professionals who had participated in the treatment and nursing of IPAA and CI patients since 1983. One patient was identified with this method.

### **The standardized interview**

A surgeon on duty performed the standardized interview, when the patients visited the outpatient clinic during the follow-up. For selected patients with rare or multiple

complications, the follow-up was done by surgeons with special interest or competence. The times between the out-patient controls varied between patients depending on the individual patients' needs and could vary during follow up for each patient depending on any potential need for extra controls. The colorectal surgeon who was responsible for the visits during the follow up after surgery set the time to next visit. During admittance at the hospital due to complications or planned surgery the standardized interview was not done.

The interview chart (Appendix) included questions about standard functional outcomes. BM was given by average, and a minimum and a maximum value. The patients often indicated that the BM was dependent on diet and they reported adjustments in their everyday life due to occupational circumstances. The average BM recorded was based on the patient's information. When the average was missing - average was calculated if the difference between max and mean was more than one. When difference was one, the max BM was chosen as the average number.

In the analysis of BM, the average BM was used. Analyses of maximum and minimum values were done in long-term time dependent assessment to find any time-dependent results that might deviates from the average BM analysis and long-term changes. The analyses of maximum and minimum BM did not change the results of average BM analyses. (Data are not reported)

Urgency was defined as the inability to defer evacuation for more than 30 minutes after feeling the need to defecate. The patients were asked if they could separate stools from gas. Long lasting evacuation was recorded when evacuation lasted for more than 15

minutes at least once in a week. Incontinence was defined, as uncontrolled evacuation of faeces, whereas soiling was understood as uncontrolled seepage of coloured liquid.

The usage of pads was defined as all kind of absorptive protection devices to wear in the perineum irrespective of the cause.

Frequencies of incontinence and usage of pads were counted as events per week and divided by diurnal and by night. Perineal soreness was recorded as “never”, “sometimes” or “always”. Diet restriction was recorded but was included in analysis.

Medications to alter functional outcomes and the use of loperamid were recorded. Loperamid was given per day and as “never”, “sometimes” or “always”.

When patients had relevant symptoms and corresponding endoscopic inflammatory signs, the diagnosis of pouchitis was set. Biopsies were not routinely performed. If cuffitis was diagnosed it was recorded in the medical chart. For both pouchitis and cuffitis the diagnoses and treatment were recorded.

Other function like impotence, dyspareunia and general impact on social behaviour and satisfaction was recorded. These data has not been analysed.

#### **Technical consideration IPAA**

Stapled anastomosis was done as a double stapling technique. Most J-pouches were constructed by stapling from the apex of the J-pouch whereas some were constructed by inserting the stapling device from the middle of the pouch, opening the septa between the two limbs and firing the transecting stapling device upwards and downwards. Sutures closed the opening for the stapling device in the pouch. All S- and K- pouches were hand-sewn.

The hand-sewn anastomosis has been performed by different techniques. One technique included four quadrant sutures of the apex of the pouch and then anchored to the proximal part of the dentate line. The anastomosis was completed with eight sutures through the pouch-wall to the dentate line. In the last decade, pouch-anal anastomosis was sutured using 14 to 16 full one layer interrupted sutures at the pouch-dentate line.

In most cases, a diverting loop ileostomy was performed and the ileostomy was rotated counter clockwise about 120-180 degrees. The efferent loop was fixated flush to the skin and a catheter was fixed and inserted down to the inlet of the pouch. The afferent loop of the ileostomy was matured. A rod was used to support ileostomy up to the last few years. Another catheter was left in the reservoir through the anus. The pouch could then be cleansed by the instillation of saline through these catheters. At the 4-5th postoperative day the catheter, from below was removed and the washout was continued from the stoma catheter for 4-5 days. If a secondary diversion was necessary due to complications, an end ileostomy was most often preferred. Closure of the loop ileostomy was done by hand-sewn anastomosis, preferably without a midline second laparotomy.

Time to stoma closure was planned at 12 weeks, but the reality was mean 17 weeks. In the analysis of pouch duration concerning complication and comparing IPAA with CI the time with defunctioning stoma, both primary and secondary were subtracted from the crude observational time after IPAA construction.

For stapled anastomosis, the aim was to leave a rectal cuff of less than 1.5 cm. In hand-sewn anastomosis, the intention was to excise the ATZ completely, and the intention was to have the anastomosis at the dentate line.

The anastomotic site includes the dentate line, ATZ, rectal cuff and the area of the anastomosis if stapled. When hand-sewn, the anastomotic site includes the dentate line, remnants of ATZ and the anastomotic suture line area.

#### **Technical consideration CI**

Two continuous layers of hand-sewn suture-lines constructed the K-pouch. When creating the nipple valve, the mesenteric fat was meticulously stripped off. The intussusception was fixated with three staple rows with a length of 4.5 centimetres. Three staples were removed from the device to omit stapling at the tip of the nipple. A fourth stapler row anchored the nipple valve to the pouch wall. There was no rotation of the nipple limbs and no foreign material was used. The pouch was anchored to the abdominal wall by non-absorbable sutures. The T-pouch was constructed as described by Kaiser and Beart (2002).

#### **Complications related to IPAA**

Complications can be classified and defined in many different ways. In this study, we have used the following:

The anastomosis can have early breakdowns *i.e.* a dehiscence or separation of the continuity of the suture lines in the pouch wall or the inner layer of the anastomosis at the anal sphincter line including the mucosa. Early dehiscences often result in anastomotic leaks. These leakages may give rise to infections and abscess formation. Infections usually manifest as pelvic sepsis. Pelvic abscesses can occur at different sites (page 47). Pelvic sepsis can result in infectious and inflammatory sinuses and fistula tracks.

Leaks in the suture line in the pouch can also result in pelvic sepsis. Surgical and technical complications below the anastomosis are prone to infection. Fissure can occur in the anal canal below the anastomosis and may be difficult to distinguish from complications related to the anastomosis itself. In addition, ulcerations in this area are difficult to distinguish from fissures.

Early complications can have different meaning with or without a protecting loop-ileostomy. The pouch-anal related complication after closure of the ileostomy has to be regarded as early complications irrespective of the time to closure. Late complications occur after an interval of an acceptable function of the pouch.

Poor function that did not result in diversions or excisions was not included in the analyses as pouch failure. Pelvic pouch failure was analyzed as an entity including indefinite diverting of the pouch both with an ileostomy or a continent ileostomy, or an excision of the pouch.

Classification of pouchitis in this study included acute pouchitis defined by episodes of pouchitis, which usually responded to antibiotic treatment. When patients needed continuous antibiotic treatment to restore function or depended on self-medication to cure repeatedly relapses they were classified as having chronic pouchitis. In addition, if patients had more than 15 episodes of pouchitis during follow-up after surgery irrespective of time from surgery, they were classified as having chronic pouchitis.

### **Complications related to CI**

Nipple valve sliding is the desuspension of the valve, and leads to incontinence. Nipple valve sliding can be associated with loosening of the pouch from the abdominal wall.

Fistulas from the pouch to the skin, from the pouch to the nipple and from nipple to the skin can develop. Standardized procedures to handle these complications exist. These complications are common and the surgical procedures to restore pouch function have been thoroughly described by Kock and colleagues (Kock 1977).

Stricture or stenosis can occur. The skin level or the apex of the nipple is the most common site for stricture. Stenosis of the outlet can occur at several sites, most often as it passes through the different layers and fascias of the abdominal.

Other surgical complications were classified according to commonly used diagnosis.

#### **Primary sclerosing cholangitis and extraintestinal manifestations**

PSC was suspected if patients had elevated liver enzymes and the diagnosis was confirmed by characteristic imaging features of endoscopic retrograde cholangiogram, computed tomography cholangiogram and/or magnetic resonance imaging. Liver biopsy was not routinely performed.

Pyoderma gangrenosum was verified by biopsies. Rheumatologists diagnosed arthritis or ankylosing spondylitis. Arthralgia with no clinical signs of rheumatic disease was not included in EIM.

#### **Salvage of the pouches**

Salvage procedures of the pouch were defined as all surgical intervention to restore function including revisions redoes by laparotomy or interventions at the anastomotic site. The aim of these procedures was to prevent removal of the pouch or conversion to a

permanent ileostomy. Redoes by laparotomy has to be considered a major salvage procedure.

In CI salvage, procedures included nipple valve revisions or construction of a new pouch. Other surgical procedures in need of laparotomy to restore function of the pouch and continence were also defined as salvage procedures.

All dilatation procedures were excluded from the concept of salvage both for CI and IPAA.

### **Measurements of time**

In the long-term follow up study on functional outcome weeks was the unit of time. The time points in Paper II (Table 2, 3 and 5) was defined by the year  $\pm$  10%. In Kaplan Meier plots and analysis months has been the unit of time.

## **3.1 Material**

In Paper I patients operated in the period 1984-2006 included 304 patients with a primary IPAA. In Paper III the material included 50 patients operated in the period 1983-2002 with CI. Papers II, IV, V and VI included patients operated from 1983-2007. A total of 317 patients had IPAA and 63 were operated with CI.

No patients were missing during the follow-up period and data were recorded on every patient. The standardized follow-up program and the hospital register routines made the collection of these data possible.

The variables included in the database are listed below. Variables, which were not analysed, are also given. These were excluded from analyses due to poor reliability,

accuracy and uncertain of completeness. In addition, some of the data were irrelevant in the different studies in Papers I-VI.

### **3.2 List of Variables.**

#### **Patient characteristics and diagnosis:**

Gender, age at diagnosis, age at first surgical procedure, and age at pouch construction.  
Age at death.  
Previous surgical procedure related to the primary indication for colectomy. Emergency operations.  
Diagnosis of UC, FAP, IC and CRC. Dysplasia. Delayed CD.  
Functional indications for CI: Ileostomy, dysfunctional stoma and dysfunctional IPAA (failure).

#### **Other diseases or procedures before or in the follow-up:**

PSC, Arthritis, Pyoderma gangrenosum, Uveitis, Desmoid formation, Thromboembolism, Diabetes, Psoriasis, Cardiovascular diseases, Cholecystitis. Malignancy. Small bowel obstruction and procedures. Cholecystectomy

#### **Time variables:**

Time to closing the loop ileostomy  
Time to complications  
Time to outpatient visits and each follow-up contact with the hospital  
Time to re-operations  
Time to secondary ileostomy and its closing  
Time to pouchitis  
Time to failure  
Time to childbirth, deliveries and caesareans. Partus before IPAA and CI.  
Pouch duration (crude and functioning)

#### **Procedure**

Stage procedures  
Stapled or hand-sewn anastomosis  
Loop ileostomy/secondary ileostomies  
Close rectal wall proctectomy  
Different kind of revisions and procedure due to complications  
Stapling and nipple valve construction in CI

#### **Functional outcomes:**

IPAA: (See Appendix: the formula of the standardized interview)  
CI: Intubation frequency, intubation problems. Incontinence, discharge. Pads and collecting devices.

**Complications:**

CI (see page 41 Introduction)

IPAA (see page 47 Introduction)

**3.3 Statistics**

General descriptive and associative statistics were: Students T- test and the non-parametric Mann Whitney-test on continuous quantitative variables to compare differences in distribution between groups. The first were used where the data indicates a normal distribution and the latter when this was not anticipated or known. One-way Anova was conducted to compare differences between several groups in Paper VI. Comparing qualitative proportion between groups the Pearson chi-square were used. Comparing small number the Fischer exact test was used. (Equal variance was only anticipated in paper VI – to indicate two questions: The problem of studies with few numbers due to very infrequent diseases and associations, and to illustrate the trend in association between PSC and chronic pouchitis).

The significant was set to  $p= 0.05$  and confidence interval (ci) was reported. Both were given. The p value is the likelihood to reject an association, which is not analytical, in a situation where the association is real. The p value is the demarcation threshold for falsification.

Confidence interval was given as supplement information to the p value. Ci is based on the standard error of mean and gives the 95% interval wherein the likelihood of the real mean is. A narrow ci indicate an additional support for the conclusion displaying

the quality in the relation between the data and the anticipated population of all actual cases. A broader ci weakens the conclusion despite a significant p value.

Times Series Cross Section data were used in long-term analysis in Paper II. Time to the observations was allowed to be treated as an independent variable. The model needs three or more observations at different time points to perform analysis.

The analysis was conducted on pooled TSCS data with patient-controls as the unit of analysis. Ordinary least squares multivariate regression analysis with Huber-White estimation of standard errors was used. To address the problem of temporal dependency in the OLS models and to assess change, a lagged dependent variable is included in each model. Parts of the multivariate regression analysis are conducted by logistic regression. In these models employing temporal dummies in the model controls for temporal dependence. In both cases, in order to adjust for panel heteroscedasticity, observations are clustered by patients. No symptoms of multicollinearity were detected in either model.

In regression and time-series modeling is the assumption that the errors or disturbances have the same variance across all observation points. If this is not the case, the errors are said to be heteroscedastic. The estimation of the variance in the data set is done by the Huber-White estimation. When heteroscedasticity is present the linear coefficient does not change, but the standard error differs, which make the testing of significant differences invalid.

When two or more independent or predictor variables in a multiple regression model are highly correlated a multicollinearity is present. Multicollinearity render possibility to estimate each variable singular effect on the dependent variable. When present, it leads to underestimated significance tests This does not affect the model, but

the interpretation of each variable are made more difficult because the correlation between each independent variable make the distinction/demarcation in each variable less clear.

Odds ratio was used as the indicator to support judgment on differences and associations. The Odds is given by the equation:  $\text{Odds}_y (\text{percent of Odds}_x) = (1 - \text{Oddsratio}) \times 100$



## 4.0 Reviews of paper I-VI. Results

### 4.1 Review of Paper I: Long-Term Surgical Load in Patients with Ileal Pouch-Anal Anastomosis

**Aim** The aim of this observational study was to evaluate surgical load and complications in patients who had undergone restorative proctocolectomy, through long-term follow-up in one single institution with a smaller caseload than high-volume centres.

**Material and Method** From 1984 to 2006, 304 consecutive patients underwent IPAA.

All patients were prospectively followed on a regular basis. There were 186 men and 118 women. Age at surgery was 36 and 32 years, respectively. The primary indication was: Ulcerative colitis (280) including 79 patients having had fulminant acute colitis, indeterminate colitis (4), familial adenomatous polyposis (10), colorectal cancer (5), and mucosal dysplasia in ulcerative colitis (5). In the follow period seven patients with initially ulcerative colitis had the diagnosis changed to indeterminate colitis (2) and Crohn's disease (5). There were 182 stapled and 122 hand-sewn anastomoses. A protective loop ileostomy was established in 256 patients (84%), whereas 48 patients (16%) were operated without a covering stoma. Six surgeons operated 284 patients (range 21-78) and at least one of the trained surgeon participated in the remains operations. Observational time was mean 10 years (range 1-22 years).

**Results** There was no mortality related to the surgery or IPAA. Twenty-nine patients (10%) suffered from early anastomotic leakage/dehiscence and 10 patients had pelvic abscess. Two patients developed perineal fistulas from the leakage. Early pelvic sepsis was then 4% and overall anastomotic/pelvic early complications were 13%. Other early

complications were bowel obstruction (5), surgical site infections (4) and four haematomas.

A protective stoma did not prevent early anastomotic dehiscence ( $p=0.11$ ) or the number of pelvic abscesses ( $p=0.09$ ). Early complications required 20 laparotomies with creation of a diverting stoma in nine of the cases. There were 16 (6%) complications related to closure of the loop ileostomy.

The estimated removal rate of a functioning pouch at 20 years was 11% ( $CI \pm 6$ ).

Altogether 100 (33%) patients had one or more surgical procedures, excluding dilations of anastomotic strictures and closing of a loop ileostomy. These 100 patients underwent 187 surgical procedures. The estimated rate of a first re-operation due to complications was 52% ( $CI \pm 16$ ) in 20 years. Sixty-six of the 100 patients needed additional re-operations related to the IPAA procedure. There was created 29 secondary diverting stoma and sixteen had laparotomy. There were 19 redoes, 16 locally and three by laparotomy. Anastomotic dehiscence were sutured 22 times, there were 13 fistula revisions, 10 setons, 7 perineal abscess drainage and 3 others. Patients with Crohn's disease and indeterminate colitis had more late complications.

There were significantly more dilatation procedures in hand-sewn than in stapled anastomosis. Hand-sewn anastomosis did not have more complications or a higher failure rate than the stapled variety.

**Conclusions** More than half of patients operated with restorative proctocolectomy will need surgical intervention within 20 years and the failure rate is more than 10%.

Although excellent functional result can be expected in most patients, the high risk of complications and failure inherent in the procedure should not be ignored.

## **4.2 Review of Paper II: Long-term functional after ileal pouch-anal anastomosis – function does not deteriorate with time**

**Aim** There are conflicting reports regarding long-term function after ileal pouch-anal anastomosis (IPAA). The study investigated the influence of the interval from IPAA as an independent factor on long-term function and other factors influencing the functional outcome.

**Material and Method** Between 1984 and 2007 315 patients underwent IPAA and were followed by a standardised interview and endoscopy protocol at the out-patients clinic. There were 1802 interviews. 235 patients had three or more visits and these data were analysed by Time-Series-Cross-Section multivariate regression analysis. The mean time follow up in the analysis was 13.3 years (range 2-24) and the mean interval between visits was 34 months. This method was contrasted to the use of common long-term analysis as cohort studies and analysing on groups at different intervals.

**Results** Mean frequency of defecation was 5.2 in the day and 0.55 at night. This did not change with time. Daytime and night incontinence occurred in 13% and 21%. There was no change in incontinence, urgency, soiling or perineal excoriation with time. Diurnal and nocturnal incontinence never occurred in 87% and 78.5% respectively. Soiling was more frequent and experienced by 130 patients at daytime and 174 by night. Urgency was reported for 37 patients.

After 24 years the cumulative incidence of pouchitis was 43.5 % in 112 patients. The crude rate was 35.5%. Eighty-two per cent of pouchitis had its onset in the first five years. Twenty patients had chronic pouchitis (6.3%).

Pouchitis was the dominant factor, which influenced the functional outcome most. Early anastomotic complications increased the odds for urgency and soiling at night, whereas hand-sewn anastomosis increased soiling and the use of pads compared to stapled anastomosis. Otherwise, the factors as duration, gender, age at surgery, indications, surgical options and anti diarrhoeal medications had little impact on functional outcome. Patients having the diagnosis changed to Crohn`s disease in the follow up and without failure (2) had similar outcomes except to more soiling at night. Indeterminate colitis had more BM at night than ulcerative colitis.

In tables 5-7 (Appendix) the overall TSCS data analysis is given.

**Conclusion** The interval from IPAA did not influence the long-term functional outcome. Pouchitis influenced the outcomes negatively but did not contribute too deterioration with time. Other factor, gender, age at surgery, long term finally diagnosis, surgical options, early complications and medications did not influence the functional outcomes markedly.

### **4.3 Review of Paper III: Surgical load and long-term outcome for patients with Kock continent ileostomy**

**Aim** The aim of the study was to evaluate the surgical load and long-term outcome after Kock continent ileostomy (CI), in the same period when ileal pouch-anal anastomosis (IPAA) was the preferred surgical method for patients with ulcerative colitis (UC) and familiar adenomatous polyposis (FAP).

**Material and Method** During the period 1983-2002 fifty patients underwent a CI procedure. The surgical technique, with stapling of the nipple valve, was unchanged during the period. It is a single surgeon material. Follow-up included all patients. Follow-up time was mean 12 years (2-21).

**Results** Forty-eight patients had UC, two had the diagnosis changed to Crohn's disease and two had FAP. Twenty-two patients had 38 re-operations; four of which had their pouch removed (8%). Main causes for re-operations were leakages and intubations obstacles due to sliding of the nipple valve (42%), fistulas (29%) and stenosis (21%). Seventeen procedures (45%) were revisions of the nipple valve and the pouch, nine were local procedures (24%). The rate of re-operation was higher among patients having an ileostomy converted to CI than among those having primarily CI ( $p=0.016$ ). The risk of a second re-operation was higher for those re-operated within the first year after having a CI, than for those re-operated later ( $p=0.007$ ). The repeated revision was not associated with removal and conventional ileostomy. The revisions did not influence the duration of pouch. Sporadic pouchitis was successfully treated with antibiotics in eight patients and five developed chronic pouchitis of whom two had the pouch removed due to fistula and nipple valve sliding. The crude rate of pouchitis was 26%.

Stoma varicose due to portal hypertension in primary sclerosing cholangitis was locally operated successfully.

The continent ileostomy was intubated for emptying mean 3 times a day (1-5)

**Conclusions** Patients with CI accept repeated re-operations rather than conversion to conventional ileostomy. Pouch removal rate is low. Rate of removal is not associated with a high rate of revisions. CI is a good alternative to conventional ileostomy in patients not suitable for IPAA, failed IPAA or stoma dysfunction

#### **4.4 Review of Paper IV: Failed pelvic pouch substituted by continent ileostomy**

**Aim** The long-term failure rate of ilea pouch-anal anastomosis is 10-15%. When salvage surgery is unsuccessful or not possible most surgeons recognise the limits of surgery, and prefer and accept pouch excision or exclusion. A definitive ileostomy is created, scarifying 40 – 50 cm of the ileum. Conversion of a pelvic pouch to a continent ileostomy is an alternative that preserves both the ileal surface and the pouch properties – control of the emptying and continence.

The aim of the study was to evaluate clinical outcome after construction of a continent ileostomy following a failed pelvic pouch.

**Material and Method** During 1984 – 2007 317 patients were operated with ileal pouch-anal anastomosis at St Olavs Hospital. Seven patients with failed pelvic pouch had continent ileostomy. Additional four patients with failed pelvic pouches were referred from other hospital.

The patients were followed at the out-patients clinic and the follow-up was mean 7 years (0-17).

**Results** Seven patients had the pelvic pouch converted to the pouch of the continent ileostomy and four had the pelvic pouch removed and a new continent pouch constructed from the ileal segment. Two of the pouches were removed to fistula formation and failure. One patient needed a revision of the nipple due to loosening of the pouch from the abdominal wall. One patients who had Crohn`s disease had minor leakage and eight patients were continent.

**Conclusion** In patients with pelvic pouch failure, the possibility of conversion to continent ileostomy should be presented to the patients as an alternative to pouch excision and permanent ileostomy. The preservation of continence and a possible better body image are the potential benefits together with the maintenance of ileal mucosal surface. Construction of a new pouch on a new ileal segment can end up with additional small bowel loss and hence have malnutrition consequently.

## **4.5 Review of Paper V: Durability of Ileal Pouch-Anal Anastomosis and**

### **Continent Ileostomy**

**Aim** The failure rate, the complications rate and the durability of the continent ileostomy are considered inferior to the results from pelvic pouch surgery. The aim of this study was to compare the durability and failure rates in patients with continent ileostomy (Kock pouch) and ileal pouch-anal anastomosis.

**Material and Method** 317 patients undergoing ileal pouch-anal anastomosis and 63 undergoing continent ileostomy were evaluated in a prospective observational study from one single institution and in the same period (1983/ to 2007. Observational time (median, range) was 10.6 years (0–23) for ileal pouch-anal anastomosis and 14 years (1–23) for continent ileostomy.

**Results** Twenty-three pelvic pouches failed (8%) and six continent ileostomies (10%) were excised (ns.). Estimated failure rates at 20 years were 11.4% (ci  $\pm$  4.8%) for ileal pouch-anal anastomosis and 11.6% (ci  $\pm$  4.8%) for continent ileostomy (p=0.8). Sixty-five ileal pouch-anal anastomosis (21%) and 21 continent ileostomy patients (30%) had one or more salvage procedures. Estimated salvage rates at 20 years were 31% vs. 38% (p=0.06). The crude success rates of functioning ileal pouch-anal anastomosis and continent ileostomy were 92.8% and 90.5%.

**Conclusions** Success rates after ileal pouch-anal anastomosis and continent ileostomy are high. Their rate of failure is the similar. Salvage procedures are substantial with both procedures. Complications and failure after continent ileostomy are not inferior to those after ileal pouch-anal anastomosis. Continent ileostomy is still an option in patients for

whom ileal pouch-anal anastomosis is not suitable and in those with a failed pelvic pouch.

#### **4.6 Review Paper VI: Primary sclerosing cholangitis and extraintestinal manifestations in patients with ulcerative colitis and ileal pouch-anal anastomosis**

**Aim** Extra intestinal manifestations affect patients with ulcerative colitis and after pelvic pouch surgery the association between pouch complications and the diseases have been investigated with conflicting results. The association between pouchitis and primary sclerosing cholangitis have been established but the kind of association are uncertain. The aim of this study was to assess complications and functional outcomes in patients having ileal pouch-anal anastomosis for ulcerative colitis with or without primary sclerosing cholangitis or extraintestinal manifestations and to assess if primary sclerosing cholangitis is a risk factor for pouchitis

**Material and method** From 1984 to 2007, 289 patients underwent proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis. Mean follow-up time was 12 years and data was recorded prospectively. Eleven patients had primary sclerosing cholangitis, six had pyoderma gangrenosum, and twelve had arthritis or ankylosing spondylitis.

**Results** Early complications were similar for patients with or without extra intestinal manifestations. Functional outcomes were similar, but more incontinence among patients with sclerosing cholangitis was found. These patients had more frequent pouchitis, 5.25 vs. 2.72 average episodes of pouchitis ( $p = 0.048$ ), and more chronic pouchitis, 4/11 vs. 17/260 ( $p < 0.001$ ) compared to patients without adjunct disease. Neoplasm of the colon was more frequent in patients with primary sclerosing cholangitis, 4/11 vs. 4/260 in ulcerative colitis patients ( $p < 0.001$ ).

**Conclusion** An association between primary sclerosing cholangitis and chronic/severe pouchitis was found, but not with other extraintestinal manifestations. Functional results were good and alike in patients with and without primary sclerosing cholangitis. Primary sclerosing cholangitis is a risk factor for chronic pouchitis and is associated with neoplasia.

#### **4.7 Non published results: The aging of the pouch or aging of the patients? Does it affect incontinence in long-term observation after IPAA? (abstract)**

**Aim** Aim of study was to assess the influence of aging and aging of the pouch regarding the long-term affect on incontinence after IPAA.

**Material and Method** From 1984–2007, 315 had IPAA. All patients had a follow-up program with a standardized interview and endoscopy. All patients had recorded data on functional outcomes and surgical complications.

**Results:** Mean observational time was 13.3 years. In 2007 35 patients were older than 60 years, whereas seven were older than 70 years (i.e.; pouch duration between 13 and 21 years).

In a times series cross sectional multivariate analysis adjusted for age at operations, diagnosis, gender, early anastomotic complications, pouchitis, use of loperamid, hand sewn or stapled anastomosis, covering loop ileostomy, the frequency of incontinence did not change by time. (0.000/month.  $P>0.1$ ). Mean incontinence per week were 0.08 at daytime and 0.29 at night.

The frequency of incontinence at daytime after one and 15 years in patients older than 60 years were 2/25 and 2/16, respectively. In patients younger than 50 years the frequency were 10/166 and 2/46 respectively. The difference between the groups was not significant ( $p=0.66$  and  $p= 0.27$ ). The difference at night was not found significant either. Two patients out of 6 older than 70 years had incontinence after 15 years compared to 5 out of 46 younger ( $p=1.0$ )

**Conclusion.** We did not find that duration of the pouch per se influenced on frequency of incontinence. Univariate analysis of elderly patients having had the pouch in more than 15 years the frequency of incontinence was not increased. The possible impact of aging on incontinence among the elderly patients has not reached enough numbers of patients to conclude.

## **4.8 Some particular experiences**

- a:** Patients with clear psychiatric diagnosis should not be offered pouch surgery.
- b:** Patients with personality disturbances and especially related to body images are patients that should not be advised to undergo pouch surgery. Patients who do not have a consolidated view on gender are not candidates of the pelvic pouch surgery.
- c:** Patients who do not understand the mechanism and function of the nipple valve in CI or the pelvic pouch are not candidates to these procedures.
- d:** Patients who consider the operations as a solution to other problems or overestimates the benefits of the operations and/or do not understand the change in bodily function and lifestyle should not be candidates. The capability of the patients has to be assessed.
- e:** Patients undergone radiotherapy to the pelvic or the small intestine should be warned about complications and failures of pouch procedure.
- f.** Patients who do not produce adhesions in abdominal surgery have a great chance of nipple valve sliding and pouch loosening in CI and are at risk of failure.
- g.** Staples protruding into the lumen of the pouch or the anal canal in the follow-up period should be removed due to the possibility of harmful damage to the tissue.
- h.** Foreign bodies have been found and can cause irritating pouchitis and damage to the anal canal ending with stricture and fibrosis.



## **5.0 General discussion**

### **5.1 Methodological considerations**

There are no standards for how to produce knowledge and present results in the field of pouch surgery. Materials, methods and study designs differ considerably and most of the entities and categories used to analyse and present results are not universally defined.

There are myriads of definitions. Biases and confounders do exist. The results differ and are in many respects contradictory. It is reasonable to discuss some of the methodological issues that are found in the extraordinary huge number of publications of pouch surgery; issues that also involves the present study. Is it possible to make coherence and to bridge different results into one common understanding of the field of pouch surgery? This strive is the essence of all sciences.

In clinical medicine, randomized control trials (RCT) top the hierarchy of evidence-based knowledge, while “expert opinions” are at the bottom (Oxford Centre of Evidence Based Medicine: [www.cebm.net](http://www.cebm.net)). However, it is well known that in many fields of medicine and science randomized studies are not always possible; in surgery, even very difficult to accomplish. In surgery, different observational studies are the dominant method used, which is reflected by the fact that only 3.4 % of publications in leading journals are RCTs (Wente 2003).

Meta-analyses are seldom performed in pouch surgery due to the considerable heterogeneity in studies. It is difficult to undertake the methodology of a meta-analysis in aggregating data from non-randomized studies to perform the analysis. Reviews are frequent in IPAA. However, the problem concerns the conclusions drawn from the induction and deduction of different results, as the selection criteria and weighting of the

publications included in the reviews not always are made clear. Statements may end up in practical dogmas, locking the clinic. Furthermore in many publications there are factors, which are taken as preconditions or as granted that are not included in the discussion of results. In present study – the close rectal wall dissection and the aiming on very low-stapled anastomosis are examples of such factors that can be missed in reviews.

The hierarchy concept might give the impression that knowledge produced by observational studies is inferior to the results obtained from RCTs. Nick Black and others have challenged the concept of this hierarchy of methods in clinical studies (Black 1996, Concato 2004.) Knowledge obtained by observational studies can be of the same importance as randomised studies, but only if the methods are properly critiqued. RCT must also be critiqued, although this is easier and more standardized because of the possibility of extensive control over the variables and preconditions overt in the study design. In this way observational studies are regarded as inferior to all types of RCTs, due the necessity of comprehensive critical interpretations, although the end point of knowledge could be of the same significance. On the other hand, the preconditions in RCT exclude many patients, which in turn miss the heterogeneity of the real panoramas of the diseases that is studied. Furthermore, from the history of surgery it is well known that observational studies including few patients have had a great impact in advances in surgery.

### **Observational studies**

Observational study design can be prospective, retrospective or mixed. Data collections can be obtained in the same way. In long-term evaluations, different time series designs

are often conducted; the length and number of time intervals differ among the vast number of such studies. The use of only one time interval for long-term analysis is common in many of the leading publications. Often, a large number of patients, historically aggregated, are observed during a short period after surgery and this huge group is then compared with a smaller group of patients who were treated as the first patients in the study, but observed for a longer period of time. This constitutes selection bias. Historical changes in indications for surgery, patient inclusion criteria, surgical learning curves and other factors contribute to selection bias. Large numbers of patients cannot compensate for this bias.

In order to overcome selection bias, adjustments can be made by multivariate logistic and linear regression analyses. This has been done in studies of pouch surgery, although many statements have been made on basis of crude observational studies. The problem of such statements is that they constitute a surgical praxis, which in turn is the empirical basis for other studies confirming and freezing of actual surgical praxis. This is called tradition, which is fallible. Competitive and alternative strategies in surgery therefore enrich the accumulation of new knowledge. The history of pouch surgery is an example of accumulation of new knowledge by questioning procedures and tradition.

In observational studies the variables and the unobserved factors can be quite heterogeneous. Publications on pouch surgery often include continuous variables are dichotomized or made ordinal without giving the reason. The example of age demonstrates this. Age is often grouped into interval, which is not necessary since it is a continuous variable. Cut-off points may be more or less arbitrary. They can be valid because biological age has steps as it progresses, such as in young people and at the

menopause. Biological aging is not correlated with time in a fixed manner. Both the aging and the risk of co-morbidity differ considerably between individuals, as they grew older. Age is a troublesome variable in functional observational studies.

Other main examples: Observational time, which in nature is a continuous variable, is often grouped in wide intervals. Gender is another factor in this field. Without adjusting for gender and age at surgery in functional outcome analysis, the results changed in the present study.

In surgery, the surgeon is a variable, which is not standardized. The impact of the surgical skill is seldom analysed and is a confounder in the evaluation surgical results. This subject invites discussion (Koh 2006, Burns 2011).

Indexes and scoring systems of different functional outcomes is in use, but seldom. They are not universal and seem not to have been validated. They are used in long-term comparison. The results can be difficult to interpret because each variable that is included in the index/score can change without a change in the total index or score value. Using indexes and scores it is difficult to be sure that the factors do not influence each other. We find it more reasonable to investigate the factors separately.

Multivariate analysis cannot adjust for unobserved factors. The use of a propensity score to make groups comparable is done to overcome the impact of unobserved factors. The precondition is that the scores are linked to the possible distribution of unobserved factors that, from a theoretical point of view, can influence the results.

Cohort studies can overcome many of the problems associated with observational studies and some are published in the field of IPAA. A cohort can be

defined by the last observation or by the first observation. In the studies of Hahnloser (2004) and Bengtsson (2007), the cohorts were defined by the last observation in long-term analyses. This method has the disadvantage of excluding patients with failure and dropouts for other reasons. Prospective cohort studies can overcome this problem, but are not found in the pouch literature. Cohort studies can be paired, increasing the power of evaluation of the results.

The method of data collection can have an inherent effect on the data. Surveys undertaken by mail and telephone are common, and diaries can also be used. Interviews conducted by the operating surgeon or other dependent or independent clinicians, dedicated registrars, nurses or others, have advantages and disadvantages with respect to data reliability and feasibility, and even to the possibility of conducting a particular study.

Recall bias, respondent bias and reporting bias hamper observational studies and are reflected in the analysis and interpretation of results. Having to answer questions including “ever”, “never”, “always”, “often”, “sometimes”, “more than”, for example, are sources of interpretation difficulties.

Missing patients are a universal problem in any study. With discrete time intervals patient dropouts often occur, whereas this is a minor problem in studies without fixed intervals, where all patients potentially are available for assessment. It is unlikely that these missing patients in pouch surgery occur randomly. Deceased patients or patients with failures can easily be missed in observational studies. The number and impact of these dropouts depend on the number of intervals and the length of the intervals between observations in the study design.

The motivation for answering questionnaires varies between patients. This can be due to different functional outcomes. Also, it is likely that the decision to enter a follow-up programme is influenced by patient outcome, complications, discomfort and complainants, along with other factors such as: costs, travel expenses, accessibility, the added burden to patients of investigations such as endoscopies or blood sampling, and many other psychological and social factors. Even in optimal settings, patients with an acceptable function may have less interest in assessment and evaluation than patients with poor outcomes. The latter could even expect help and treatment, which may influence both response rate and self-assessment in describing their functional outcome.

In addition patients lost to follow-up, missing data hamper many observational studies. Underreporting of complications and problems gives rise to more favourable results. Missing data concerning functional outcomes may not be random, and sensitive data, for example related to sexual behaviour, may not be reliable. The psychology of answering more or less sensitive questions is a complex subject that influences the composition of questionnaires and their answers. The overall aim the composition of a questionnaire is to minimize the possibility that different questions will influence each other, giving rise to a hidden “skewing” of the results.

Many different methods are used to collect information and study data. In medical records, information is obtained according to standard information and information relevant for the purpose of a particular clinical setting. These data can be of varying quality, and not meant to meet the data requirements for studies. If such data are not adequate, or even wrong, the continuous medical chart will most likely come up with

new, corrected information. Missing data and/or inadequate data in medical charts is a well-known problem. Many studies collect data from medical records.

In standardized questionnaires, the quality of the collected data is not only dependent on the responders understanding of the questions asked, but also on the reporters understanding of the subject. The amount of missing data and the overall quality of the collected data depends on the reporter's qualifications and accuracy. This phenomenon has been documented in quality assessments of clinical surgery (Herbert 2004, Dindo 2010). The question of whether residents, consultants or other dedicated investigators (trained or untrained, dependent or independent) should perform follow-ups is debatable, and has to be outweighed by the possibility of running a study for more than 20 years. Data collection as a routine in practical surgery is possible to achieve with a high and adequate quality (Herbert 2004).

Publishing bias and tutor bias are general considerations that are relevant both to the interpretation of results and the conclusions drawn from observational studies. Favourable results are more likely to be published. The transparency in clinical practice and outcomes has generally been low and to relay a self-report does not seem to be sufficient, although it is indispensable. The era of national registry in several domains of clinical medicine and quality assurance is in its infancy.

In the huge amount of publications it is possible, to select results to support particular statements. Citation bias is likely to increase as the amount of published reports increases and also when differences in results increase. The presentation of data and results varies considerable and misinterpretations are not unlikely. To day more than 1400 publications are found at Pub Med using only IPAA as word reference.

In clinical studies, the number of cases included is a factor that in most studies influences the final results. Studies with large number of patients tend to have a higher impact on clinical practice than studies with fewer cases, regardless the quality of small studies. The statistical power of the conclusions drawn from a study is generally suggested to correlate with the number of cases. High volume clinics may even be more liberal in the indications for pouch surgery than low volume clinics. Factors like such can constitute differences in the results, which complicates interpretation and comparison of studies.

Reality does not always provide a vast number of cases, which would be preferred. How accurate are predictions drawn from studies with less than an ideal number of cases? In paper I and II, the number of reported IPAA cases is slightly greater than 300. Compared to other studies, the absolute number of cases included in this study is relatively small (10% of the leading series from the Cleveland Clinic). However, more than 1800 standardized interviews were available for analyses supplied with data from the medical records. The mean length of the long-term follow up is 13 years. This enabled us to conduct a robust statistical analysis. This is shown in the narrow ci in Tables 5, 6 and 7.

The problem with small size series is a particular concern in the study about CI and PSC or other EIMs. However, other studies have also only small series in these particular patients. It is therefore legitimate report these patients. Any kind of robust statistical analysis is not available if not the data are striking by itself. Caution in interpretation of the results should be undertaken. The experience has to be summed up for continuous scientific discussion. At present, this is the only method for clinician to

exchange experience and increase knowledge about these rare but challenging medical problems.

### **Study design**

This study was a single institution observational study. All surgical procedures were either performed or supervised by a senior surgeon. No institutional learning curve is expected because the senior surgeon had been performing the procedures included in this study for many years; since the pioneer days of pouch surgery. The surgical procedures evaluated in this thesis are thus very standardized. Six surgeons performed >90% of the pelvic pouch procedures, and at least one of these surgeons participated in all of the operations. Five surgeons performed more than 29 procedures over a 10 years period and more than 43 procedures each, which qualifies them as high volume surgeons according to conclusion from the UK study by Burns (2011). Helge E. Myrvold performed or supervised in the CI operations.

At the outpatient clinic, the surgeons filled out a standardized chart containing easy questions (Appendix). Other essential information was recorded in the medical records according to medical chart regulations as required by law. Sensitive question regarding sexual behaviour and satisfaction were often omitted in the clinical setting, and therefore were not included in the analysis.

The questionnaire used in this study focused on the present, and thus recall problems were minimized.

Information from patient admission record was obtained from medical records. All sources of information listed above constitute the basis of the data set used in this study.

The follow-up programme was designed to ensure the availability of prospective data on function and complications from all patients over long-term follow-up visits. In addition, this programme also ensured that retrospective recordings in the database were linked to consecutive registrations. At the end of this study, no patients were missing, and all patients were included in the follow-up.

Although the study questionnaire was not always completed, documentation could always be retrieved from medical records. In the Time Series Cross Section (TSCS) structuring of data and the analysis only data from the questionnaire was used. For patients with CI, no questionnaire was used, thus documentation from the medical records constitute all data in the database.

In paper II, many of the problems associated with observational studies were demonstrated. In this paper, functional analysis was performed using different levels of analysis to show that different levels give different results. If only a univariate analysis was done on group level comparing functional outcome in the first years with the outcome after 20 years we found a significant change in outcome. Analysing a cohort demonstrated no change in long-term outcome. The multivariate regression analysis employed in TSCS supersedes both of these methods and revealed other factors influencing on outcomes. The extensive number of outpatient follow-up visits and frequent contacts with the clinic resulted in a huge database of reliable data and enabled a robust analysis.

## Biases to be kept in mind when reading the published papers

### *Economic interests and institutional bias*

Although economic interests and their effect on results are the strongest bias in favour of publishing outstanding results, the Norwegian specialist health care system is not driven by economic incentives, neither at the institution level nor the level of a single surgeon performing pouch surgery. However, personal and institutional prestige can bias the results. This study was conducted after the retirement of one of the pioneers of ileal pouch surgery - H.E. Myrvold.

Recall bias phenomenon and a tendency to perceive better results in standard records are possible; however, more than 50 surgeons have filled out the standardized records. Four ETs provided valuable information on the complications and functional results. Based on the above, both economic and institutional biases seem unlikely in this study.

### *Status syndrome*

Gradients in health are associated with relative gradients in social status in communities. Although the latter may differ in egalitarian societies compared to societies with considerable social disparities, both give different outcomes with respect to patient health (Marmot 2006). There is even a gradient in the utility of the health care system concerning the treatment of patients with identical diseases that is associated with their socio-economic status (Jensen 2009).

The above mentioned phenomena may also have an impact on the functional results following pouch surgery. Therefore, selection bias based on social status in the recruitment of patients for pouch surgery may affect the results. These confounding

factors may contribute to differences reported between results from seemingly similar studies.

The Norwegian health care system includes all residents of the country, regardless of social or economic status. However, health and the use of the health care system are not equally distributed. It may be true that patients with a lower socio-economic status are less likely to have ileal pouches than patients with a higher socio-economic status, even in Norway, and that handling, coping and compliance of patients regarding ileal pouches may also differ in these populations. Recruiting potential candidates for ileal pouch surgery can therefore be biased in Norway, resulting in favourable outcomes compared to other societies. Although gradients are suggested to exist, in these studies, bias is not likely to have a substantial impact on the result, because of the free and open health care system and that the differences in social status is relative small compared to other countries.

The impact of socioeconomic and psychological conditions as a framework for pouch surgery has not been evaluated. The only related subject could be the study of Norwood (2009) that found that ethnicity had an impact on pouchitis. South Asian patients had a higher incidence of pouchitis (77%) than non-South Asian Caucasian (46%)

#### *Data acquisition*

In observational studies, where data, clinical considerations, suggestions, treatments and evaluations are more or less mixed together, particularly in medical records, the outcomes can be coloured. Hence, the method of data acquisition is not independent, but may be a dependent factor influencing the results obtained.

A thorough follow-up programme, as in this study, may offer patients better and earlier treatment for complications and functional disturbances, resulting in better long-term outcomes. The intention of the thorough follow-up programme is included as a part of pouch surgery treatment and the surveillance. The follow-up is thus an independent factor, and should not be regarded as a bias for possible improved outcome. This is not unique in this study; the concept of a dedicated pouch clinic is implemented at several institutions.

#### **Assessments and analyses, which have not been adjusted for in this study**

- The extent of ulcerative colitis was not included in the analysis of functional outcomes in IPAA patients. Pre-operative conditions in IPAA-patients were not controlled for when analysing the surgical complications. The extent of the disease (UC) has been shown to be a risk factor for pouchitis (Lipman 2011).

- During the first few years of the study, many of the patients were treated with steroids at the time of pouch surgery. The use of steroids has subsequently been shown to have a negative impact on surgical complications and so for pelvic pouch surgery too. The use of steroids was not included in the data analysis in this study because no patients were given doses > 20 mg, the steroid dosages were not always recorded and data may also be missing. Thus the impact of steroids is assumed to be minimal in this study. In the IPAA study 38 patients were record to be on low dose steroids at the time of surgery.

- The analysis was not been adjusted for co-morbidities, such as diabetes, cardiopulmonary diseases or other diseases. Three patients had diabetes. The effect of extraintestinal manifestation in UC on IPAA outcomes are reported and discussed in Paper VI. PSC and other EIMs were not included in the analysis of the other papers. No adjustments were made for malnutrition or disturbances in metabolism. Smoking habits were not recorded in the database and hence smoking as a risk factor for complications was not included in the analysis.

- Back-wash ileitis was not recorded in the database and was seldom recorded in the histo-pathological reports. BWI could be an unobserved confounder in the analysis.

- One, two and three-stage procedures have not been controlled for in a systematic way. Although different options were used in this study, the surgeon responsible decided which strategy to employ, and this decision was not the result of a prospective consensus protocol. Thus, the analysis only included the use of a protective loop ileostomy. In the IPAA study, 13 patients underwent a one-stage procedure. A total of 48 patients did not initially have a loop ileostomy.

- The different pouch designs used were not analysed. In IPAA, six patients had an S-pouch and 30 patients had a K-pouch. The J-pouch design was performed in 281 patients.

- Most females in this study who gave birth after the IPAA had caesarean sections. The method of delivery was no adjustment for; neither was any vaginal delivery before pelvic pouch surgery.

- The operating or responsible surgeon as a variable was not analysed or adjusted for. The quality-volume debate and evaluation of the learning curve have two levels: the institution and the single surgeon, while the operating team is at the intermediate level. In this study, the level of this variable was the institution level. The presumption in this study is that there was no learning curve during the study period because the surgical team had experienced tutor during all procedure. The skill and individual performance in the surgical field during an operation are not matters that can be fixed variables. At the very least, performance can be suggested as being bell-curved under the precondition of no learning curve. However, this is a matter of an extensive discussion about surgical skills, quality and surgical performance and several studies address this as main confounders of outcomes in surgery (Koh 2006, Kiran 2010, Burns 2010). Perioperative blood loss was not measured or analysed. Increased blood loss has been found to a risk factor for complications after IPAA (Kiran 2010).

- BMI was not measured at the time of IPAA or CI construction. Patients with overt obesity were not offered pouch surgery, but no absolute limits were given. No patients with a BMI >30 or >100 kg in weight were treated with IPAA or CI in this study. The BMI as a variable was not adjusted for.

- The indications for continent ileostomy are quite similar to the indications for IPAA. As IPAA became the method of choice for the surgical treatment of UC and FAP in the eighties, this had an impact on the selection, indications and frequency for CI. This impact was only suggested and was not possible to analyse in the present studies. The fact that failed IPAA was converted to CI in about 30% of cases is presented in paper I, but this fact was not analysed as a factor in paper of III or paper V.

- The level of the anastomosis above the dentate line in this study was not included as a variable under. The ATZ or the cuff was not measured. This may be a confounder when comparing studies because the level of anastomosis may differ substantially, particularly between hand-sewn and stapled anastomosis. The level of anastomosis is seldom given in IPAA studies, but is suggested by many to influence the rate of complications and the outcome. In this study the low rectum was transected 1-1.5 cm above the dentate line in the double stapling technique. Hand-sewn anastomosis included mucosectomy and was performed at the dentate line.

### **Statistical considerations**

Common statistical analyses that are often used to establish likelihoods of associations between entities were used in these publications. These were Pearson's chi square test and Fischer's exact test to compare proportions of attributions between groups, and the Student t-test and the Mann-Whitney test were used to compare differences in continuous variables between two groups. One-way ANOVA was used in paper VI to compare several groups when analysing differences in bowel movements.

The TSCS structuring of the data and the use of multivariate regression analyses (both logistic and linear) enabled us to utilize longitudinal data for each patient that had been accumulated since 1984 from standardized interviews during outpatient visits. The analysis was designed to analyse a few cases with several observations and provided a possibility of adjusting for different independent variables. The precondition was three or more observations per case, which excluded 80 patients. Ten patients had early pouch failure and the observational time for 35 was too short to allow three or more visits. These patients were not subjected to long-term analysis in TSCS. Thirty-five other patients did not attend at enough outpatient visits. They still have the opportunity to visit whenever they like and without cost. Many of these attended twice and we found that it was most likely that these patients preferred not to visit the outpatient clinics because they felt well.

Dealing with poorly defined clinical entities with no clearly demarcations, statistical analysis always had to be interpreted with cautions and since clinical surgery do exist the interpretation had to fit into the context of a more or less reasonable preconditioned ideas of the handling of surgical options. The other side of the statistical testing of hypotheses is the history of testing invalid statements, giving rise to the phenomenon of why true medical statements are continuously falsified. This is described by Ioannidis in several publications such as: "Why most published research findings are false?" (Ioannidis 2005). Testing different hypothesis in observational studies is hampered with great difficulties. Aggregating statistical significant results from different studies are subjected to the Bayesian correction, which stated by Ioannidis (2008) reduces

the significant of the results found. The interpretation of observational studies in clinical surgery is an exercise, which differs from testing of hypothesis in RCT.

Reviewing on one or all subjects regarding the clinic of pouches is difficult. The quality of each study in the high volume of publications is difficult to assess due to the different study designs in observational studies. All studies have their strength and weakness, and to compare and evaluate contradictions is a real challenge. To conclude and to make statements is a continuous audit that has to be critically undertaken in a free, unbiased society of surgeons and scientists – and with patients too.

## **5.2 Discussion of the results**

In the present study, two trends in pelvic pouch surgery were found. After a peak era during the nineties, the incidence of new pouches operated declined despite a suggested increase in the incidence of UC. The decline in IPAA operations is a general trend in Norway (Table 1), which others too have reported (Hahnloser 2007). A common explanation for this is the improvements in medical treatment of IBD and the lower risk of malignancy than previously anticipated. A different explanation could be that documentation of complication rates, failure rates and long-term functional outcomes may have reduced the enthusiasm for pelvic pouch surgery. The information resulting from the documentation reaches not only the informed physicians, but also the information-seeking patients. In addition, patient organisations provide patients with information and counselling. Thus, patients today have access to more or less balanced information and comparative experiences. The functional outcome, reduced QoL and the adverse effects of IPAA in a considerable proportion of patients may have become a nemesis for this procedure, in the same way that the knowledge of the flip side of CI contributed to the decrease in its use.

After the introduction of IPAA, the rate of CI operation has been a very low and constant rate. Our experience is that the patients are referred for CI on their own initiative based on acquired knowledge from the literature, the Internet, and information from other patients.

Another trend found was an increased age at surgery, similar to the result in other studies (Hahnloser 2007). The explanation is most likely the improved medical treatment options for IBD.

In the present study, there was also a significant age difference between the genders. Females are younger at surgery for IPAA. Rottoli (2011) analysed the Cleveland Clinic experience of 3407 patients and found similar results as well as a worse functional outcome and more failures among females. The suggested explanation of this phenomenon was that females might have a more aggressive form of UC.

The results for complication rates and long-term functional outcome in the present study for both IPAA and CI were within the same range and were similar to the results of many of the leading centres that define the standard of excellent results (Tables 2, 3, and 4).

### **Indications**

The proportion of preoperative diagnoses of UC was 92 % in IPAA patients, and 96 % in CI patients. Familial adenomatous polyposis (FAP) contributed with 3% for IPAA patients, and 4 % for CI patients. Colorectal cancer was a rare indication (1.6 %). These patients were selected based on age and the oncological treatments and prognosis. The surgery was oncological proctocolectomy. These carefully selected patients preferred pouch surgery instead of ileostomy.

### **Crohn`s disease**

Patients with known CD were not offered pouch surgery in the present study. Delayed diagnosis of CD was found in a few cases. This diagnosis is difficult to establish and confirm. Most cases are based on a clinical assessment of refractory complications associated with CD: fistulas, strictures, sepsis, and secondary pouchitis (Melton 2008),

with or without histopathological confirmation. Pathology reports often include “CD cannot be excluded” or “CD is likely”. The failure rate in under-diagnosed CD varies, but it is considered high (>50%). However, as the study by Melton (2008) and others reported, some of these patients have favourable outcomes after IPAA. Compared with the common rates of 5% - 10% of delayed CD (Hahnloser 2007), the proportion in the present study was low (1.7%). Therefore, there is most likely a higher proportion of concealed CD in the group of other IBD patients in our material. These patients may not have a poor outcome, but assessments are obviously not possible to carry out. There was no increase in early complications in those patients with delayed CD, but the complications related to CD appeared at a later stage. This was seen for IC too. The reason for this is that preoperative diagnoses indicated adequate preconditions for pelvic pouch.

Delayed CD in CI was established based on the presence of fistulas and skipped lesions in the intestine. This could suggest that CD in CI is not a *de novo* CD, but a true small intestinal CD. In pelvic pouch patients *de novo* CD, small bowel CD and diseased cuff could all be the source of delayed CD.

The results from the Cleveland Clinic (Melton 2008) indicate that extrapolating from high complication and failure rates in “delayed CD” to exclude known Crohn’s disease exclusively limited to the colon from pouch surgery is invalid. Kock (1980) was of the same opinion regarding indication for CI.

CD is a troublemaker in intestinal surgery. Pouch surgery is complicated and it is not easy to establish selection criteria for patients with CD. Today it seems that the surgeons hesitate to introduce CD into pouch procedures.

### **Indications for continent ileostomy**

Dysfunctional ileostomies are common and the conversion to a continent ileostomy could be reasonable and because other options are few. Dysfunctional ileostomy was the indications in 34% of the patients in the present study and mere inconvenience with their ileostomy in 46%. This is in accordance with the studies of Sjödaahl (1990) and Cohen (1982), where most of the patients wanted CI because of the inconvenience of ileostomy. Patients with a previous ileostomy had more complications than CI performed at the same time as proctocolectomy. Dozois (1981) reported a similar result. Part of the explanation for this may be the thickening of the intestinal wall seen after ileostomy. This might further increase the strength of contractions that enhance the risk of desussception of the nipple. A slim nipple seems to be more stable. It is commonly accepted that stripping the mesenteric fat off the intussuscepted part of the nipple not only facilitates intussusceptions, but also prevents late valve sliding. Males were more prone to nipple valve sliding. This was mainly due to them having more fatty mesenteric than females (Dozois 1981). Females may also have more stable nipples due to enhanced adhesions formation, which may reinforce the nipple valve construction.

Weight gain after proctocolectomy might result in a more fatty mesenteric mass within the nipple; which may contribute to nipple valve sliding in the long run (Denoya 2008). The indication for conversion from a dysfunctional ileostomy should not be restricted because of this association. On the contrary, more patients who suffer from dysfunctional ileostomies should be informed of the CI option. Obese patient was not offered CI in this study.

During operation for IPAA, it is sometimes not possible to perform the anastomosis due to technical or anatomical problems. In such a situation, Fazio (1988) argued that the CI should be an option for patients well informed preoperatively. This per-operatively conversion procedure was done for one patient in the present material.

With an incidence of failed IPAA between 10%-20% or more, the conversion of failed IPAA to CI could emerge as an important indication for CI and which could be a revival of the Kock procedure.

In a study by Lian (2009\*), 75 % of the CIs were created on a new ileal segment after removal of the pelvic pouch. In the present study, seven out of eleven patients had the pelvic pouch converted to CI with no intestinal loss. This is the preferred option when the pouch is not damaged by surgical release or disease. In the present study, the patients operated with primary CI and failed IPAA converted to CI experienced similar outcomes. About one third of the patients (7/25) with failed IPAA had CI. Pelvic sepsis, fistulas and cancer in the rectal remnant (cuff) might not necessarily be contraindicated to the conversion procedure. Preservation of the pouch is possible despite these causes of failure. If conversion is not possible a new CI can be constructed on distal ileum, but this option is debatable. If this again fails a substantial loss of small intestine will be the consequence.

Perineal sinus after excision of failed pelvic pouch is common and represents perineal morbidity (62%) (Karoui 2004). In the present study sinuses after conversion from IPAA to CI occurred less often than in patients with pouch removal (2/11 vs. 5/16). These sinuses were also easier to treat. This may be due to the meticulous surgical

technique for preserving the pouch in the conversion, or to the severity of the pouch complications, which led to the failure.

Half of the patients with failed IPAA were not suitable for conversion (14/25) due to CD, chronic pouchitis, severe PSC, pyoderma gangrenosum or psychiatric disorders. In these cases removal of the pouch and a conventional ileostomy are the only option. There are few studies of the conversion procedure, and those that exist have few patients. These studies report results that favour the procedure (Ecker 1999, Börjesson 2004, Lian 2009\*). We think it is reasonable to inform patients with a failed pelvic pouch about the possibility of conversion to CI. The competence of the informer is crucial. The need for further revision surgery, complication rates, the risk of losing additional intestine and the consequences if the procedure fails, are issues to be discussed with the patients. Many of these patients are extremely competent because they have already undergone several procedures before the failed IPAA, and have experienced conventional ileostomy for months or years. In present study, eight of eleven patients had 20 procedures and re-operations on IPAA even before the conversion procedure. This indicates that they tolerate a high burden of surgery and complications in order to restore continence. It is likely that a high proportion of the patients suitable to conversion would prefer the conversion procedure.

The arguments against the substitution of the failed IPAA with CI are often based on the same studies favouring the conversion procedure and claiming that the rates of complication, revision and failure are far too high in CI surgery.

Revision procedures must be anticipated in CI, also after a conversion. In the present study, two out of eleven patients required further surgery. Lian (2009\*) reported a

57.8 % complications rate with a 43.8% revision rate, and Börjesson (2004) reported revision in eight out of thirteen patients after more than 6 years of observation. No mortality has been reported after the conversion procedure. The complexity of revisions of CI is not more difficult than the primary construction and seems to be well tolerated by the patients (Denoya 2008). In contrast, the salvage procedure of IPAA is different from the primary IPAA construction, and the complications may be regarded as being more severe than in CI revision. In the present series the proportions of complications, salvages and failures were similar for CI and IPAA, but the types of complications are different and not directly comparable.

Pelvic pouch salvage can be performed. Major salvage procedures after failure occur at a very low rate, and only few centres have performed more than 100 (Baixauli 2004, Tekkis 2010). The second failure rate is tripled after the salvage procedure in IPAA. It is claimed that a salvage procedure could involve the construction of a new pelvic pouch. The potential loss of intestine after a second failure in this situation would be an argument for the alternative of the conversion procedure. We find it reasonable to inform all patients with a failed pelvic pouch about all aspects of salvage and about the option of conversion to CI. They are already known to the conventional ileostomy.

#### **Age and age at surgery**

Twenty-five patients were older than 60 years at surgery. When comparing this group of patients with patients younger than 50 years old, the rate of incontinence was similar and did not change in long-term follow-up (15 years).

Age at surgery (mean 34 years, range 13–65 years) was found to have some impact on function. The changes in outcomes were however of minor importance in this age cohort (Tables 5,6 and 7). The small changes found in BM and soiling may indicate that age has an impact in older patients at surgery. The natural biological effect of aging on body function does not occur in a linear manner. Extrapolation from these considerations may lead to a reserved attitude to offer old patients IPAA. The age limit is however not easy to establish exactly.

In a study, by Kiran (2011) the conclusion regarding functional outcome and QoL was that IPAA could be offered to patients irrespective of their age at surgery. The analysis was conducted on 23 patients older than 55 years at surgery who had had the pouch for more than 15 years. Burns (2011) concluded that being older at surgery was an independent risk factor for failure. Thus, the matter does not only concern having responders, but also how many old patients you have to treat to achieve pouch survival for more than 15 years in older patients, and to what expense of the failure and complication rates?

Ho (2005) reported excellent results for 17 patients older than 70 at surgery. These patients were healthy and had a significantly low BMI ( $21 \text{ kg/m}^2$ ). Highly selected and motivated older patients with compensatory favourable low risk factors may constitute a small population of older patients who could be offered pouch surgery.

Generally, we found no deterioration in pouch function for patients who have had the pouch for several years and who had passed 60 or 70 years in age. The number of these patients, however, is small. The suggestion of a synergy of deterioration due to long follow-up and the general aging process (Hahnloser 2007) for changes in incontinence

could not be supported by the present study. Sooner or later, the biological aging will influence the pouches. In the next decade, the long-term results of CI and IPAA in older patients will become clear.

### **Surgical options**

#### *To divert or not to divert*

In the present study, diverting ileostomy was established in relatively few patients. The operating surgeon made the choice during surgery without standardized criteria. Nine out of forty-two patients without a primary diverting ileostomy needed a defunctioning ileostomy in the postoperative period due to complications. This discouraging experience of the few patients without diverting ileostomy made us reluctant to omit the diverting stoma. This was also experienced in the study by Mennigen (2011), where six of thirty-three patients in the “no ileostomy” group had secondary ileostomy.

There were more thirty-day (early) anastomotic complications in patients without ileostomy than in those with (12/48 vs. 8/256), but at closure of the ileostomy, (mean 17 weeks) the rates were similar, even though there was a tendency towards fewer pelvic abscesses in patients with protecting ileostomy. In the study of Mennigen (2011), the rate of septic complications in patients with loop ileostomy was reduced. The comprehensive study by Rottoli (2011) indicated that the loop ileostomy reduced the serious consequences of anastomotic separation.

Many of the studies reporting on the issue, like the present study, were biased by the selection policy for omitting the loop ileostomy. In a study by Williamson (1997), it was a serious concern that the rate of septic complications was high in patients who

were routinely without a covering stoma. The only randomized controlled study (with 23/22 patients with and without ileostomy, respectively) showed no differences in the rate of septic complications (Groebler 1992). This study has been criticized for being underpowered. It is interesting to note that since 1992 no other randomized study has been conducted. Yet, many observational studies have been undertaken to determine selection criteria for omitting ileostomy. In practice, this is a general acceptance of the need for a diversion to protect the fragile pouch-anal anastomosis. In some patients, the anastomosis is not under threat, and some selection criteria have been found. The factors that should be considered when planning to omit the loop ileostomy are: age, female gender, no IBD, no steroids and a stapled anastomosis (Lovegrove 2011)

Potential septic complications of the pouch-anal anastomosis could be regarded as being more adverse than complications due to stoma formation and closure. Furthermore, septic complications from the anastomosis are easier to handle when a loop ileostomy have been established. In this study, the loop ileostomy seems to postpone the appearance of anastomotic dehiscence.

The complication rates of the closure procedure were dominated by bowel obstruction (6%) and anastomotic leakage and abscesses, which is similar to those found in other publications (Wong 2005).

It is possible to refine the closure procedure and reduce the complication rate to a minimum according to Wong (2005). When constructing a temporary loop ileostomy there is no need to suture the mesentery to abdominal wall, the intestine to the fascia, or to use a supporting rod. Scar formation is reduced and the closure is facilitated. The need for a rod is an indication of tension of the mesentery, which may lead to tension in the

pouch-anal anastomosis. Tension of the mesentery can also compromise the blood supply to the anastomosis. In our hospital rod was routinely used during 1980s and 1990s. The loop ileostomy was rotated 180° counter clockwise to lateralize the afferent loop to improve stoma function. This procedure can complicate the closure. Time to closure was mean 17 weeks in present material. Scarpa (2010) found that the number of complications increased with increasing time to closure. An earlier closure of the loop ileostomy could therefore be better. When diverting the faecal stream, the demand for blood supply to the intestine of the pouch is reduced, this then not will compete with the demand for healing of the anastomosis.

The effect of continuous drainage and repeated washout of the pelvic pouch in the postoperative period can help decrease the risk of leakages and their consequences. This praxis is a based on tradition only.

Theory, current literature and our experience suggest that the routine loop ileostomy must be regarded as a relevant safety precaution in pelvic pouch surgery. It will be continued in our clinic.

#### *Stapled and hand-sewn anastomosis*

Mucosectomy was performed with a hand-sewn anastomosis in most of the patients in the first decade of the IPAA era at St. Olavs Hospital. The overall proportion was 41 %. The results of the present study support the view that hand-sewn anastomosis is safe and comparable to stapled anastomosis. It is not inferior with regard to complication rates and long-term functional outcome (Lovegrove 2006, Mennigen 2011). In the long-term there were slightly more soiling and usage of pads among patients with hand-sewn anastomosis, but BM and incontinence were similar in the present study. No studies have

reported better results with hand-sewn anastomosis. In the review by Chambers (2007), the stapled anastomosis was found to have improved outcomes compared to hand-sewn. Some surgeons have performed stapled anastomosis in patients with FAP, CRC and other conditions where diseased or potentially pathological rectal remnants are left in situ (Kirat 2010). For those with the risk of serious disease of the rectal cuff it seems logical to perform mucosectomy. This is particularly important since mucosectomy can be performed with minimal risk of complications and good long-term functional outcomes.

Stapled anastomosis is the preferred technique because it is easier and faster. Mucosectomy and the hand-sewn anastomosis at the dentate line are preferred in patients who need as much as possible of rectal mucosa removed. In FAP patients, the risk of adenoma formation in the anal canal is reduced after mucosectomy (Roon 2011). The reflection given by Church (2005) is noteworthy because it takes the necessity of taking neoplasia formation in pouches in FAP patients more seriously.

Hand-sewn anastomosis with mucosectomy may be considered a different operation than stapled anastomosis. The length of the mesentery must be longer. The suture line is in the anal-canal, something that can disturb the anal structures. This in turn causes a higher rate of strictures. The procedure of mucosectomy can also damage the underlying smooth muscle. Furthermore, the hand-sewn anastomosis is under the influence of the striated muscles in the anal canal. The adequate length of the mesentery, which secures no tension and good blood supply, is seldom a problem when the surgical technique described by Goes (1995) is performed. Here both the ileal-colic artery and the right colonic artery arcade are preserved. The hand-sewn anastomosis usually requires the precaution of a loop ileostomy, which challenges the tension of the mesentery. All these

factors may contribute to the reported increased risk of complications and the worse functional outcome after hand-sewn anastomosis, but these factors may be compensated by proper surgical technique.

The lengthening procedure was adopted at our institution during the last six years. Araki (2006) from Paris proposed that this procedure could reduce the need of a temporary ileostomy. In the study, half of the patients needed ileostomy. Although the lengthening procedure prevents tension on the anastomosis, it may compromise the blood supply. The ileostomy may still protect a fragile anastomosis.

As mentioned above there are several situation were hand-sewn anastomosis is preferable including redoes. After misfiring of the stapler in attempted stapled anastomosis, hand-sewn is in the most cases the only option. Therefore, surgeons performing IPAA surgery must be familiar with both methods.

The different pouch designs were of special interest during the first decades of the IPAA era, but evolution has favoured the J-pouch because of its ease of construction and the reports on minimal differences in outcome between different pouch designs. In this thesis, we took these similarities for granted, and therefore it has not been possible for us to conclude otherwise on this subject.

Few studies have investigated the importance of close rectal wall excision. This method was the standard for the IPAA's performed in this study, as in many other studies (Meagher 1998). Patients with dysplasia or CRC were the exceptions. The decision to perform a total (or partial) mesorectal excision (TME) as the standard procedure is based on expert opinion. In the series of Michelassi (2000), excellent results were documented with mesorectal excision, but preservation of the mesorectum has also been reported with

good results (Walker 2008, Rink 2009). Preserving the mesorectum may reduce the risk of pelvic sepsis, by reduction of dead space. Preservation of well-vascularized mesorectum will also increase the surface for absorption. The risk of nerve damage after TME disturbing urinary and sexual function in both genders is obvious and documented (Kartheuser 1996, Panis 1996, Nyam 1997). It is also well known from rectal cancer surgery (Nesbakken 2000). The benefit of total or partial mesorectal excision for proctectomy in IPAA is general difficult to understand, if it is not for cancer or dysplasia because this dissection do challenge the nerves, the vesicula seminalis and the prostate. Time saving is in our opinion not a valid motive.

A study from Oxford (Lindsey 2001) did not reveal any significant differences in rate of impotence between close rectal and mesorectal dissection. At the Cleveland Clinic Gorgon (2005\*) described a technique for identifying the presacral nerves in a proximal mesorectal excision. The rate of male sexual dysfunction was low.

The discussion about mesorectal excision has to be raised as the laparoscopic approach is now gaining support for IPAA. The laparoscopic mesorectal excision in rectal cancer surgery has been shown to increase the nerve damage. This is a concern about the laparoscopic procedure (Ohatani 2011, Sartori 2011). The close rectal dissection of the rectum can be performed by laparoscopy, which is the experience from our institution. We find it therefore safe to perform close rectal wall dissection for proctectomy, open or laparoscopic.

It is worth mentioning that the preservation of mesorectum may reduce the morbidity after performing salvage or pouch excision procedures, because the mesorectum can protect the presacral nerves and veins.

## **CI construction**

The CI consists of a low-pressure reservoir provided with a nipple valve, which secures continence. The low-pressure reservoir was created by double folding of a split open ileal segment. By intussusceptions of the ileal segment used for the outlet an invagination valve is created which prevents leakage of faeces. The nipple valve has a natural tendency to desinvaginate resulting in leakage. This usually starts on the mesenteric side when the reservoir dilates. This event is the nipple valve sliding. The nipple valve is the weak point of the procedure and may occur in as much as 50 % - 60 % of the patients. During the years several methods have been advocated in order to stabilize the valve: cauterisation of the seromuscular layer of the intussuscepted segment, rotation of the two walls of the intestine forming the nipple valve, insertion of foreign material between the layers among others. Isoperistaltic versus antiperistaltic outlet has been tested, but no difference in outcome was found in the analysis by Nessar (2006). The current procedure of four rows linear stapling of the nipple valve with a special designed linear staple instrument was introduced in 1980 and has improved stabilization of the nipple valve considerably (Kock 1980\*, Fazio 1992). A study from Helsinki by Lepistö (2003) reported a reduced number of revisions and reduced failure rates in CI after the introduction of the stapling technique. In the present study, all patients have been provided with a stapled nipple valve and with no use of foreign material other than the staples. These facts are important when comparing old and new studies and for the interpretation of the history of ileal pouches.

Twenty-two patients were re-operated one or more times due to nipple valve problems and leakage. In spite of this most patients wanted to have the reservoir repaired,

having experienced the benefit of a stoma flush with the abdominal wall and no external ileostomy appliances.

The surgical solution for a permanently stable nipple has not been solved. Improvements in surgical options, such as the use of new foreign body materials or other types of nipple constructions, may reduce the incidence of nipple valve sliding. However, the low number of patients referred to CI makes it very difficult to do studies on new techniques.

In a primary CI the nipple is constructed with an isoperistaltic valve, and in the revision procedure with rotation of the pouch, the nipple is constructed using an antiperistaltic segment of the intestine. This changes in the nipple valve was not analysed in our present study, but as mentioned Nessar (2006) found no differences in outcomes for the two methods.

#### **Surgical load and complications in IPAA**

The mortality rate in IPAA is reported to be very low. No patients died postoperatively in the present material. Early complications required 20 laparotomies, and the estimated rate of surgical procedures related to the IPAA procedure was 52% in 22 years.

The estimated failure rate in the long-term follow-up of 20 years was 11%. The reason for failures was anastomotic dehiscence, fistulas and incontinence and in one patient refractory pouchitis. Besides complications, poor function with incontinence (4) or BM > 15 (2) required pouch removal. We regard a frequency of BM exceeding ten per 24 hours as poor functioning, noted as failure. Early anastomotic complications were associated with later complications, as was the case in the study by Lovegrove (2007) as

well as with failure. Early complication was found to negatively influence soling at night and urgency. The frequency of early anastomotic complication below 10% is consistent to the results found in other reports (Table 3). Four percent of the patients had early pelvic sepsis/fistulas.

One third of all the patients needed one or more additional surgical procedures due to complications. Of these patients, 21% had a salvage procedure. The surgical load is high and the rate and the panorama of complications were comparable to what is generally reported in the literature (Table 3). This should not be neglected when informing patients of the procedure.

The risk factors for anastomotic complications resulting in anastomotic separation, pelvic sepsis, fistulas, stricture and subsequent failure have been analysed in many studies. Factors that are possible to handle are the use of high dosage steroids (Heuschen 2002\*, Sagap 2006), the tension on the anastomosis (Heuschen 2002\*, Forbes 2009), diverting ileostomies (Mennigen 2011), pouch-related bleeding (Tekkis 2005), training of the surgeon (Kennedy 2006), and the use of the appropriate anastomotic technique, which is often the easier stapled anastomosis (Sagap 2006). Patient-related factors are delayed CD, IC, co-morbidity, high BMI (Nisar 2011) and previous anal pathology (Fazio 2003, Tekkis 2005\*\*). These elements can be considered as relative selection criteria for surgery.

All possible means have to be employed to reduce the risk of anastomotic complications. A well-nourished patient covered with antibiotic and thrombotic prophylaxis at the operation is mandatory. Meticulous surgery with minimal blood loss, a tension-free anastomosis with good blood supply is mandatory, and with no incorporation

of the posterior wall of the vagina or any other structures in the staple device. Protective loop ileostomy and drainage of the pelvis is favourable. The necessity of postoperative washout of the pouch is debatable, and has not been empirically determined.

At our institution, detected early separation was re-sutured before sepsis evolved in 29 patients. The patient was covered with antibiotics. The separation was diagnosed in the postoperative recovery period after patients complained of pain in the anal region. Pain in the anal region must be investigated in case of separation and/or sepsis. Ten patients had pelvic sepsis. Abscesses are treated with adequate drainage. Drainage can be performed by laparotomy, through the defect in the anastomosis or percutaneous. Persistent anastomotic sinuses are difficult to treat, and it is recommended that sinus should be treated before closing the loop ileostomy (Lian 2010).

The fistulas can appear at any time during follow-up. In this study, seton was often used to reduce the symptoms and to treat the sepsis of fistulas. Pouch flaps, pouch advancement or redoes by laparotomy was the next surgical procedure for fistulas originating at the anastomotic site. Fistulas to the vagina can be managed either from a vaginal route with flaps or from an advancement of the whole pouch (Burke 2001, Shah 2003). The success rates are between 79% and 52%. Cryptoglandular fistulas can be managed in the same way as among patients without IPAA.

The salvage algorithm is difficult to accomplish, and persistent fistulas and sepsis lead to failure. Failures caused by mechanical factors have better prognosis after salvage than those with a septic cause (Fazio 1998, Mathis 2009). Repeated attempts to treat complications surgically can be done. The recommendation by Gorfine (2003) is to start with local procedures. This approach was taken in our study. Most of the IPAA salvage

procedures are highly demanding procedures; but they can restore pouch function for many patients (Fazio 1998, Mathis 2009). The reported reduced function after septic complications and salvage procedures (Fazio 1998, Baixauli 2004, Remzi 2009) must be considered and discussed with patients when counselling them before further surgery. Although a high success rate of 79% was reported by Tekkis (2006), this rate does not seem to influence the newly reported increase in failure rate (16%)(Burns 2011).

Strictures were significantly more common after hand-sewn anastomosis, similar to what Prudhomme (2003) reported. Most strictures, as in the present study, are non-fibrotic and could successfully be treated by dilatation. Fibrotic and chronic strictures are due to ongoing pathological processes in the anal canal. When chronically inflamed fibrotic strictures, often with ulcers, fissures or fistulas occur, Crohn`s disease must always be suspected. The treatment can be repeated or continuous dilatation or evacuation of the reservoir by intubation. Damage to the sphincter and the anal canal will lead to failure.

The panorama of complications in IPAA is wide and range from common bowel obstruction and pelvic sepsis to infrequent complications such as foreign body inflammation of the pouch. Another example, the present material included one patient with pouch prolapse. The treatment was pouchpexy. Although the incidence of pouch prolapse is relatively low, Ehsan (2004) in a survey in US collected information on 83 cases. Fifty-two patients required surgery and in most cases the pouch were salvaged by a combination of transanal repair, abdominal pouchpexy and transabdominal revision.

### **Surgical load and complications in CI**

Revision surgery due to nipple valve sliding, the pouch loosening from the abdominal wall and fistulas was necessary in more than one third of the patients in this study. The success rate after revision was generally excellent, and the ultimate failure rate was 11% in long-term follow-up. The Cleveland Clinic reported a failure rate of 16.7% in 20 years among patients with UC and FAP (Nessar 2005). Thus, the result from the present study is comparable to the high volume centre (Table 2).

The revision procedure is comparable to primary construction and unlike redoes in IPAA; it does not represent a risk of damage to pelvic structures, which influences essential functions. In the present study, a relatively low revision rate was observed together with a relatively low removal rate. This could have been otherwise; high revision rates could produce low definitive removal rates. In the study of Lepistö (2003), a high revision rate (56%) was followed by a relatively high and long-term failure rate of 27%.

In the present study 44% of the patients needed surgical intervention. This is in accordance with reports in the literature that nearly 50% of the patients with CI will have to undergo re-operations (Lepistö 2003, Hoekstra 2008)(Table 2).

At the Cleveland Clinics 330 patients had CI. The rate of valve slippage was 29%, fistula formation 25%, pouchitis 26% and stomal stricture 10% (Nessar 2006). These results are similar to those obtained in the present study. A higher percentage of parastomal hernias (15%) were reported and the crude excision rate (22%) was higher than in the present study 0% and 8%. The material from the Cleveland Clinic was, however, more heterogeneous than ours since 73 patients had foreign body implants to stabilize the nipple valve, 42 patients had Crohn's colitis, and seven patients had the

Barnett continent reservoir. A total 44% of the patients needed surgical intervention at our institution

In the studies by Dozois (1980), Litle (1999) and Nessar (2006) they found previous operations were associated with a higher risk of re-operations after CI. A similar trend found in the present study supports this. In the present material, the patients who had had CI due to failed pelvic pouches or dysfunctional ileostomies had undergone several surgical procedures before CI (22 patients had had 80 operations). In spite of this experience, they chose to undergo repeat revision surgery in order to achieve continence. This indicates the competence the pouch patients have in making decisions concerning surgery and discussing conversion of the failed pelvic pouch. The complication rates, although high, in the present study seem to be tolerable for these patients, including the patients who underwent a conversion of a failed pelvic pouch. Many of the latter patients had also experienced conventional or/and loop ileostomies, which obviously influenced their decision.

### **Pouchitis**

According to the recent estimates in the cited literature, nearly half of the patients with IPAA will suffer one or several episodes of pouchitis. Pouchitis usually occurs within the first years after surgery. In the present study the 20 years estimated pouchitis rate was 46%, and 82% of the pouchitis appeared during the first five years.

About 7% will develop a chronic form. Pouchitis does not seem to evolve in non-IBD patients. In CI, the crude rate of pouchitis was 26% vs. 36% in IPAA. Chronic pouchitis may lead to failure, but it can be kept more or less silent with continuous treatment with antibiotics. Pouchitis has known deteriorated functional symptoms

(frequent BM, incontinence, soiling and urgency with protracting defecation and protective pads at night). Episodes of pouchitis do not seem to be associated with a general deterioration in long-term functional outcome. Normal function is restored after treatment with antibiotics. Although pouchitis is easily treated in most cases, the prevalence of the symptomatic disease varied (6% – 15%) at each regularly outpatient visits. The successful treatment of pouchitis with antibiotic supports the concept of a disturbance of the bacterial flora of the pouch.

In this study, only a small number of patients had PSC or EIM. An association between severe/chronic pouchitis and PSC was indicated. This association has also been reported by others (Penna 1996, Aitoloa 1998, Abdelrazeq 2008, Lepistö 2008, White 2010). One may consider a common constitution for PSC and pouchitis. The use of a strict definition of chronic pouchitis could compensate for the small number of patients in studies dealing with these associations, which was done in this study. The lack of consensus concerning the definitions of different types of pouchitis is a recognized problem in the study of this and other issues of IPAA. PSC is a rare disease; there are few studies in pouch surgery with few patients included. PSC is diagnosed by different methods giving different rates and ages at diagnosis. Age at pouch surgery differs considerable in these few studies, and in most of these, the PSC diagnosis is established after IPAA surgery. To adjust for these factors and many others, only a multicenter study design would secure a sufficient number of patients. This concern regards also the studies on EIMs and other rare diseases that may interfere with ileal pouches.

In a recent study from the Cleveland Clinics (Lipman 2011), pouchitis was predicted by several indicators: the extent of UC, pulmonary co-morbidity and including

rheumatic joint affection. The severity of pouchitis seems to influence the severity of joint symptoms (Hata 2003).

Pouchitis constitutes a new and common iatrogenic inflammatory disease with unknown etiology in the IBD family. It will affect half of the patients with IPAA and carries the risk of relapse and developing into a chronic form.

### **Extraintestinal manifestations**

Despite a deteriorated function in PSC patients with pouchitis, patients with PSC, pyoderma gangrenosum or joint manifestations had similar functional outcome as other patients operated on for UC. This supports the results of other studies (Kartheuser 1996\*, Gorgun 2005, Mathis 2011).

The crude pouchitis rate in the study by Mathis (2011) was high. After five years of observation in patients with PSC at surgery the crude pouchitis rate was 64%. The rate of chronic pouchitis was also high (16%) with the mild form occurring only among 8% of the patients with PSC, and recurrent pouchitis affecting 40% in the first five years. These high figures seem to be compatible with a suggested association between PSC and severe/chronic pouchitis.

The association between PSC and severe/chronic pouchitis is reasonable although the studies are few and include few patients. Among these, Gorgun (2005) reported 65 patients; Lepistö (2008) 52 patients; Penna (1996) 54 patients; Aitola (1998) 10 patients and Hoda (2008) 14 patients. As mentioned, it seems therefore necessary to perform international multicenter studies on the association between PSC, UC and pouchitis. Consensus on strict definitions has to be established in well-designed study.

Portal hypertension causes varicose veins at the skin level in CI and conventional ileostomy, but does not appear in the pouch-anal junction. Treatment of varicose bleeding in CI can be troublesome. Two patients at our institution have been successfully treated by debridement of the connecting veins. In patients with known PSC, IPAA is the preferred option advocated by Mathis (2011) from the Mayo Clinic. This is due to the risk of harmful and life-threatening bleeding from stoma varicose. The study by Kartheuser (1993) he concluded that PSC was not associated with perianastomotic bleeding in IPAA and hence that the option is safe. This is in accordance with the common experience that haemorrhoids are seldom seen or are absent after IPAA in patients. Documentations on haemorrhoids is however absent in the literature.

Patients with PSC should be informed of the increased risk of pouchitis after IPAA.

Patients with PSC have an increased risk of different neoplasia. The need for mucosectomy in PSC patients has not been established (Kariv 2010\*). It seems reasonable to offer these patients dedicated surveillance by endoscopy and additional appropriate scans at the regular visits to the outpatients pouch clinic.

### **Functional outcome and the long-term assessments in IPAA**

#### *Functional outcome*

Functional outcomes are divided into several domains; BM, incontinence, seepage/soiling, urgency, the use of pads, perineal eczema/soreness/irritation, the ability to distinguish between gas and stools, and medication to regulate functional outcome. Other functions such as the consistency of the stools, evacuation problems and sexual disturbances were not analysed in this study.

The definition of long-term follow-up varies considerable between different studies, and few series have mean follow-up times of more than 10 – 15 years. Some authors report deterioration of function with time after surgery (Table 4). In the present study the mean time follow-up was 13 years, and no time dependent deterioration in function was found.

### *Bowel movements*

The frequency of BM at day (5.5) and at night (0-1) is a commonly reported result. It has been documented in many studies despite the vast difference in methods of assessment and data collecting (Table 4). Studies that have recorded substantially higher frequencies may reflect a real difference in poor outcomes. The BM parameter is sometimes referred to per 24 h, which is inferior to the distinction between day and night. Waking up during the night is of interest when understanding pouch functioning and its impact on everyday life. Frequency of BM more than seven at day and one at night decreased the QoL significantly in the study by Røkke (2011\*).

The improvement in BM during the first year is reported in many studies, including the present. It supports the idea of an adaptation of the pouch and its function. The idea of a stable interacting relationship between pouch volume, pouch pressure and resistance (anal-canal resting pressure) some time after surgery, is likely. The stability of BM found supports this concept.

The design of the pouch could have influenced the BM. Some studies suggest that the K-pouch and the W- and S-pouches reached a stable level of BM at an earlier time than the J-pouch due to their initially larger volume (Öresland 1990, Lovegrove 2007).

When converting the J-pouch of a failed IPAA to a continent ileostomy, the frequency of intubations did not differ from the Kock-pouch in primary CI. The frequency was 3 – 5 per day, which was less than the frequency of BM in IPAA. It is most likely to claim that it is not the pouch design, but rather the environment of the pouch in the pelvic, that affects the BM. The design or the patterns of peristalsis seem not to be of much importance for the frequency of BM or intubation rate in the long run.

In the recent study on the long-term functional outcome in IPAA by Kiran (2011) from the Cleveland Clinic, the authors mentioned the problems of evaluating long-term function in their own previous studies and in others. In that study, which only included patients who had had a pouch for more than 15 years, they reportedly overcame the problems mentioned. The study identified 584 from their database of 3276 patients. Forty-two patients were deceased and 56 had failed IPAA, and after excluding 90 missing patients, 396 cases were analysed. These patients were divided into three groups according to age at surgery (<35: 189 patients, 35-55: 184 patients, >55: 63 patients). Time-dependent observational data points on function were divided into three groups: 4-6 years; 8-12 years and 12 - 18 years after surgery. The level of analysis was on groups.

For all patients the BM decreased from 5.8 to 5.5 from 5 years to 15 years after surgery ( $p=0.001$ ). At night BM increased from 1.4 to 1.8 ( $p=0.001$ ). No change was observed among patients older than 55 years at surgery. When these patients were asked if they had incontinence or urgency the percentage who answered “no” decreased significantly ( $p=0.001$ ); 71% to 37% and 52% to 40%, respectively. The conclusion was that a gradual deterioration occurred (Table 4). This was based on the results of various changes in BM during the day, improvements in seepage at night, the slight increase of

pad usage, the fact that seepage during day was stable, and that the rate of incontinence increased. The deterioration was not deemed essential whilst the conclusion was that patients having had the pouch for more than 15 years had acceptable functioning and QoL.

The changes in BM were almost identical to those found in the present study; there was no substantial change over time or between different age groups at surgery.

### *Incontinence and deterioration of functional outcomes*

For incontinence, which has been shown to negatively affect QoL (Lovegrove 2010), the Cleveland Clinic study (Kiran 2011) found deterioration in the long run. The QoL was stable. In the present study, 16 patients older than 60 years had had the pouch for more than 15 years. Only two of these reported incontinence. This rate did not differ from the rates of incontinence in younger patients.

Why are there differences in the results, in the conclusion concerning incontinence and urgency and in the question of gradual deterioration? Although several patients had experienced incontinence or urgency with time, this does not necessarily mean deterioration of incontinence in the long run for the single patients. The likelihood increases with time for an event to happen. Answering a question about incontinence after 20 years might be different from answering it after 5 years after surgery. Prevalence and incidence provide different rates, but deterioration is a different matter. A gradual deterioration is a permanent and increasingly negative change for the individual patients. This phenomenon was not found in the present study.

In the study from Cleveland Clinic/Imperial College London (Lovegrove 2010), deterioration as a function of the length of follow-up was found for incontinence (both major and minor) and urgency, but not for BM. In the follow-up, a decline in QoL was found. The aim of the study was, however, to construct a scoring system for functional outcomes that influence the QoL. Incontinence was the single factor that affected the QoL most. In the study of Tulchinsky (2009), no deterioration in function was found, but QoL decreased with time, in contrast to the results cited above (Kiran 2011, Lovegrove 2010). The paired cohort study of Bullard (2002) reported stable functional outcomes except for incontinence, which increased with time. The authors concluded that functional outcomes deteriorated with time (Table 4).

The paradox in the relationship between duration and functional outcome must have to be found in different study designs, different definitions and the lack of adjustment to factors that certainly affect the outcomes. There may be a difference in analysing time (duration) as a factor in the same manner as other factors influencing the functional outcome, and analysing changes in time. For example will the rate of pouchitis increase in the follow-up and the prevalence is likely to be higher at later points in time than at earlier ones.

It might be more likely that the functional outcome is stable, but that living with this functional strain gradually tires the patients. This will manifest itself as decreased QoL (Tulchinsky 2009). It is less likely that functional outcomes deteriorate and that the patients adjust to the situation and report stable QoL.

Both in the study by Kiran (2011) and Hahnloser (2004), patients with failure were excluded due to the study design. These patients obviously constituted a selected

group concerning outcomes, and it is likely that the rest of the missing patients were not random either. Kiran refers to the explanations of the deterioration of incontinence put forward by Hahnloser: a decreased sphincter functioning with age, which is suggested to occur after vaginal delivery, and the phenomenon of increased irritable bowel syndrome with age were the explanation factor. The caesarean rate in IPAA is high and vaginal delivery as a factor might be adjusted for in the analysis together with gender. Rottoli (2011) found no difference in failure rate between nulliparous and women who had one or more deliveries. This is not to be expected if the suggested explanation of deterioration by Hahnloser is valid. The review and meta-analysis by Pretlove (2006) oppose the explanation for deterioration of incontinence. In the general population, no deterioration of incontinence occurred among people younger than 60 years, irrespective of gender or deliveries. The aging of the patients seems then not to be a cause for deterioration found in some of the studies.

Females in the present study reported more urgency than males, but not as time-dependent. The incidence of IBS may increase with age, but the syndrome also has other names such as “irritable colon”. The prevalence of the entity of “irritable pouch syndrome” may contribute to the interpretation of these results but has not been investigated as time dependent (Shen 2002).

The prevalence of incontinence was stable and ranged between 2.1% and 6.1% during the day and 6.3% and 11.4% during night. Diurnal incontinence affected 45 patients during the day and 68 at night. Soiling occurred in the same manner, but more patients were affected: 130 during the day and 174 at night. These distributions are common in many reports. However, in the study of Hahnloser (2004) the rate of

incontinence was considerably higher, with a frequency increasing from 19% to 45% between the 5th and 15th year of observation. At night, the frequency was 53% and 76%, respectively. This huge difference is probably due to the definitions of incontinence and the lacking distinction between incontinence and soiling/seepage. To differ between soiling and incontinence seem to be appropriate.

If incontinence increases with pouch duration it could be noted by an increase in the frequency of BM. Patients may prefer to increase the frequency of emptying as a compensatory defence mechanism to avoid the consequences of incontinence. This phenomenon may have been present in the study of Hahnloser (2004), but not in the UK study by Tekkis (2009).

### *Urgency*

The crude prevalence of urgency showed a tendency to increase at each time point, but when adjusted for other factors it remained stable. The prevalence was 3.5% after the first year and 8% after 15 years. Urgency was more pronounced during episodes of pouchitis. Patients who had early anastomotic complications also had more urgency, and females reported more urgency than males. In the study by Rottoli (2011), this was documented. Females have a shorter anal canal and anastomotic complications interfere with the anal function. Patients with urgency used significantly more regulating agents such as loperamide (Table 7). Urgency can be regarded as the threshold of sensation and reflexes in the pouch-anal junction. The definition of urgency in IPAA is commonly shared in most studies to be the ability to defer emptying of the pouch for more than 30 minutes. Despite a clear definition the rates of urgency differs (Table IV). The question may affect

the answer. The unpleasant feeling of the need to defecate may interfere with the recall of time assessments. Thirty minutes is a psychological variable rather than a chronometric one, as are the recall and the time interval. Urgency can be taken as an either-or variable or as an ordinal or continuous variable within a time interval. In the UK-study by Tekkis (2009), the rate of urgency and seepage increased, whereas urgency was found to be stable in the study by Hahnloser (2004). Strangely, Erkek (2007) reported a remarkably high rate of urgency (~ 50%) among patients with FAP after five years.

Urgency is a very disturbing functional morbidity, and the rate seems to be at a low level. In the study by Lovegrove (2010), the impact of urgency on the functional score was rated as low and at the same level as the need of using antidiarrhoeals.

#### *Relationship between functional outcomes*

The frequency of BM may be seen as a function of the resistance (anal-function), the volume (pouch) and the pressure (peristalsis), incontinence as a function of a lower pressure in the anal canal compared to the intraluminal pressure of the pouch. Urgency may be seen as a threshold sensation of alterations in volume and/or pouch pressure relations. In an excellent paired cohort study by Bengtsson (2007), BM, incontinence and urgency were linked to alterations in manovolumetric assessment. The anastomosis was all hand-sewn after mucosectomy in 42 patients. The median age was 54 years (range 34-76) after 16 years of follow-up. Incontinence (soiling) and BM increased from the 1st to the 16th year of follow-up, and the prevalence of urgency increased from 4.7% to 19%. The rate of diurnal soiling increased from 8/42 to 16/42. The anal canal resting pressure increased, the squeeze pressure decreased, but the volume of the pouch at 40 cm H<sub>2</sub>O did

not change. The pouch volume was stable and the threshold sensation of urgency decreased both as a function of volume and pouch pressure. The first sensation associated with increase of volume or pressure decreased – *ie.* compliance decreased.

If the frequency of the emptying of the content of the pouch increases, both by increased BM and incontinence, one would expect a decrease in pouch volume – this was however not found in the study by Bengtsson (2007).

One would expect that an increase in resting pressure should be reflected in a decreased incontinence rate, especially at night. This was not shown, but more patients suffered soiling after 16 years. Several studies report increased incontinence during night. The increase in daily incontinence and soiling was not followed by an increased use of pads in the study by Bengtsson. Contrary to what could be expected, medication to improve functional outcome decreased. The rate dropped considerably, but the use of loperamide was mentioned as stable. Thus, it seems unlikely that the patients in the study stopped medications if this was associated with a worse outcome. The agents are inexpensive and have low rates of adverse effects. Patients often implement restrictions and changes to dietary and eating habits to control evacuation. Thus, lifestyle modifications are common adjustments that patients and people accomplish for better functional outcome.

A possible explanation for the relationship between BM, incontinence, urgency and the manovolumetric results seems to be a presumption of an alteration in the follow-up time of the sensation and the neurological aspects of pouch innervations and their relationship to anal-canal physiology. The aging of the patients is therefore the main contribution to the idea of deterioration. This, however, seems unlikely in this cohort of

healthy young and middle-aged patients, and the idea contradicts the mentioned results reported in the meta-analysis of Pretlove (2007) concerning the prevalence of incontinence and aging. The rate of incontinence in the normal population was similar between genders, but increased in the group older than 60 years of age. In addition, the increased rate was related to increased morbidity.

Another explanation could be that the pelvic pouch and the small intestine undergo a continuously morphological change as a consequence of the obstruction. (A thickening of the small bowel wall is seen in patients in the conversion procedure for failed pelvic pouch). These changes may be a response to the collecting pouch and the continence; a response that in turn overcomes the obstruction, resulting in more incontinence and increased BM. This “theory” suggests an “aging” of the pouch.

On the other hand, if the functional outcomes are stable, as shown in the present study as well as in other ones, the results of manovolumetric might possibly be more comprehensible, since volume and resistance was both stable, which was the case in the study by Bengtsson (2007).

The results on these subjects in the literature are contradictory. For example, the use of pads decreases when incontinence increases. Bowel movements increases when patients decide to the use of antidiarrhoeal medication less. In observational studies, the empirical results have to make sense both in theory and in common sense.

The physiology of the normal pelvic floor is complex and poorly understood, particularly in functional disorders and recto-anal diseases. The relationship between functional outcomes, compensatory adjustments, regulating agents and pelvic floor

physiology is even more complex after pelvic pouch surgery. The anatomy is changed considerably; as are the length of ATZ and the length of the cuff.

Pouchitis deteriorates most of the functional outcomes. In the study by Bengtsson (2007) a history of pouchitis did not influence the long-term results. This is supported by the present study; pouchitis does not influence long-term functional outcomes *per se*. This is may not be a surprise seeing that other acute, time-limited inflammations elsewhere in the body seldom impair functions permanently.

### *Gender*

The impact of gender on complications and functional outcomes was studied by Rottoli (2011) in 3646 patients. Females had more BM and reported more urgency than males. They also used more pads and experienced more soiling. This was not related to vaginal deliveries or to an impact of hand-sewn anastomosis. In the present study urgency and the use of pads was significantly increased in women relative to males in a multivariable regression analysis. The anatomic differences and the perineal function can be the causes of the difference between the genders, especially in the use of pads. In addition, it is not unlikely that differences in toilet habits can account for differences in reported functional outcome. The worse functional outcome in females was not reflected in a reduced QoL compared to males in the study by Rottoli.

### *Other functional outcomes*

In the present study, the use of loperamid was associated with soiling, urgency, the use of pads and a slight increased in BM. The fall in BM did not reach the average rate, but the

BM rate was stabilized at an acceptable level. The use of loperamid reflected the intention of use, and no strange association was found in the present study.

Perineal soreness could be regarded as a consequence of the frequency of exposure to irritating agents and the defence mechanism of the skin barrier. The frequency of BM and incontinence affected the rate of incidence of eczema, but eczema was not affected by other factors (Table 5). The composition of small bowel contents, the cleaning of the perineum and the tenderness of the skin are likely to interfere with this rate. It is likely from the present study that the pelvic pouch function by it self triggers perineal eczema. The irritating small bowel contents may indirectly and directly affect the squamous epithelium of the anal canal and the skin by effusion.

EIM and PSC did not influence the functional outcome *per se*. Ongoing pouchitis influenced the outcome, which was more frequent in PSC patients. The studies by Kartheuser (1996\*) and Gorgun (2005) found no risk of deteriorated function associated with PSC. The experience from the Mayo Clinic (Mathis 2011) confirms these results. The association between functional outcome and other EIM is less well investigated, and the present study did not indicate an influence of EIM on function.

#### **Comparing the CI and IPAA and the durability of the ileal pouches**

In this study, the durability and the salvage procedures of CI and IPAA were compared. The failure rates were similar but the salvage rates were as higher in CI than IPAA, although the difference did not reach significance. The overall surgical load did not differ, but it obviously did differ in quality. This comparison faces many difficulties. Randomized studies are not possible and case mix selection is obvious. End point studies

in QoL can indicate which of the surgical options should be preferred, but QoL studies are few and difficult to interpret (Køhler 1991, Hoekstra 2009).

In the long-term study of median 30 years from Gothenburg (Berndtsson 2004), the functional outcome and the QoL in patients having CI was concluding to be stable. In different studies concerning IPAA, they conclude that there is deterioration in functional outcome after IPAA (Bengtsson 2007, Berndtsson 2007). Incontinence, which is a lack of control, affects many of these patients with pelvic pouch.

Salvage can be defined as all procedures aimed to restore function at an acceptable level. A definitive defunctioning is the end stage of pouch failure. The estimated salvage rates did not significantly differ between CI (38%) and IPAA (31%) during an observational time of more than 20 years. The removal rates in patients with no attempt of salvage procedures were similar in IPAA and CI; 6/25 and 2/6 respectively, and the estimated definitive failure rate was equal. Lepistö (2003/2004) found great differences, but the study design and the material were different from that of the present study. However, pouch and nipple valve revisions are anticipated procedure in CI, and the revision is almost technically equal to the primary construction (Denoya 2008). Denoya made the same conclusion. In IPAA, this is not the case; salvage is due to more or less avoidable severe complications that harm the pouch and, in most cases, the anal canal.

Comparing functional outcomes between IPAA and CI is difficult. Frequencies of emptying, urgency, incontinence, soiling, intubation difficulties and other functions related to the pouch differ. The meaning and experiences of functions are quite different, and the method for comparing these is to perform QoL studies. It is worth mentioning

that about half of the IPAA patients need medications to improve functions; this is seldom necessary among CI patients.

### **Final consideration**

Comparisons are necessary to gain experience that can be communicated to patients providing a basis for a fair choice of different surgical options for reconstructions after primary surgery and failures. In pouch procedures, the surgical load and complications are considerable. Patients need to be able to understand the consequences of different surgical options and to be compliant with treatment strategies. The surgeon needs to inform the patients about advantages and risks related to pouch surgery. This is mandatory in primary pouch surgery and particularly challenging in salvage and revision surgery. If this is not done, pouch surgery should not be done.

In 1988, Vernava expressed the concern that the pelvic pouch option would shadow the option of CI and that CI could be forgotten as an option for patients not suitable for IPAA (Vernava 1988). In the same year, Victor W. Fazio repeated this concern. He found it “ironic” to exclude CI from the surgical repertoire due to the success of IPAA when CI, after 15 years of evolving, had achieved excellent results (Fazio 1988). This present study revisited these reflections after 20 years. Today the long-term failure rates, complication rates and functional outcomes in IPAA are known. We find the 30 years old reflections highly relevant today.

In spite of the concern about complications, the overall functional outcome in both CI and IPAA is favourable and offers these patients a life without the inconveniences of conventional ileostomy. When serious complications occur in pelvic

pouch patients, the option of a conversion to CI should be discussed with the patients, as should the adverse incidents that can affect all the available alternatives.

## **6. Clinical implications**

The indication for pouch surgery maintains to be UC and FAP. Patients with possible CD are not easy to identify when diagnosis states UC or IC. Known CD has not been investigated in this study as an indication for IPAA or CI. Young patients with CRC or other condition in need of proctocolectomy may be offered pelvic pouch surgery in a greater extent than to day's very low incidence.

In all kind of functional surgery the information on surgical load and long-term functional outcomes are of considerable importance. The comprehensive data on these issues provides a solid basis for consistent information and discussion between patients and the surgical team including ET. The risk factors are in general figured out and studies like this make it possible for the patients to get information about the institutional results and experience.

The main finding in the study was the stability of functional outcomes after a short period after surgery. These results are to be communicated to the patients as a factor in the decision making for IPAA.

The study of pouch surgery at St. Olavs Hospital states that it is uttermost important to avoid anastomotic and pouch related complications. This is obvious in all kind of surgery, but in pelvic pouch surgery the salvage is extraordinary difficult and have the endpoint of failure. The failure rate might exceed more than one out of eight or seven patients among IPAA patients.

The need of adequate blood supply and the necessity of no-tension on the anastomosis are crucial to manage. The J-pouch seems to be the pouch of choice not only

because it is the easiest pouch to construct, but also it provides no inferior outcomes. It is also easy to make standard.

The stapled anastomosis is the preferred technique, but we find it necessary to put forward the reason for mastering hand-sewn anastomosis.

The precaution of the loop ileostomy is not a conclusion in this study concerning anastomotic complication. However, when omitting the loop ileostomy in only few patients a great amount of these had to have a secondary ileostomy, which is indicative for the use of loop ileostomy. Together with the results from the literature it seems reasonable to advocate for the routine of loop ileostomy. It is possible to reduce the complications of the construction and closure procedure by refining the surgical performance. When creating the loop ileostomy this should not have as a consequence tension on the pouch-anal anastomosis.

Closing of the loop ileostomy was planned to occur at about 12 weeks after construction of IPAA, the reality was otherwise, mean 17 weeks. To reduce the complications of the closure procedure the period with loop ileostomy could be shorten down to about 8 weeks. Such a change is supported by published results.

In pelvic pouch surgery, the laparoscopic route is gaining support and the demand of skill is further stressed. The learning curves are challenged but it is possible to perform. Our recent experience is that the approach of laparoscopy will be the main access in colectomy, proctectomy and IPAA.

### Continent ileostomy

The study opposes the practical trend of the vanishing CI surgery – it is possible to offer patients the CI excellent results in short and long term in the same manner as we offer patients the IPAA. The conversion of a failed pelvic pouch is an option, which has defended its place. It is not possible to accept primary and other indications for CI and to reject the conversion as an option.

The well-informed patient is competent to take part in a clinical decision making process. The non-informed physician should not take part. The low incidence of CI may have many reasons. We find it noteworthy that the patients themselves now seek the institution. The failure rate of IPAA is high and many patients are living with dysfunctional ileostomies and other inconvenient conditions where CI could be an improvement.

It is difficult to do studies in improvements of the CI technique because of the small recruitment of patients. The surgery of continent ileostomy is demanding and the handling of all small details and technical solutions are random, which causes success or failure.

A comparison between IPAA and CI was done. In spite of different selection, both groups have similar fate concerning failure rate and the need of different revisions and re-operations although these are not of the same quality or magnitude. Accepting IPAA as an excellent option for patients in need of proctocolectomy it is thus reasonable to offer patients in the same situation, who for different reasons are not suitable for IPAA the option of CI. In addition, the many patients with failed pelvic pouch should be informed

of the CI. These patients have already found the conventional ileostomy more or less unacceptable.

### **Quality and volume relationship**

The paradox of centralisation of pouch surgery is demonstrated in the study. The CI surgery is sporadic but the volume of pelvic pouch surgery is the most comprehensive in Norway, although it is sporadic compared to the huge centres. In spite of the paradox the results are excellent and comparable to the world literature.

The question is then not to end pouch surgery at small volume hospital, but to create conditions for improving the quality of clinic of pouch surgery. The improving is the argument for centralisation, not only approved results.

IPAA are done at a very low rate at many Norwegian hospitals. The annually incidence is about 50 IPAA in Norway. The complications rate is high, documented from the most excellent centres in the world and also from this study. The procedure is demanding. As discussed the long-term follow-up program could be a part of the treatment after pouch surgery. These conditions seem to recommend a minimum of procedures and most of all a team of dedicated surgeons, ET and nurses. This is the concept of pouch clinic. In CI this is mandatory. We find it obligate to offer all these patients a life-long follow-up at a structured pouch clinic. This might further imply that a pouch clinic include both IPAA and CI. A discussion of centralisation might therefore likely end up with centres performing both IPAA and CI. With 50 IPAA performed each year in Norway 2 or 3 centres might then be reasonable.

## 7.0 Conclusion

Complication rates, early and late, after IPAA were high in this study. More than half the patients experienced pouch related morbidity after an observational time of 22 years. Nearly half the patients needed surgical intervention. Thirty-one percent needed surgical procedures to restore the function of the pelvic pouch. Failure rate was estimated to 11.4% after 20 years. Pouchitis affected more than 40% of IPAA patients after 20 years (43%). Severe morbidity was related to septic complications, usually located at the anastomotic site. Abscesses (7%) and fistulas (5%), early or late, dominate the severe complications and are difficult to treat. Pouch-vaginal fistulas (4.9%) constitute a serious and challenging complication and successful surgery is difficult to achieve. Strictures were relatively common (29%), particularly after hand-sewn anastomosis, but this complication is often easily treated by dilatations. Complications were related to delayed diagnosis of Crohn's disease. The panorama of complications and the surgical load in present study are in the same range and comparable to published results from high volume and leading centres in Europe and the US.

Functional outcomes were stable after long-term follow-up. Incontinence did not deteriorate with time, also when including elderly patients (>60 years). Although episodes of pouchitis negatively influenced functional outcome, the function of the pouch was not permanently deteriorated by episodes of pouchitis. Protective loop ileostomy or hand-sewn vs. stapled anastomosis did not affect complication rates or long-term functional outcomes substantially. Apart from delayed diagnosis of Crohn's disease,

which negatively influenced bowel movements, different indications for IPAA had no particular influence on functional outcomes.

The failure rate after continent ileostomy was estimated to 11.6% after 20 years. Half the patients needed surgical procedures because of complications, whereas one third needed one revision or repeatedly revisions of the nipple due to nipple valve sliding. Other complications were fistulas, strictures and loosening of the pouch from the abdominal wall. Surgical revisions were successful and well tolerated by the patients. Pouchitis occurred in 26% of the patients. The intubation rates ranged from 3 to 5 during daytime. Incontinence is failure, and patients suffering from incontinence were offered revisional procedure. Delayed diagnosis of Crohn`s disease cause fistula formations, which can results in failures.

The results in the present study are similar to what have been reported by high volume centres and leading centres in pouch surgery.

The overall surgical salvage rates and failure rates in long-term follow after pelvic pouch and continent ileostomy are comparable. The types of complication and surgical revisional surgery differ. However, the prospects of success after pouch construction are similar after IPAA compared to CI.

Pelvic pouch fails in more than 10%. A conversion procedure to continent ileostomy is feasible. Pelvic pouch failure due to fistulas, pouchitis or Crohn`s disease are generally not candidates for conversion. Half the patients with pouch failure can be suitable and

one third had a conversion procedure in this study. It is preferable to use and convert the pelvic pouch in the conversion procedure. In this study, seven out of eleven patients had the pelvic pouch converted to the continent ileostomy and four had a new reservoir constructed.

The complication rates and long term failure rates were similar to primary continent ileostomies.

Eleven patients were diagnosed with primary sclerosing cholangitis after pelvic pouch procedure for ulcerative colitis. PSC was associated with severe/chronic pouchitis compared to ulcerative colitis patients without PSC. Patients with primary sclerosing cholangitis also had more dysplasia in the colonic specimens compared to UC patients without PSC. The functional outcome was similar in the two groups, although during pouchitis in PSC patients the functional outcomes obviously were deteriorated. The changes, which was associated with PSC was not found to be associated with other extraintestinal manifestation like pyoderma gangrenosum or joint affections.

The incidence of new pelvic pouches has decreased since the peak in the 90ies and is now at rate of 10 or less per year. This trend is similar for the total rate of pouch procedures in Norway.

## **8. Suggestion for further research**

### **Quality of life**

In two recent studies the relationship between long term functional outcome and Quality of life were investigated. In the study of Tulchinsky (2010) she found no deterioration in functional outcome, but found a decrease in QoL among the patients as times go by. In the latest study from the Cleveland group by Kiran (2011) they reported deterioration in functional outcome, but not followed with any decrease in the QoL score in patients having had the pouch for more than 15 years. Some studies did not find any association between incontinence and QoL (Holubar,2003) , others, like the study from Norway, Oslo (Anderson 2009) reported decreased QoL scores associated with increased BM and incontinence rates. Carmon (2003) found a strong correlation between functional outcomes scores and QoL scores. In the study Lovegrove (2010) there was established a weighted association between different functional outcome and QoL. The literature is conflicting on long-term outcome and QoL.

1. In the present material with long-term data with robust statistic a study of the QoL is possible to undertake in a survey. The QoL, HRQoL and HS assessment can also include survey on sexual function and fecundity together with questions on capability related to socioeconomic status. The capability study and QoL study are the endpoint of functional outcomes assessments. The strength in this material is the high including rates and the patients' loyalty to the clinic. The expected response rate can be high.

A secondary aim of such a study could be a comparison between IPAA and CI on the subjects mentioned. Some studies have reported difference in QoL between IPAA and CI.

2. The relationship between functional outcomes and adjustments and adaptations to alterations in bodily functions is poorly understood and investigated.

Using a quality method in selected patients, an understanding of the intentional management of daily life capability of normally body function can be undertaken.

### **Pouchitis**

Pouchitis can be divided into several entities. The difference between pouchitis in UC, CD, IC and FAP are may be different on histopathological features. To distinguish only on endoscopic or clinical appearances seems to be insufficient, as well as only on histology.

The pouchitis in IPAA and CI may differ and a comparison is possible adjusting for different variables such as microbiology and mucosal changes.

Investigation on immune histochemistry or on molecular genetics can be undertaken to separate and to classify subtypes of pouchitis – particularly between acute/episodic and idiopathic chronic pouchitis.

At the out patient clinic a controlled study with biopsy is possible to undertake for all groups of patients.

The relationship between PSC and EIM and pouchitis seems only possible to be studied in large scale by multicentre design. An initiative could be taken.

### **Adhesion formation after laparoscopic colectomy**

It is claimed that laparoscopy reduces adhesion formation. Stage procedures in surgery allow a model to investigate the issue by randomization. Open access vs. laparoscopy can be undertaken when performing colectomy. Assessments of adhesion formation can be evaluated in the next stage of IPAA construction. The assessment can be blinded by a standard video uptake of a laparoscopic investigation at the beginning of the IPAA procedure for both arms. A third assessment can be performed at closure of the ileostomy.

A study protocol has been made and a study is in its beginning.

### **Incidence and prevalence of UC and IPAA in UC patients**

The incidence of UC seems to increase in Norway. There is decrease in restorative proctocolectomy. Historical changes have been seen, but the cause of the trend for new IPAA is not analysed.

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# Paper I

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# Appendices



Table 1. Hospital volume: Primary ileal pouch-anal anastomosis (IPAA) in Norway. 1997- 2009. Number given by the National Patient Registry (NPR)©. [Codes\*: 4653, 4654, 4824 (1997-1998) and JFH30, JFH 33, JGB50, JGB 60 (1999-2009)]

Hospital	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
University hospitals:													
A	10	14	18	15	9	11	4	9	4	5	1	0	3
B	8	15	22	12	9	3	4	6	3	6	3	8	2
C	2	7	3	4	6	1	2	4	0	4	6	3	7
D	1	5	8	5	8	14	5	11	9	3	2	5	7
E	7	5	3	2	3	5	7	8	6	5	8	4	0
F	14	17	11	11	6	3	5	11	12	6	5	9	9
G	18	11	19	18	15	12	11	10	9	8	4	9	3
St. Olavs Hospital	26	16	14	10	10	15	15	17	10	16	7	5	8
Other hospitals:													
a	4	1	2	4	3	2	5	1	5	2	3	2	2
b/c	0	0	0	0	6	5	7	3	7	7	2	2	2
d	1	1	4	1	1	0	0	0	0	3	1	0	0
e	0	0	0	0	1	0	0	0	0	1	3	4	0
f	3	3	4	2	1	5	5	5	3	5	5	3	3
g	1	1	3	2	1	5	1	1	1	2	2	2	0
h	0	2	3	2	2	1	1	2	0	1	3	1	1
Other low-volume hospitals (n=14)	5	4	2	3	0	4	4	1	0	2	2	1	2
<b>Total</b>	<b>100</b>	<b>102</b>	<b>116</b>	<b>91</b>	<b>83</b>	<b>84</b>	<b>76</b>	<b>89</b>	<b>63</b>	<b>76</b>	<b>57</b>	<b>58</b>	<b>49</b>

\*There could be miss-typing in the medical charts at the local registry in each Hospital given wrong number of procedures. The overall number and trend is likely to represent the true number of primary IPAA's in Norway each year.

Table 2. Complication, failure and revision rates after continent ileostomy from some publications and centres

Study	Number	Follow-up/ periode	Definite failure	Success rate	Nipple valve sliding	Fistulas	Stenosis	Nipple stenosis	Skin stricture	Nipple necrosis	Complica- tions rate	Pouchitis	Major revision
Hälvorsen 1978	36	1973-79	16 %	75 %	36 %	24 %		3 %				15 %	45 %
Dozois 1980	299	1973-79	10%-3%*	95%#	43%-22%*	7 %							43%-22%*
Cohen 1982	85	<1	0 %	96 %	7.5%								30%†
Gerber 1983	100	1977-80			18.7%	11.5%				2 %		10 %	
Failes 1984	49	<11 year	8 %	86 %	22 %	2 %			4 %				34 %
Huitén 1985	61				11 %	3 %				5 %			28 %
Koock 1986	435	1975-84	3 %	97 %	44%-17%*	1.9%-0.7%*	16 %			1.2%-2.2%*	73%‡	17 %	66 %
Järvinen 1986	76	9 mean	5 %	83 %	41 %	9 %						30 %	28 %
Bloom 1986	95	1975-1984											
Olsson 1987	60	4.5 mean	2 %	>95%	25 %								
Fazio 1988	168	1977-85	6 %	91 %	19 %	12 %			10 %	35		29 %	31 %
Sjödahl 1990	55		0 %	95 %	9% (first year)						18e-29%‡		12.5%
Öjerskog 1990	36	16-20 years	5 %										52 %
Little 1990	129	11.4 mean	36 %										44 %
Svaninger 1993	84	8.5											
Ecker 1999	73	1987-98	4.1%		20 %	13 %		2.5%§		1 %		33 %	
Lepistö 2003	96	1972-2000		71%‡	28	3 %	20 %			2 %		30 %	59 %
Berndtsson 2004	88 (121)	31 (1967-74)		87 %								28 %	65 %
Castlilo 2005	24	1993-2003	8.3%	92 %	45 %	4 %	4 %						54 %
Nessar 2006	330	11 median	16 %		29.7%	25.2%			10 %			26.4 %	≈30%
Hoekstra 2008	28	1996-2007	4 %	96 %	≈24%							4 %	56 %
Parc 2011	43(49)	1973-2007	10 %		42 %	10 %	14 %	4 %	10 %		35e-51%‡	24 %	51 %
Present study	50	1983-2002	8 %	90 %	18 %	6 %	14 %	6 %	8 %	4 %	44 %	26 %	34 %

\* stapled nipple; # = patients responded; e = early; † = late; § = only substitution after failed IPAA; ‡ = all reoperations; § = intubationproblems;

β = 29 years cumulative rate

Table 3. Complication and fail rates after ileal pouch-anal anastomosis from some publications and centres. Rates in percentage

Study	Number initial	Mean obs. or time interval	All pelvic sepsis	Abscess	All fistula	Vaginal fistula	Anastomotic leaks, all	Anastomotic separation	Stricture	Pouchitis crude	Pouchitis estimated	Chronic pouchitis	Failure crude	Failure estimated	Bowel obstruction	Early complication rate	Late complication rate	Overall morbidity
<b>Cleveland Clinic</b>																		
Fazio 1995	1005	2.3	11.1	8.2	5.2	4.2*	2.9		14	23.3			4.5		25.3	27.5	50.5	62.7
Fazio 2003	1965	4.1	6.6		7.1	2.2		5.3	15.5	31.2		6.8	4.1					
Kiran 2010	3233		6.2															
<b>Mayo Clinic</b>																		
Meagher 1998	1608	1981-94	6.0							35	48 (10y)		10.9 (10y)	22 (10y)				
Chapman 2005	2002	10.1	5.5	10(f) 4.5(m)					20.1 (10y)	48 (10y)	70 (20y)		5.6 (10y)	23.6 (10y)				
Hanhloser 2007	1762 (UC)	10		16 (20y)	1.4 (20y)				39 (20y)				8 (20y)	42 (20y)				
<b>St Marks Hospital</b>																		
Thuidchinsky 2003	634	7	10										9.7	13 (10y)				
<b>UK</b>																		
Tekkis 2008	2491	4.5 (median)	11.8		11.8		5.5		16.8	14.2			16.1	10y)	12.3			
<b>Toronto</b>																		
Kennedy 2006	1285																	
<b>Hyogo Col. Japan</b>																		
Ikeuchi 2010	1000 (UC)	1983-2007											4.7	11 (20y)				
<b>Reviews/meta-analysis</b>																		
Husting 2005	9317	3	9.5		5.5				9.2	18.8			6.8	8.5 (5y)	13.1			
Lovegrove 2006	4183	1.5-2.2	7.2		4.7	0.2	6.9		12	16.8			3.8					
<b>Other</b>																		
Heuschen 2002	494 (UC)	4.5	22		15	3	3.6											
Lepisto 2002	450	1985-1999			13(f) 7(m)				10	46			5		26	27		
Ferrarie 2008	173	6.5	14										6.8					
Forbes 2009	1554	1981-2005	13.3		1.4		4.6											
<b>Norwegian</b>																		
Johnson 2001	64 (UC)	5	5		11				5	19			9					36
Stornes 2010	43	1989-2006			16				21	13			10		5			
Rokke 2011	134	1988-2002	3.7(e.c.)		4.5		4.8		4.5	26			9.8		13	14.9	43.6	
<b>Present study</b>	304/317	10/11	4 (e.c.)	7	5	4.9*	4(e.c.)	10 (e.c.)	29	33	43 (24y)	6.3	6.5	11 (20y)	5	23	22	56 (22y)

y = years of observation; m = male; f = female; e.c. = early complications; \* = among females; UC = Ulcerative colitis

Table 4. Functional outcome and QoL after ileal pouch-anal anastomosis (IPAA) reported from some publications and centres. Rates in percentage

Study	Number initially	Observational time; years	Number at end of observation*	BM 24h	BM day	BM night	Urgency	Incontinence day	Incontinence night	Soling day	Soling night	Soling day and night	Anti-diarrhoeals	QoL	Conclusion on function
<b>Cleveland Clinic</b>															
Fazio 1995	1005	3.3 (1-10)	645	6 median s	5.8-5.5 ≤	1.4-1.8 ≥	3 s	28.5-62.5\$			29 s	18 s	15	stable	stable
Kiran 2011	584	>15	396		6.1/5.5(f/m)	2.3/2.1(f/m)	47.9-69.6\$	75/78(f/m)\$		24/20(f/m)				stable	stable
Rottoli 2011	3407	9.5 (0-24)					61/67(f/m)\$								
<b>Mayo Clinic</b>															
Hahnloser 2004#	409	15	409		5.5-6.2 >	1.1-2.0 >		19-45\$ >	53-76\$ >>				≈50 s	stable	change
Chapman 2005	2002	10.1	1450 (10y)		5.7 s	1.5-1.7 s		5-5.6 s	11.1-13.3 s				≈50 s	"stable"	stable
Hahnloser 2007	1885	10.8 (0-23)	251 (20y)		5.7-6.4 >	1.5-2.0 >		29-40\$ >	57-68\$ >				≈50 s	stable	stable
<b>UK national ileal pouch registry</b>															
Tekkis 2010	2491	4.5 (0-29)	39 (≥20y)	5-5 ≥		0-1 s	5-9(15y) >	4-20 >>	8-15.4 >				38.9-38. s		"deteriorate"
<b>Oxford</b>															
Wheeler 2005	151	12 (8-20)	98		6 s	1 s		26 ?	47 ?				58	stable	stable
<b>Other</b>															
Bullard 2001	314	12 (8-19)	154	7 s		2-1.4 s		15-33 >	2-25 >>	4-16	11-19 >		52-19 <	stable	"deteriorate"
Lowardi 2008	294	>10	197 (12.3y)	7 s	5 s	1 s		absent						stable	"stable"
Lovegrove 2010	4013	7 (±5.1)	98 (20y)	7-6.5 s		2-2 s	51-59 >	16-25 >	29-45 >				57-41 <	worsend	deteriorate
Tulchinsky 2010	77	11	63		6 s	1-2 s		44-22 s	37-40 s					stable	stable
<b>Nordic studies</b>															
Mikkola 1995	100	5.6		(4,6-6,9 s				5				57	40-0 <<<		"stable"
Johnson 2001	72(68)	5.1 (1.6-14)	58	6.5 s	5.5 s	1 s		3	3	22	14		53 s	stable	stable
Wemyrb 2003	51	>7	40												
Bengtsson 2007	42	16 (14-18)	42 (37)		5.5 >	0-1 >	4.7-19 >			19-38 >	33-45 >		73-42 <	stable	deteriorate
Anderson 2009	184	12 (2-22)	110		7	2	34	64 (all kind)	82 (all kind)				42	stable	stable
Rokke 2011	125	6.8 (1-15)	111	7	6 s	1 s		9 s						stable	stable
<b>Present Study</b>	315	13 (1-24)	37(20y)	5.9-5.0 s	5.2 s	0.5 s	≈10 s	13 s	21 s	41 s	5 s		53 s	stable	stable

y= years; s= stable; > increasing by time; >> highly significant increasing; ≥ slight increase; < decreasing; "..." suggestions; # Cohort study; f/m=female/male  
 \*= Given years indicates the number of patients observed at that time, without years given, the number is the patients assessed in the study; \$=never/rarely;%=100- never experienced incontinence

Table 5. Multivariate ordinary least square (times series) regression analyses of various controls for Bowel movements (BM) and Incontinence. (n=number of visits with data, UC = Ulcerative colitis CRC = Colorectal Cancer, FAP= Familial Adenomatous Polyposis. Coef = absolute change in number per day or night or week, Age (year) = age at operation

	BM at day (n=1160)			BM at night (n=1130)			Incontinence per week (n=1061)		
	Coef.	95%CI	P=	Coef.	95%CI	P=	Coef.	95%CI	P=
Male	-0.079	-0.38-0.22	0.606	0.023	-0.09-0.13	0.682	-0.01	-0.20-0.18	0.927
Age (year)	0.011	-0.00-0.2	0.077	0.006	0.001-0.011	0.011	-0.001	-0.01-0.01	0.762
Protective stoma	-0.096	-0.51-0.32	0.650	-0.229	-0.40-0.06	0.010	0.085	-0.12-0.29	0.415
Stapled anastomosis	0.031	-0.28-0.342	0.844	0.029	-0.09-0.15	0.672	-0.11	-0.35-0.12	0.349
Diagnosis (UC=0)									
Crohn's disease	-1.216	-1.62-0.82	0.001	-0.528	-0.67-0.38	0.001	-0.074	-0.34-0.19	0.587
Indeterminate colitis	0.653	-0.66-1.93	0.337	0.586	0.22-0.95	0.002	-0.327	-0.61-0.05	0.023
CRC/FAP	0.807	-0.77-2.38	0.315	0.228	-0.35-0.81	0.441	0.036	-0.20-0.28	0.765
Early anastomotic complications	0.264	-0.18-0.71	0.242	-0.065	-0.24-0.11	0.474	0.396	-0.26-1.05	0.234
Pouchitis	0.653	0.25-1.06	0.002	0.497	0.27-0.72	0.001	0.457	0.02-0.89	0.041
Perineal eczema	0.357	0.28-0.43	0.000	0.331	0.25-0.41	0.000	0.240	0.80-0.40	0.003
Loperamid	0.046	0.01-0.09	0.030	0.029	0.01-0.05	0.005	0.037	-0.003-0.08	0.068
Constant	2.879	2.07-3.69	0.000	0.183	-0.10-0.468	0.209	0.132	-0.44-0.70	0.651

Table 6. Multivariate logistic regression (times-series) of various controls on functional outcomes. (Observations are clustered on patient) UC= Ulcerative colitis, FAP= Familial Adenomatous Polyposis, CRC= Colorectal cancer, BM = Bowel movements, OR= Odds ratio, CI= confidence interval, n= number of visits.

	Urgency (n= 1077)			Protracting bowel movements (n=994)			Separate gas/stool (n=1068)			Perineal eczema (n=1098)		
	OR	95%CI	P=	OR	95%CI	P=	OR	95%CI	P=	OR	95%CI	P=
Male	0.56	0.32-0.98	0.042	0.86	0.47-1.58	0.628	0.72	0.48-1.08	0.109	0.84	0.58-1.22	0.357
Age (in years)	1.01	0.99-1.03	0.506	0.97	0.97-1.03	0.832	0.99	0.97-1.01	0.230	1.01	0.99-1.03	0.253
Protective stoma	1.18	0.55-2.51	0.677	1.44	0.54-3.89	0.469	0.97	0.63-1.51	0.894	0.63	0.38-1.04	0.073
Stapled anastomosis	1.07	0.64-1.78	0.798	1.42	0.69-2.95	0.336	1.08	0.71-1.63	0.725	1.13	0.78-1.62	0.518
Diagnosis (UC=1)												
Crohn's disease	*			2.53	0.60-10.0	0.204	4.54	0.67-30.6	0.657	0.47	0.08-2.84	0.411
Indeterminate colitis	**			**			**			0.38	0.15-0.99	0.048
FAP/CRC	0.98	0.12-8.10	0.99	***			1.50	0.47-4.76	0.493	0.57	0.25-1.29	0.178
Early anastomotic complications	2.62	1.12-6.11	0.026	1.38	0.58-3.29	0.464	1.06	0.48-2.34	0.894	0.99	0.54-1.83	0.972
Pouchitis	2.36	1.41-3.94	0.001	3.59	1.91-6.75	0.000	0.68	0.42-1.06	0.085	0.85	0.57-1.26	0.405
Loperamid	1.16	1.09-1.23	0.000	0.96	0.85-1.09	0.506	0.99	0.93-1.05	0.625	1.08	0.99-1.11	0.105
Constant	0.43	0.01-35.3	0.706	0.05	0.01-0.50	0.010	1.12	0.14-69.8	0.478	1.05	0.06-17.3	0.972

\*All patients with Crohn's disease had reported "no" at 7 and 8 visits, \*\* Patients with Indeterminate colitis had reported "no" at 11 and 12 visits except for one "yes", and \*\*\* Patients with FAP/CRC reported "no" at 43 visits and only "yes" at two, which excluded perfect prediction analysis.

Table 7. Multivariate logistic regression (times-series) of various controls for Soiling and the usage of Pads. (Observations are clustered on patient) UC= Ulcerative colitis, FAP= Familial Adenomatous Polyposis, CRC= Colorectal cancer, OR= Odds ratio, CI= confidence interval, n= number of visits.

	Soiling at day (n=1126)			Soiling at night (n=1131)			Pads at day (n=1118)			Pads at night (n=1131)		
	OR	95%CI	P=	OR	95%CI	P=	OR	95%CI	P=	OR	95%CI	P=
Male	0.55	0.33-0.92	0.353	0.82	0.53-1.25	0.353	0.29	0.16-0.53	0.000	0.55	0.32-0.94	0.030
Age (per year)	1.04	1.02-1.07	0.000	1.03	1.01-1.05	0.012	1.06	1.03-1.09	0.000	1.05	1.07-1.08	0.000
Protective stoma	0.93	0.43-2.01	0.858	0.99	0.57-1.76	0.995	0.72	0.33-1.57	0.413	0.86	0.45-1.63	0.641
Stapled anastomosis	0.45	0.26-0.77	0.004	0.48	0.31-0.76	0.002	0.32	0.16-0.61	0.001	0.32	0.89-0.56	0.000
Diagnosis (UC=1)												
Crohn's disease	1.65	0.18-14.9	0.657	2.99	1.13-7.90	0.027	*			*		
Indeterminate colitis	7.78	0.11-57.5	0.349	1.97	0.18-21.1	0.577	2.27	0.30-17.3	0.428	0.87	0.12-6.30	0.890
FAP/CRC	2.58	0.86-7.70	0.090	1.79	0.53-6.01	0.347	3.23	0.91-11.5	0.071	2.46	0.61-10.0	0.209
Early anastomotic complications	1.92	0.90-4.08	0.090	2.43	1.16-5.10	0.018	1.20	0.47-3.07	0.698	1.89	0.68-5.24	0.221
Pouchitis	2.04	1.21-3.46	0.008	2.84	1.76-4.57	0.000	1.51	0.87-2.60	0.142	2.87	1.56-5.15	0.000
Loperamid	1.15	1.06-1.24	0.001	1.08	1.01-1.16	0.026	1.15	1.05-1.26	0.003	1.15	1.05-1.25	0.002
Constant	0.15	0.01-2.52	0.185	0.25	0.02-2.86	0.262	0.11	0.01-1.86	0.127	0.02	0.00-0.28	0.003

\*All patients with Crohn's disease had reported "no" at 7 and 8 visits

Figure 1. The continent ileostomy; Kock pouch

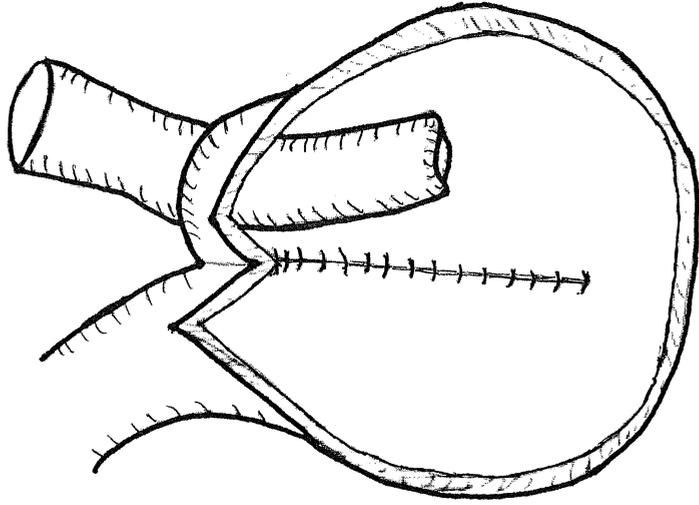


Figure 2. Hand-sewn and stapled ileal J-pouch-anal anastomosis

(ATZ: Anal transitional zone)

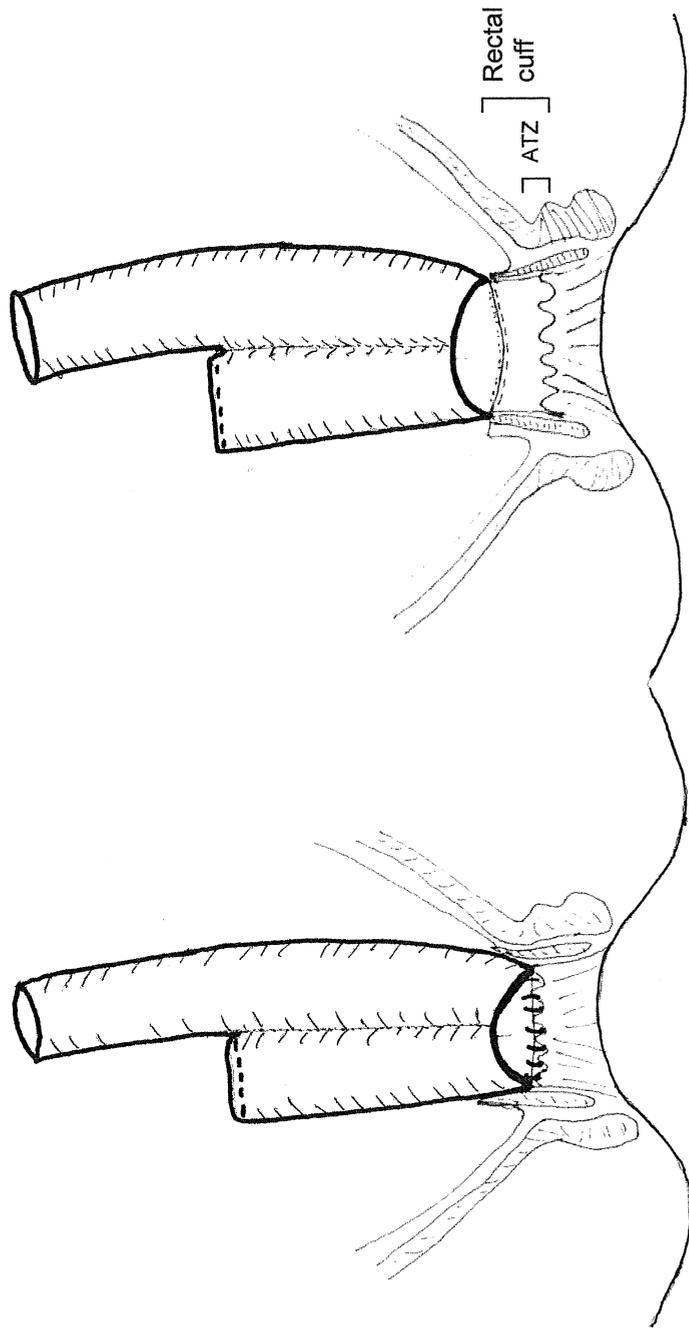
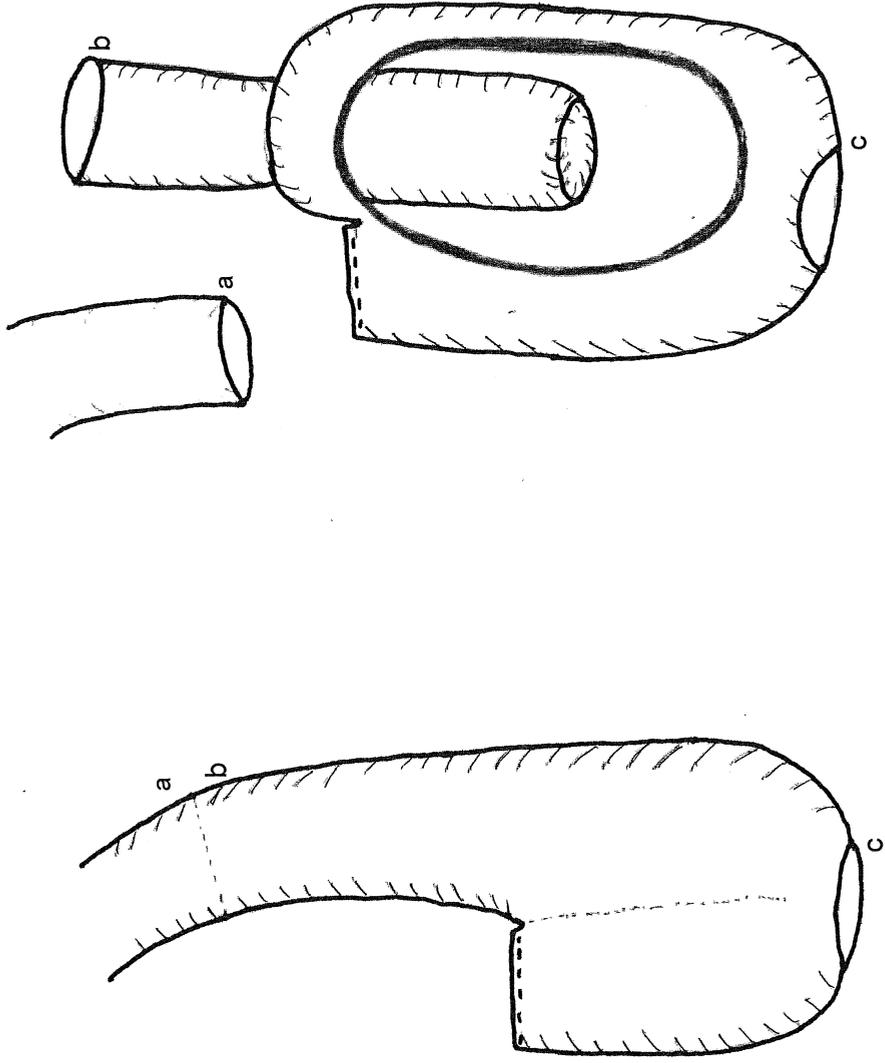


Figure 3. The conversion from J-pouch to continent ileostomy.  
a to c, b to stoma





## Dissertations at the Faculty of Medicine, NTNU

### 1977

1. Knut Joachim Berg: EFFECT OF ACETYLSALICYLIC ACID ON RENAL FUNCTION
2. Karl Erik Viken and Arne Ødegaard: STUDIES ON HUMAN MONOCYTES CULTURED *IN VITRO*

### 1978

3. Karel Bjørn Cyvin: CONGENITAL DISLOCATION OF THE HIP JOINT.
4. Alf O. Brubakk: METHODS FOR STUDYING FLOW DYNAMICS IN THE LEFT VENTRICLE AND THE AORTA IN MAN.

### 1979

5. Geirmund Unsgaard: CYTOSTATIC AND IMMUNOREGULATORY ABILITIES OF HUMAN BLOOD MONOCYTES CULTURED IN VITRO

### 1980

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7. Arne Olav Jenssen: SOME RHEOLOGICAL, CHEMICAL AND STRUCTURAL PROPERTIES OF MUCOID SPUTUM FROM PATIENTS WITH CHRONIC OBSTRUCTIVE BRONCHITIS

### 1981

8. Jens Hammerstrøm: CYTOSTATIC AND CYTOLYTIC ACTIVITY OF HUMAN MONOCYTES AND EFFUSION MACROPHAGES AGAINST TUMOR CELLS *IN VITRO*

### 1983

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### 1984

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**1988**

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**1997**

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127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
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**1998**

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#### 1999

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157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

#### 2000

158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
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- 162.Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
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- 164.Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
- 165.Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
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- 167.Geir Falck: HYPEROSMOLALITY AND THE HEART.
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- 174.Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
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- 177.Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

## 2001

- 178.Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENCES
- 179.Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR HISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
- 180.Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
- 181.Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
- 182.Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
- 183.Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
- 184.Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
- 185.Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
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- 188.Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTURAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
- 189.Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
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- 191.Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT

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200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

## 2002

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203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING  $\beta$ -CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
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