OBSERVATIONS ON ESSENTIAL BIOCHEMICAL DATA PROFILE IN CONNECTION WITH RESTORATIVE PROCTOCOLECTOMY IN HUMANS.

Vitamin B_{12} and Fat absorption cited

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Surgery and Urology

Stockholm 2001

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1.
ABSTRACT

PATIENTS: The material includes 99 patients who consecutively received handsawn pouch and ileoanal anastomosis, after mucosectomy. Sixty-five patients were men and forty-four were women. The mean-age was 31.4 (range 17-59) years. Fifty-nine patients initially underwent subtotal colectomy and ileostomy and 40 had colectomy at the time of pouch construction. Ninety-six patients suffered from ulcerative colitis, two had familial adenomatous polyposis and one was healthy but belonged to a dominant cancer inherited family. All patients obtained a loop ileostomy at the pouch operation. After loop ileostomy closure, the patients were followed up regarding homeostasis in a prospective fashion by the surgical team at 2, 6, 12, 18, 24 and 36 months after surgery.

ELECTROLYTES: Pathologic values of sodium and potassium in serum were rarely seen. Low values of calcium were found preoperatively among acutely operated. Sixteen percent of the patients with ileostomy had high values of zinc, while 2% to 5% had low values during the manipulative and follow-up phases. Magnesium was decreased at all stations in 16 to 36% of the patients.

PROTEINS: Low albumin values were seldom seen except for in patients who were to be acutely colectomized. In our observations, we noted an elevation of serum IgG and IgA with time during the functioning pouches after loop ileostomy closure and with serum IgM during the period with loop ileostomy, compared to preoperative values.

LIVER ENZYMES: A high percentage of patients had increased ALAT and/ or ALP in serum (36% and 42% respectively) during the time with loop ileostomy compared to a preoperative percentage of 14% and 12% in the elective group and 13% and 14% in the acute group. Fifty percent of the patients with increased ALAT also had increased ALP. The levels of mean values did not normalise until after closure of loop ileostomy.

HEMATOLOGY: More patients with low serum haemoglobin and iron were seen before colectomy (44% and 50%) than with ileostomy (18% and 23%) and/ or with loop ileostomy (12% and16%). During the 6 to 36 months of IPAA follow-up, 7% to 14% and 11 to 21% had low values. Although only 3% and 11% of the ileal pouch anal anastomosed patient had low serum vitamin B_{12} at the 12 and 36 months follow-up, 31% and 36% had decreased Schilling test. In five patients vitamin B_{12} deficiency began during the first 6 months of IPAA function. Ten percent of the patients have had substitutional therapy with vitamin B_{12}. Five patients continue with substitution after 40 to 60 months. At 12 and 36 months follow-up, 35% and 41% had decreased ^{14}C-triolein breath tests but no patient showed any symptoms of anorexia.

LIPIDS: There was a significant difference of mean serum cholesterol preoperatively between patients who were operated on electively versus on emergency basis. In electively operated patients, serum levels of cholesterol decreased when patients had loop ileostomy. The decrease was significantly correlated to the length of the excluded ileum but not the time duration with loop ileostomy. During the same period, serum triglyceride was significantly increased, but there was no relation to the length of the diverted ileum.

Changed pattern of lipoproteins in serum was noted. Serum alpha-lipoprotein decreased (HDL) during the period with loop ileostomy. At 12 months after loop ileostomy closure, serum cholesterol, triglyceride and alpha-, pre-beta- and beta-lipoprotein levels were not significantly changed compared to precolectomy time. In the emergency patients there was a tendency to increased serum cholesterol after colectomy with terminal ileostomy. After construction of the pouch and diverting loop ileostomy, serum cholesterol was not significantly changed while mean serum triglyceride was significantly increased compared to values prior to colectomy.

GASTRIC ACID SECRETION and GI HORMONES and ENZYME: There was a significant increase in retention, basic, and stimulated gastric acid secretion after 12 months with pouch in function, compared to preoperatively. An increased output of gastric acids may change/ decrease the intestinal passage time and contribute to looser stool. The levels of serum gastrin, pentagastrin and pepsinogen were identical.

 ISBN 91-7349-007-5

Karolinska University Press

2.
SUMMARY OF THE ORIGINAL THESIS PAPERS

The thesis is a summary of the following papers, which will be referred to in the text by the Roman numerals I-VI

I. M´Koma AE, Lindquist K, Liljeqvist L. Biochemical Laboratory Data in Patients Before and After Restorative Proctocolectomy. A Study on 83 Patients with Follow-up of 36 months. Ann Chir 1994;48:525-534.

II. M´Koma AE, Lindquist K, Liljeqvist L. Observations in the Blood Lipid Profile in Patients undergoing Restorative Proctocolectomy. Int J Surg Invest 2000:00:1-9 in press

III. M´Koma AE, Lindquist K, Liljeqvist L. Effect of Restorative Proctocolectomy on Gastric Acids Secretion and Serum Gastrin Levels. Dis Colon Rectum 1999; 42:398-402.

IV. M´Koma AE. Follow-up Results of Haematology Data Before and After Restorative Proctocolectomy: Clinical Outcome. Dis Colon Rectum 1994;37:932-937.

V. M´Koma AE, Lindquist K, Liljeqvist L. Adaptive returns to normal serum electrolytes after depletion following restorative proctocolectomy and ileal-pouch anal anastomosis. A controlled, prospective study. Int J Surg Sci 1995;2:330-334.

VI. M´Koma AE, Lindquist K, Liljeqvist L. A study on plasma Immunoglobulins Profile in Connection with Restorative Proctocolectomy. Int J Surg Invest 2000;01:01-07.

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Paper II.
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ABBREVIATIONS (Bailliére´s Abbreviations in Medicine)

ANOVA	Analysis of variance
IgG	Immunoglobulin G
IgA	Immunoglobulin A
IgM	Immunoglobulin M
SIgG	Secretory immunoglobulin G
SIgA	Secretory immunoglobulin A
SIgM	Secretory immunoglobulin M
ESR	Erythrocytes sedimentation rate
WBC	White blood cells
Schl-w-IF	Schilling test with intrinsic factors
Schl-wt-IF	Schilling test without intrinsic factors
^{14}C-bt	Oleath breath test
ASAT	Aspartate transaminase
ALAT	Alanine aminotransferase
ALP	Alkaline phosphates
B_{12}	Cynocobalamin
RAIR	Recto-anal inhibitory reflex
FPC	Familial polyposis coli
UC	Ulcerative colitis
FAP	Familial adenomatous polyposis
IF	Intrinsic factor
IAP	Ileoanal pouch
IPAA	Ileal pouch-anal anastomosis
IAA	Ileoanal anastomosis
SC	Sclerosing cholangitis
PSC	Primary sclerosing cholangitis
Hapt	Haptoglobin
AlphaI-AGP (or Oros)	Orosomucoid
CAH	Chronic active hepatitis
Ileo	Conventional ileostomy
Loop	Loop ileostomy
Mon	Months
ANCA	Antineutrophil cytoplasm antibody
HCl	Hydrochloric acid
Pt	Patient
Pp	paper
GI	Gastrointestinal
TG	Triglycerides
E	Electively operrated patients
A	Acutely operated patients (Emergence)
RPC	Restorative Proctocolectomy
VLDL	Very low-density lipoprotein (Pre-Beta-lipoprotein)
LDL	Low-density lipoprotein (Beta-lipoprotein)
HDL	High-density lipoprotein (Alpha-lipoprotein)

6.

INTRODUCTION:

In patients with ulcerative colitis (UC), familial polyposis coli (FPC), and cancer family syndrome, restorative proctocolectomy and construction of an ileoanal pouch is to date the ideal surgical treatment of choice [1-2]. The procedure means total excision of the colon and different manipulations with the distal ileum that may influence the gut-associated metabolic systems and interfere with normal body functions jeopardizing the homeostasis. In ulcerative colitis, colectomy or proctocolectomy is indicated in severe life-threatening disease and otherwise when conservative medical treatment fails, or as an ultimate step for cancer prevention in a surveillance program. An ideal is that despite removal of the entire colonic mucosa normal bowel evacuations, continence and fertility are preserved [3-7]. Concerning the restorative proctocolectomy there has been and is still an increase in research concerning operative technique [4, 8-10], the functional outcome [6-13], complications [14-16] and the behaviour of the pouch mucosa [17-22]. Little has, however on short-term (< 10 yrs), been described concerning biochemical changes [20, 21, 23-29] following the operation procedures or during the follow-up [23-32]. Long-term follow-up studies considered as 10-year surveillance are to date rare [22, 33-37]. This thesis reveals the behaviour of different biochemical variables during the course of the pouch procedures.

7.

BACKGROUND:

Ulcerative Colitis:

The disease is of unknown aetiology characterised by inflammation of the colonic mucosa. The severity of the disease varies, depending on the intensity of the inflammatory process and the extent of the colonic involvement. Ulcerative colitis almost always occurs in the rectum and extends continuously cephalic to a variable distance but usually never involves the small bowel. Rarely, in severe cases of total colitis (pancolitis), the mucosa of the distal ileum will be inflamed - a condition referred to as backwash ileitis.

The symptoms of ulcerative colitis vary considerably, depending on the severity of the disease. The hallmark of the disease is bloody diarrhoea (hematochezia). If severe proctitis is present, tenesmi and incontinence may be present. The patient with acute fulminant colitis may complain of severe cramping abdominal pain accompanied by almost constant bloody diarrhoea, fever, leukocytosis, dehydration and anaemia. Dilatation of the colon (toxic mega colon) with systemic signs of toxicity (fever, tachycardia, leukocytosis) is a complication associated with ulcerative colitis. The objective findings vary according to the severity and extent of the colonic inflammation. The abdominal examination may be unremarkable in the patient with distal proctitis but tender in patients with fulminant colitis. Systemic complications include electrolyte deficiencies, microcytic anaemia, hypoproteinemia, avitaminosis, amyloidosis, osteoporosis, amenorrhea, retarded sexual development and retarded growth. The most common complications in other systems include arthritis, ankylosing spondylitis, and sacroileitis, conjunctivitis, iritis, and episcleritis; gallstones, fatty liver, hepatitis, pericholangitis, cirrhosis, and carcinoma of the bile ducts; erythema nodosum, pyoderma gangrenous, aphthous stomatitis, and clubbing of the fingers; pyelonephritis and urolithiasis; interstitial pancreatitis; peripheral neuropathy and vascular thromboses.

Rectoscopy, colonoscopy and mucosal biopsy are the most important examinations to verify the diagnosis and evaluate the severity of the mucosal inflammation. Rectoscopy will reveal granular, friable rectal mucosa, and despite the appellation, desecrate mucosal ulcers are usually not present.

It is important to assess the severity of the disease because therapy depends on this judgement. If symptoms consist of minimal diarrhoea and mild distal proctitis, no treatment may be required. On the other hand, if abdominal tenderness, severe proctitis, fever, leukocytosis, dehydration, and anaemia are present, the patient must be admitted and given intravenous fluids, blood transfusions and steroids. Ulcerative colitis with chronic debility is caused by persistent symptoms that fail to respond to intensive medical treatment, including

corticosteroid therapy, nutritional support, and sulfasalazine and is the most common indication for surgical treatment of ulcerative colitis.

Therapeutic strategy is based on the severity of the disease and the initial response to treatment. The four indications for surgical treatment of ulcerative colitis are chronic illness with debility, toxic megacolon, acute haemorrhage and dysplasia with cancer risk. Ulcerative colitis, unlike granulomatous colitis, is confined to the mucosa of the rectum and colon. Total proctocolectomy should therefore cure the patient. Unfortunately, until recently proctocolectomy necessitates a permanent ileostomy, a condition not readily accepted by many patients. However, considerable experience with sphincter-saving procedures has accumulated in recent years. These techniques allow eradication of the diseased mucosa with preservation of anal continence. The sphincter-saving procedures advocated in the treatment of selected patients with ulcerative colitis basically entail total colectomy with mucosal proctectomy, followed by creation of a reservoir using the distal ileum with anastomosis of the ileum to the anus. The muscular coats of the distal rectum are preserved, allowing preservation of anal sphincters function.

Familial Polyposis Coli:

The disorder is characterised by large numbers of colorectal adenomatous polyps that appear at an early age. Many patients are completely asymptomatic, and diagnosis is possible only because the family history indicates the possibility of inherited transmission. Sometimes patients complain of fatigue, passage of bloody stools and mucus, intermittent abdominal pain, and weight loss. The condition usually results in cancer by the time a patient is around 40 years old. The diagnosis is established by proctosigmoidescopy with biopsy of one of the polyps to verify its adenomatous nature and rule out juvenile polyposis. The lesions can also be demonstrated radiologically by contrast enema.

Cancer family syndrome:

The syndrome is rare and characterized by an increased incidence of adenocarcinima, primarily of the colon and endometrium, early age of onset, and autosomal dominant inheritance [277]. There are no symptoms or signs before the

onset of malignancy. There are no known markers for this genetic disorder. Hence, a pedigree has to be designed to disclose potential carriers. These should be recommended a surveillance programme. Prophylactic proctocolectomy might be indicated when the fear of cancer becomes intolerable.

Restorative Proctocolectomy Evolution:

In 1933 a successful result after an ileo-anal pull through procedure in a patient with familial polyposis coli was reported by Nissen [38]. Ravitch and Sabiston [39] devised complete colectomy and removal of the entire mucosa of the distal rectum and anal canal from the dentate line, the distal ileum being then passed through the bared tube of rectal muscle coat and stitched to the anal skin as a straight ileo-anal anastomosis. Ravitch first described total colectomy, with preservation of the anal sphincters, by means of mucosal proctectomy and ileo-anal anastomosis, in the treatment of ulcerative colitis in 1948 [40]. Later in 1951 [41] he claimed satisfactory functional outcome. Other researchers [42-44] reported great frequency of defecation and poor continence and severe perineal soreness with the method. Moreover, mucosectomy was often technically difficult with this method, which also showed a high rate of complications. The technique was abandoned and with the introduction of the eversion technique and immediate mucocutaneous suture by Brooke [45] and the development of better appliances, proctocolectomy and conventional ileostomy became the first choice for treatment of ulcerative colitis. During this period, several reports [46-48] produced evidence that the incorporation of an ileal reservoir in the ileoanal anastomosis improved functional results considerably in dogs as compared to a straight ileo-anal technique. The operation was sporadically reported during the following decades. In 1969 Kock [49] introduced the continent ileal reservoir.

Later studies showed that the presence of a pouch was consistent with normal intestinal function. In 1978 Parks and Nicholls [9] presented the pelvic pouch.

There are some reports on the early functional and metabolic results of this operation [9, 50-54]. The functional results in terms of frequency and anal continence were very encouraging as compared to those reported after straight

ileo-anal anastomosis. However, 50% of the patients were not able to defecate spontaneously but emptied the reservoir with a catheter [50, 54]. Moreover, there was a high incidence of major complications with reported pelvic sepsis rate of about 20% [13, 55-58]. Parks et al. [50] advocated preservation of a long rectal muscle cuff almost enclosing the ileal pouch. The procedure then involved mucosal dissection performed via abdominal and endo-anal approach, and a long outlet between the pouch and the anal canal. The reason for such an approach was firstly to preserve rectal sensation considered being essential for continence [56, 59], and secondly to reduce disturbances in sexual function commonly encountered after conventional proctocolectomy [60]. Mucosal dissection of low muscular cuffs contributed to a high pelvic sepsis rate and a long pouch outlet to functional imperfection [13]. This led to a search for other techniques both for the pouch construction and the proctectomy. Transection of the rectum just above the pelvic floor, e.g. omitting the tedious mucosal dissection from above leaving only a short rectal muscle cuff and a short outlet was proved to eliminate the need of catheterization [54, 57, 61] without affecting continence adversely [62, 63]. Different pouch designs were put on trial [55, 64, 65]. In the original S-shaped reservoir design [9] the terminal ileum is folded into three loops 12-15 cm long, leaving a short segment of bowel projecting distally. The loop is sutured side-to-side and the lumina opened. The ileo-anal anastomosis is made end-to-end between the short projecting ileal segment and the anal canal. The J-shaped reservoir with a direct reservoir-anal anastomosis introduced by Utsunomyia of Kyoto [51] soon became one of the most popular pouch configurations, partly due to its technical simplicity but also due to its favourable functional characteristics. It is constructed by folding the terminal ileum into two segments about 15 cm long which are sutured side-to-side, opened and joined together forming a pouch by a lateral anastomosis. The ileo-anal anastomosis is constructed side-to-end at the apex of the reservoir. Later, Nicholls introduced the W-shaped or quadruple pouch, which is accomplished by adding another J to the first, which implies that, an additional length of ileum, is used in its construction [66]. During the 1980s restorative proctocolectomy with construction of an ileal reservoir has attracted

great interest all over the world, and the operation become the first alternative for curative treatment of ulcerative colitis and familial polyposis in most specialised centres.

Several studies regarding early and late postoperative morbidity have been reported, and the enigmatic syndrome of pouchitis caused by an unspecific inflammation of the reservoir mucosa seems to be the main cause of late morbidity. The functional outcome has been extensively reported and although patient satisfaction is considered to be high, results are still not always perfect. The goal for the ileo-anal pouch anastomosis in patients with ulcerative colitis, familial polyposis coli and cancer family syndrome is the removal of the entire colonic mucosa with preservation of bowel continuity, continence and fertility. The relative importance of the sphincter mechanism as a contributory factor to overall continence is not fully understood, and different techniques have been employed for the proctectomy. The endo-anal approach with coring out of the mucosa has been considered to cause sphincter damage, and the technique has been employed to avoid sphincter stretch by performing the dissection entirely from above. In a more recent modification the rectum is transacted at or just distal to the levators preserving the anal canal intact. The results are contradictory in many reports and comparative studies are scarce. Attempts have been made to evaluate the functional merits of different pouch designs. Although Nicholls and Pezim [66] report superior results with the W-pouch both as regards defecation frequency and leakage. However, other studies fail to confirm this statement [67]; there appear to be no major functional differences between the S- and J- shaped pouches [65, 68].

When performing an ileal reservoir, the most distal part of the ileum is used after colectomy. There are several reports on changes of enteric bacteriology [20, 21], morphology [17, 20-22, 67-70], and absorption [20, 21, 71-73] of the functioning reservoir.

In the present dissertation thesis, we have in detail monitored serum/plasma, electrolytes, haematological variables, liver enzymes, proteins, lipid profile, GI-hormones and enzyme, gastric acids secretion and vitamin B_{12} and fat absorption data as well as clinical outcome preoperatively and after colectomy with ileostomy, during the loop ileostomy period, and with the ileoanal pouch in function. As there is no other study which is comparable to this one, it is a necessary task to describe the findings in order to obtain a reference with basic data for better estimation of the risk of homeostasis that await the patients who are offered this type of operations.

Earlier Knowledge of Changes of Homeostasis in Ulcerative Colitis and after its Surgical Treatment.

ELECTROLYTES:

Patients with ulcerative colitis are reported to be depleted in serum magnesium, calcium, zinc, copper, and sodium [24, 74, 76-82]. Others [83, 84] found normal levels while Ringstad and Kildebo [75] found levels higher than in controls. Studies on electrolytes in patients with ileostomy (IL) [72, 74, 77], with Kock pouches (KP) [72, 74, 77, 84], in ileal pouch-anal anastomosis (IPAA) [11, 14], and in ileoanal anastomosis (IAA) [8, 11], showed no disturbances. Nicholls and Moskowitz [78] had six patients who developed electrolyte depletion postoperatively before closure of the ileostomy.

Magnesium: Magnesium deficiency has been described in patients with ulcerative colitis [79-81], Crohn´s disease [82, 83], and in patients with ileostomy [84, 85]. The depletion was common in those with chronic diarrhoea [86, 87] and/ or to those who underwent ileal resections [80]. Since colectomy and loop ileostomy leaves part of the intestine defunctionalized [14, 55, 88], magnesium abnormalities developed because of deprivation in intestinal surface. Other causes for hypomagnesemia include high stoma output [78], (chronic) diarrhoea, steatorrhea and malabsorption [89].

Zinc: Depletion of zinc in serum in ulcerative colitis patients has been reported by Puri et al. [90]. Pathogenesis of zinc deficiency includes impaired intestinal

absorption of zinc [79], increased losses associated with intestinal malabsorption and/ or losses of zinc into the intestinal lumen, with inflammatory exudates [14, 95-99]. Postrestorative proctocolectomy surgery, atrophy of reservoir mucosal has been reported [17, 18, 20, 21, 27, 68, 74, 84]. Low serum zinc in patients with atrophy of intestinal mucosa (villi), has been observed [95-99] and a reduced zinc uptake from an oral test doses has also been reported in patients with mucosal atrophy.

Calcium: Low levels in serum calcium have been shown to characterise patients with ulcerative colitis, before and after surgery [14, 95, 100-103]. Burke et al. [103] verified that patients with ulcerative colitis are significantly protein depleted before surgery and that low calcium has to do with circulating low protein. Moreover, there are publications demonstrating that calcium absorption may be decreased by corticosteroids treatment [100-105]. A condition that may alter calcium absorption has been described in detail by Allen [93] and Levinne et al. [94].

Sodium and potassium: During his functional and biochemical studies on patients with an ileal pouch, Athanasiadis [106] found normal sodium and potassium values.

HAEMATOLOGY:

Haemoglobin (Hb) and Iron (Fe): In ulcerative colitis patients, low serum Hb and Fe has been reported [90, 107]. The possible factors leading to iron deficiency were described [108-110] to be secondary to insufficient iron intake (in the diet), impaired absorption, increased requirements or loss of blood. In many instances, more than one of these factors could be responsible for the resulting low values. After surgical treatment Nilsson et al. [16] in Kocks pouches and Nicholls et al. [14] in pelvic pouches noted normal levels of haemoglobin in all their patients although the 4 patients with low iron were found. Fiorentini et al. [23] reported normal values in all his pelvic pouch patients.

Cynocobalamin (B_{12}): Booth and Mollin [111] reported that the distal ileum is an active part for the absorption for vitamin B_{12}. Further, Seetharam and Alpers [112] confirmed that vitamin B_{12} is absorbed in the distal ileum in man. The question

whether the surface of the excluded intestinal segment is or is not sufficient for the cause of malabsorption of vitamin B_{12} has been discussed [71, 113-116]. It has been repeatedly confirmed that vitamin B_{12} in sufficient amount cannot be absorbed in the absence of the terminal ileum. A reversible absorptive loss of small intestinal capacity was demonstrated by Herbert [117], in the case of vitamin B_{12} deficiency. It was also suggested that a depletion of vitamin B_{12} further impairs the absorption of vitamin B_{12}. A jejunocolic shunt in obese patients was invariably followed by a lack of vitamin B_{12} [118-120]. Payne and DeWind [113] claim that a 13 cm long portion of the distal ileum was sufficient for the absorption of vitamin B_{12} in adequate amounts. Dano and Lenz [121] suggest 36 cm. On the other hand other researchers [111, 115, 122-124] failed to demonstrate this and instead noted gradual deficiency of vitamin B_{12} in their patients. Reduced vitamin B_{12} absorption has also been reported after colectomy [72].

In previous studies [21, 119, 120] the fact that the pouch and defunctionalized loop favours bacteria growth has been realised. Further observations found that despite the morphological changes in the intestinal mucosa and microbial flora, a reservoir retains a stable absorptive capacity [21, 114]. However, it has been noted that abnormal overgrowth of the bacterial flora may lead to changes in the intrinsic factors (IF), the ileal receptor for the IF-B_{12} complex. Bacterial utilization of vitamin B_{12} and decreased transit time due to anatomic constrain also might interfere with vitamin B_{12} absorption [21, 125].

Erythrocyte sedimentation rat (ESR) and White blood cells (WBC): Dozois [126] and Dozois et al. [127] noted in their patients that erythrocyte sedimentation rate (ESR) and leukocytes (WBC) were oftenly elevated in patients with ulcerative colitis in the emergency group prior to colectomy. During functional IPAA, ESR and WBC were occasionally seen elevated, mostly associated with complications such as difficult/ inability to empty the bowel or while having pouchitis. Anaerobic overgrowth, due to faecal stasis is suggested as a possible factor [125].

LIVER ENZYMES:

Ulcerative colitis: Patients with ulcerative colitis have an increased incidence of primary sclerosing cholangitis (PSC) [128-132] and liver cirrhosis [129-131]. In ulcerative colitis cases, about 5% and 27% are reported to have pathologic high liver enzymes (ASAT, ALAT and ALP) values [107, 132]. Rasmussen et al. [132] noted in patients with PSC, a raised ALP mean value 3.7 times the upper normal limit.

Postoperative jaundice of varying degree has been reported [133-135]. In a postoperative study, Evans et al. [133] found in overall incidence of 20 per cent (3.7 per cent severe and 16.5 per cent mild jaundice). This may be a consequence of surgery and anaesthesia unrelated to the specific procedure but multifactorial [134-136].

Clark et al. [137] and Loeschke et al. [138] wrote that the first case of post-transfusion hepatitis was reported in 1885. Postoperative hepatitis was identified as a complication of receipt of whole blood and human plasma transfusion [139-144].

Olsson [145, 146] and Sherlock [147] reported in accordance to their observations, that drugs in common use can cause toxic effects on the liver. Sherlock [147] observed that drug induced hepatitis resembles an attack of acute viral hepatitis. Clinical features and routine serum tests of the liver function are similar. Some evidence supporting that a drug immunoallergic idiosyncratic reaction [146] may cause liver damage is also reported.

Postanesthetic hepatic necrosis most commonly is associated with halothane anaesthesia but may occur with other anaesthetic agents as well [148-152]. Enfluran anaesthesia is reported to cause less damage to the liver compared to halotane anaesthesia but is in turn more hepato-toxic than isoflurane anaesthesia [153, 154]. It has been observed that Isoflurane is the least metabolised of the currently available haloalkanes. Kantrowitz [129], Sherlock [147], and Cobb [155] reported a marked elevation of liver enzymes in the early postoperative period. Schiff [131], and Sherlock [147], published that in such elevations the cause may be postanesthetic hepatic necrosis. To date sevofluran (sevoran) anaesthesia is used because the inhalation is no toxic to the liver.

In patients who have had long and extensive-vascular surgery, hepatocellular dysfunction can be due to hypotension, hypoxia and renal impairment [129, 131, 148]. Serum enzyme values may increase before any other hepatic tests show abnormal results [153].

Cobb and Chapman [155] pointed out that if blood transfusion is rapid, massive, or occurs in a patient with impaired liver function; the capacity of the liver to conjugate bilirubin may be exceeded. Hepatic dysfunction (jaundice) in this situation occurs 10 to 12 hours after transfusion.

The first reported case of cholestasis related to total parenteral nutrition was reported in a premature infant in 1971 [155]. Cholestasis was reported in 14 of 27 patients on TPN, and it was suggested that cholestasis in these patients predisposed them to cholelithiasis [155]. In patients receiving total parenteral nutrition (TPN), hepatobiliary abnormalities are the second most common problem, after catheter sepsis [155]. Changes in liver function are seen within the first few days of total parenteral nutrition, and are often paralled by a rise in the transaminase levels. Cobb and Chapman [155] report that, the rise in transaminase levels that usually accompanies these changes most commonly resolves spontaneously, even when total parenteral nutrition is continued.

Controversially, Grant et al. [156], Lindor et al. [157], and Bengoa et al. [158], reported that the elevated liver function tests returned to baseline only after TPN was discontinued. Bengoa et al. [158] observed that patients with inflammatory bowel disease frequently developed liver function test abnormalities during balanced TPN that normalised after TPN discontinuity.

The elevations of ALAT and ALP may be associated with a disturbance of enterohepatic circulation [155]. Bacterial overgrowth secondary to stasis in the excluded distal bowel is another possible factor [21, 138, 155]. Patients with intestinal shunt are reported to have developed hepatic function disorders [159-161]. About 95% of postbypass patients for obesity are reported to have hepatic dysfunction [160, 162-164]. Thus the finding of the long lasting increase of liver enzymes may be an equivalent to the hepatic dysfunction in patients with intestinal bypass for obesity [160, 162-164].

PROTEINS:

Immunoglobulins: Patients with ulcerative colitis are reported to have increased Immunoglobulin G (IgG) in plasma [165]. The increase of IgG may contribute to the pathogenesis of inflammatory reactions and tissue injury in the intestine [106, 165, 166].

Plasma Immunoglobulin A (IgA) has been found to increase in UC patients [167, 168] and when there is antigen feeding to the intestine [166, 167]. IgA, which is produced locally by plasma cells within the intestinal lamina propria [167], is a large antibody responses mediator.

There are no studies concerning IgA in pouch patients. However, Esteve et al. [30] compared IgA antineutrophil cytoplasm antibody (ANCA) between his patients with ulcerative colitis and ileal pouch anal anastomosis and Brooke's ileostomy, and found that the percentage of IgA ANCA was significantly higher (45%) in ileal pouch anal anastomosis (IPAA) patients than in patients with Brooke's ileostomy (22%). He also noted that, total production of ANCA (IgA and/ or IgG) tended to be higher in non-operated UC patients and in colectomized patients with IPAA than in those with Brook´s ileostomy.

Immunoglobulin M (IgM) is degraded in the intestine by proteolytic enzymes [164, 165, 168-176]. A marked increase in IgM-producing cells in the lamina propria is found in some individuals with IgA deficiency [176]. This suggests that IgM may be playing a protective role in the intestinal mucosa [177-180].

Orosomucoid: Alpha 1-AGP (orosomucoid), as described by Chambers et al. [233] is an acute sensitive marker (100% specificity) of inflammatory disease. Its role in inflammatory bowel disease is of value in monitoring the response to treatment and correlates to the disease activity [181, 182].

Haptoglobin: Haptoglobin, like alpha 1-antitrypsin, and orosomucoid, is an acute phase reactant [183]. The precise nature of haptoglobin abnormality that occurs in ulcerative colitis is not understood. Increased values in pouch patients were

correlated to subclinical pouch inflammation, which was found in 87% of pouch patients by Moskowitz et al. [184].

LIPIDS:

Regoly-Merei and Ferencz [185] studied cholesterol and triglyceride in UC patients and noted that cholesterol did not differ from healthy volunteers while tryglyceride except for two persons, was higher in patients. Hakala et al. [186] noted a significant decrease of total serum cholesterol and triglyceride in his patients with functional ileal pouch anastomosis (IPA) for 16 ± 5 months (M ± SEM), compared to controls. In his studies [31, 186] however the control material consisted however only of males with a mean age of 50 or 51 years, while the study material consisted of males and females with a mean age of 38 or 41.5 years. This may at least partly explain the differences between the study and the control group. Further, it is found that in one control group [186] the mean value for triglycerides is 1.58 mmol/l and in the other 1.14 mmol/l [31]. The significant difference is therefore only reached in one of the studies [186].

In a study of patients with defunctional loop ileostomy after ileal pouch-anal anastomosis Max et al. [26] and also Åkerlund et al. [187] in patients with ileal exclusion, found significantly decreased levels of serum cholesterol and significantly increased serum triglyceride levels. In other previous studies, it was reported that ileal exclusion leads to decreased circulating cholesterol [26, 187-194]. Grundy [190] reported that ileal dysfunction or resection of the distal ileum leads to deprivation in the distal ileum surface and that the cholesterol levels in serum correlates with the length of the excluded ileum. This exclusion may cause bile acid malabsorption and an increased faecal loss of bile acids [187, 195-197]. Bile acid malabsorption affects the micellar solubilisation of cholesterol, thus resulting in impaired cholesterol absorption and decreased serum cholesterol, triglyceride and alpha-lipoprotein absorption from the intestine [196, 198]. In accordance with Åkerlund et al. [187] patients with terminal ileum exclusion, had apparent selective malabsorption of bile acids. The malabsorption of bile acids leads to a condition similar to that occurring after cholestyramine treatment with

increased synthesis of both cholesterol and bile acids and decreased concentration of circulating cholesterol.

Grundy et al. [190] studied four patients with resection of the terminal ileum. Only two of these patients had a slight malabsorption of cholesterol. Buchwald et al. [199] showed that hyperlipidemic patients subjected to removal of 200 cm of the distal bowel had malabsorption of both bile acids and cholesterol. Åkerlund et al. [187] found malabsorption of both bile acids and cholesterol in his patients with 95 cm of distal ileal exclusion,. Angelin and Einarsson [200] and Fiorentini et al. [23] discussed that increased VLDL as a consequence of the increased cholesterol synthesis causes the increase in triglycerides with a common pool for bile acid synthesis and VLDL secretion. Another explanation by Grundy et al. [190] and Angelin and Einarsson [200] could be the direct stimulation of phospholipids and triglyceride synthesis sharing early steps in their biosynthesis.

In his patients with long small terminal ileum exclusion Färkkilä et al. [196] observed low plasma lipoprotein levels and emphasised that, plasma levels of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol are regulated more effectively by cholesterol than bile acid malabsorption.

GASTRIC SECRETION:

Gastric acids: Clinical investigations have demonstrated increased gastric acid secretion following small intestinal resection or exclusions [201-208]. The mechanism whereby reversal segments increase secretion is argued by Sircus [201] to be due to proximal intestinal dilatation.

Serum gastrin: Recent results [209-212] consider colon an endocrine organ, producing regulatory peptides. Gomez et al. [209] and Whang et al. [212] reported that colon resection exerts an influence on remnant bowel including a proliferate adaptive phenomena resulting in significant decreases in plasma somatostatin, neurotension and cholecystokinin post surgery while serum gastrin and peptide YY (PYY) are elevated [210, 211]. These elevations have an important role in the physiologic control of gastric acid secretion [210].

8.
AIMS OF THE PRESENT INVESTIGATION.

The purpose of the present investigation was to assess assayed variable adaptive changes in 99 patients before and after the different steps of restorative proctocolectomy and following the ileal pouch-anal anastomosis (IPAA). The most important aspect of this work was the identification of patients with serum biochemical changes during the functional period.

The specific AIMS for each study were:

Study I

To register a battery of supposed relevant laboratory data in patients before and after colectomy with ileostomy, during the loop ileostomy stage and with the ileoanal pouch in function.

Study II

To analyse in serum the lipid profile in patients who were operated on electively or on emergency basis, before and after colectomy (with terminal ileostomy) with ileal-pouch while having loop ileostomy and with a functioning pouch at 12 months after loop ileostomy closure.

Study III

To analyse gastric acid secretion, GI hormones and enzyme (pepsinogen, pentagastrin and gastrin levels) after restorative proctocolectomy.

Study IV

To investigate the development of haematological data with specific focus on anaemia in patients with a functional ileoanal pouch.

Study V

To assess serum electrolyte levels predisposed the subsequent development after ileal pouch-anal anastomosis in 83 patients who underwent abdominal colectomy with restorative proctocolectomy.

Study VI

To study the plasma concentrations of immunoglobulins in connection with restorative proctocolectomy, an operative procedure involving different manipulations with the distal ileum which may influence the function of gut-associated lymphoid tissues.

9.
PATIENTS (ref. annex VII):

All patients were referred to the Department of Surgery and Clinical Chemistry at Huddinge University Hospital and were included in a program for regular routine follow-up after surgery. All patients received pouch surgery at this hospital.

Study I

The studies were based on the material that includes 83 patients who consecutively received a hand stitched pouch and ileoanal anastomosis, after mucosectomy. Fifty-seven patients were men and thirty-six were women. The mean-age was 33.6 (range, 17-59) years. Fifty-one patients initially underwent subtotal colectomy and ileostomy and 32 had colectomy at the time of pouch construction. In the former group, all patients underwent emergency surgery because of failing conservative treatment of their ulcerative colitis. In the latter group, 2 underwent surgery on emergency, 17 because of chronic continuous disease, 8 because of dysplasia, 1 because of carcinoma (Dukes A), and 1 because of multiple benign stenoses. Eighty patients suffered from ulcerative colitis, two had familial adenomatous polyposis and one was healthy but belonged to a cancer family. The patients obtained a loop ileostomy at the pouch operation and kept it for 1.5 to 36 (median 4.5) months. No patient lost more than 10 cm of the ileum during the operations and, with a few exceptions; the ileum was not resected at all. The length of the ileum diverted during loop ileostomy was 45 to 212 cm of the bowel including the bowel used for the pouch. The pouches (57 S, 25 J, and 1 H) were constructed from 3 x 10 (7 to 16 cm) of the bowel for S, 2 x 20.5 (13 to 40 cm) for J and 2 x 17 for H pouches.

Table I

Number of Patients studied for blood electrolytes, proteins, liver enzymes, hematology and absorption of B_{12} and fat preoperatively, during the manipulative period and at 6 to 36 months of functional pouch (E = elective; A = Acute patients)

Subject	Preoperative		Manipulative		Months of Functional Pouch				
	E	A	Ileo	Loop	6	12	18	24	36
Na	27	33	48	75	75	70	62	64	54
K	26	33	49	77	76	70	63	62	53
Ca	28	30	46	65	73	71	59	62	55
Mg	24	23	42	70	74	71	64	62	50
Zn	24	19	44	63	76	65	62	53	49
Alb	26	35	47	72	73	73	59	60	54
IgG	20	22	38	44	51	45	23	21	28
IgA	16	21	38	41	51	40	23	17	22
IgM	17	20	40	41	49	39	20	8	18
Hapt	22	27	43	64	64	62	40	34	34
Oros	21	26	44	60	61	69	35	35	39
ASAT	29	31	47	76	80	73	69	70	64
ALAT	28	31	46	76	80	73	69	72	65
ALP	25	28	40	70	77	74	69	72	64
Hb	27	36	48	76	80	73	64	67	52
Fe	28	27	40	57	72	70	58	62	53
Folates	21	21	44	62	70	66	60	58	45
B_{12}	22	19	43	61	76	59	60	66	48
Schilling test	17	-	-	-	-	67	-	-	36
^{14}C-breath test	9	-	-	-	-	46	-	-	32

Study II

Thirty-eight (n = 38) patients underwent the procedure of ileal pouch anal anastomosis (IPAA). Twenty-three patients were males and 15 females. The mean age was 35 (range, 18-57) years. Nineteen patients were operated on electively and 19 on an emergency basis. No patient had either underlying diseases such as diabetes, hypothyroidism, dyslipidemias, primary sclerosing cholangitis (PSC) nor other liver or renal diseases, nor were they under any medication such as oestrogens, oral contraceptives and/or diuretics. No patient had a history of significant alcohol use. Preoperatively, the emergency patients were on parenteral nutrition, while otherwise all patients were on their ordinary diet and without parenteral nutrition for at least 3 months during the investigation. The patients denied any significant change of diet during the period.

Elective group: Nineteen patients were operated on electively. Eleven were men and 8 women, with a mean age of 34 (range, 18 - 57) years. Sixteen were operated on because of ulcerative colitis. The duration of the disease was 1.5 - 31 (median 10) years. Eight of them had developed dysplasia. Two patients were operated on due to familial polyposis coli and one prophylactically because of cancer history in the family. In the majority there was no small bowel resection at all during the operation and no patient lost more than 10 cm of the ileum. The diverted ileum used for loop ileostomy was 95 (range, 60 - 127) cm (including the small bowel used for the pouch) was out of function. The median time with loop ileostomy was 4 (range, 3 - 8) months. Twelve (12) S-pouches, 3 x 10 (8 to 15) cm and 7 J-pouches, 2 x 22 (15 to 40) cm were constructed (Table XVII). Prior to the pouch operation, 9 patients had received oral corticosteroid therapy.

Emergency Group: Nineteen patients first underwent subtotal colectomy with terminal ileostomy on an emergency basis due to failing medical treatment of fulminate ulcerative colitis (UC). Thirteen were men and 6 women of mean age 36 (range, 24 - 55) years. The duration of the disease was 1.5 - 29 (median 6) years. These patients had their ileostomy for 3 - 26 (median 9) months prior to the pouch operation. Eleven (11) S-pouches, 3 x 12 (8 to 15) cm and 8 J-pouches, 2 x 15 (6 to 19) cm were constructed (Table XVII). No patient lost more than 10 cm of the ileum and in most cases they lost no ileum at all during the operations. The length of the diverted ileum for loop ileostomy was 92 (range, 57 -

131) (M ± SD) cm (including the bowel used for the pouch) out of function. The duration of loop ileostomy period was 7 (2.3 - 25) (M ± SD) months. All nineteen patients received total parenteral nutrition (TPN) for at least 10 days, prior to the sampling before the colectomy. The TPN consisted of infusions of glucose, amino acids and fat emulsion. The fat emulsion Intralipid® 200 mg/ml (Pharmacia & Upjohn, Sweden) AB contained soybean oil composed of triglycerides stabilised in aqueous glycerol and egg phospholipids. All 19 patients were treated with parenteral corticosteroids in a dosage of 300 mg per day during the same period.

Table II
Number of Patients studied for cholesterol, triglycerides, alpha- lipoproteins (HDL), pre-beta- lipoproteins (VLDL) and beta- lipoproteins (LDL) before the colectomy, during the manipulative period and at 12 months of functional pouch after loop ileostomy closure (E=Elective; A=Acute patients)

Subject	Preoperative		Ileostosmy		Loop		12 Months of IPAA	
	E	A	E	A	E	A	E	A
Cholesterol	15	19	-	19	15	19	15	19
Triglycerides	14	13	-	14	14	13	19	13
Alpha-lipoprotein (HDL)	12	-	-	12	12	-	7	-
Pre-*B*eta-lipopro (VLDL)	12	-	-	12	12	-	7	-
*B*eta-lipoprotein (LDL)	12	-	-	12	12	-	7	-

Study III

Eleven patients were operated with restorative proctocolectomy. Eight patients were males. The mean age was 28.5 (range, 19-42) years. All patients were operated electively. No patient took any drugs before or after the operation and there was no change of diet. Eight S-pouches, 3 x 12 (9-21) cm, and 3 J-pouches 2 x 22.5 (13-38) cm were constructed. All received a diverting loop ileostomy at the pouch operation and kept it for a median of 9.1 (range, 2.5 to 28) months. No patient lost any ileum during the operation. Aspects studied included Gastric acid secretion, serum Gastrin, pentagastrin, and pepsinogen levels.

Table III
Number of Patients studied for hydrochloric acid secretion and volume of

Gastric fluid before the proctocolectomy and at 12 months of functional reservoiafter loop ileostomy closure

Subject	Preoperative	12 Months of Functional Pouch
Retention mmol HCl	7	7
Basal mmol HCl	7	7

Table IV
Number of Patients studied for hydrochloric acid and gastric fluid/ volume after pentagastrin stimulation, before the proctocolectomy and at 12 months of functional reservoir after loop ileostomy closure.

Subject	Preoperative	12 Months of Functional Pouch
Mmol HCl	10	10
Volume (ml)	10	10

Table V
Number of Patients studied for serum gastrin, pentagastrin and pepsinogen, before the proctocolectomy and at 12 months of functional reservoir after loop ileostomy closure**.**

Subject	Preoperative	12 Months of Functional Pouch
Gastrin	11	11
Pentagastrin	11	11
Pepsinogen	10	10

Study IV

Eighty three patients received an ileoanal pouch. The haematology data between the preoperative periods, defunctionalized loop ileostomy stage, and after ileal-pouch in function were monitored. Aspects studied included serum haemoglobin, iron, folates, vitamin B_{12}, white blood cell/ count, erythrocyte sedimentation rate, pt- B_{12}, and fat absorption. Specimens were collected before colectomy, during ileostomy prior to pouch operation, prior to loop ileostomy closure, and at 6, 12, 18, 24 and 36 months after loop ileostomy closure.

Table VI
Number of Patients studied for hemoglobin, iron, folic acid, cynocobalamin, schilling test, breath test, erythrocyte sedimentation rate and white blood count

Data before the proctocolectomy, during the manipulative period and at 36 months follow-up of functional pouch (E = elective; A = Acute patients).

	Preoperative		Manipulative		Months of Functional Pouch				
Subject	E	A	Ileo	Loop	6	12	18	24	36
Hb	27	36	48	76	75	65	55	50	30
Fe	28	27	57	57	68	61	49	46	31
Fol	21	21	43	61	66	56	51	44	25
B_{12}	21	20	43	61	69	58	53	51	28
Sch test w-IF	16	-	-	-	-	67	-	-	35
Sch test wt-IF	17	-	-	-	-	67	-	-	36
^{14}C-Breath test	9	-	-	-	-	46	-	-	32
ESR	27	30	44	69	72	60	53	45	31
WBC	29	30	44	69	73	62	55	50	32

Study V

Eight-three patients who underwent abdominal colectomy with restorative proctocolectomy were studied. Fifty-one patients were first operated on an emergency basis subtotal colectomy and ileostomy due to failing conservative treatment of their ulcerative colitis. Thirty-two patients of which 29 had ulcerative colitis, two had familial polyposis coli and one had familial adenomatous polyposis underwent elective colectomy at the time of pouch construction. Data of Serum magnesium, calcium, sodium, potassium and zinc were collected, before loop ileostomy closure and at 6, 12, 18, 24 and 36 months following loop ileostomy closure.

Table VII
Number of Patients studied for sodium, potassium, calcium, magnesium and zinc Data before proctocolectomy, during the manipulative period and at 36 months follow-up of functional pouch (E = elective; A = Acute patients).

	Preoperative		Manipulative		Months of Functional Pouch				
Subject	E	A	Ileo	Loop	6	12	18	24	36
Na	27	33	48	75	75	70	62	64	54
K	26	33	49	77	76	70	63	62	53
Ca	28	30	46	65	73	71	59	62	55
Mg	24	23	42	70	74	71	64	62	50
Zn	24	19	44	63	76	65	62	53	49

Study VI

Fourty-five patients received an ileoanal pouch (IAP) because of ulcerative colitis. Twenty-seven patients were males and 18 were females. The mean age was 34 (range 18 - 55) years. Twenty-six patients were first operated on an emergency basis by subtotal colectomy with terminal ileostomy. In a second operation, the rectum was excised and an ileoanal pouch and a loop ileostomy that diverted the bowel content from the distal ileum were performed. Eighteen elective patients had their colectomy performed at the same time as the pouch operation. As a last procedure the diverting loop ileostomy was closed and thereby the distal ileum and the ileoanal pouch was put into function. Blood for immunoglobulin analyses was collected from the patients before the colectomy, with terminal ileostomy before construction of the pouch, during the period with functional pouches prior to loop ileostomy closure and 12 months after its closure.

Table VIII
Number of Patients studied for Immunoglobulin G (IgG), Immunoglobulin A (IgA) and Immunoglobulin M (IgM), before the proctocolectomy and at 12 months of functional reservoir after loop ileostomy closure (E=elective; A=Acute patients).

	Preoperative		Ileostomy		Loop		12 Months of Functional Pouch	
Subject	E	A	E	A	E	A	E	A
IgG	26	19	19		26	19	26	19
IgA	26	19	19		26	19	26	19
IgM	26	19	19		26	19	26	19

SURGERY:

The operation: A complete pouch operation was performed in two (elective) or three (emergency) stages [22, 46]. The abdominal colectomy, proximal proctocolectomy, distal mucosectomy, ileal pouch-anal anastomosis, and diverting loop ileostomy comprise the first two stages. The loop ileostomy is closed 12 weeks later as the third and last stage.

Proctectomy: A premuscular dissection was carried down almost to the levators. A surgeon working from the perineal aspect passed an anal retractor through the anal canal into the rectum. The lower 5 cm of rectal mucosa was exposed and, even if a stenosis was present, this can be overcome by gentle stretchings should the mucosa be split in the process, this presents no problem. A solution of normal saline containing adrenaline was injected under the submucosa above the dentate line to lift the mucosa off the underlying circular muscle. It is difficult but possible to do this even when there is quite severe inflammation in the mucosa itself. The mucosa was then excised from the surface of the muscular layer using sharp pointed scissors. The dissection commenced at the dentate line and extended upwards to the cut margin of the rectum. The mucosa of the rectum can be entirely removed in this way in three strips; the anal retractor was rotated by about 60^{0} to expose a new aspect of the rectal wall. Bleeding points were dealt with using diathermy coagulation.

Constructing the pouch (Fig. I): At a point on the antimesenteric aspect of the ileum 12 to 15 cm from the transacted end, the ileum was pulled downward. If the ileum reaches comfortably beyond the symphysis pubis, it was likely that pouch would reached the dentate line. If this cannot not done, tension was placed on the loop of the bowel, and the area of mesenteric foreshortening was sought. The tethering vessels were then isolated with vascular clamps, and, if the terminal

ileum remained viable, it was divided. The S-ileal pouch was constructed: the terminal 30 to 50 cm of the ileum is measured and is folded twice to give three segments of bowel, the proximal two of which are 10 cm long and the distal segment 12 cm long. The additional length of the terminal portion allowed for a 2 - 3 cm length of the ileum to project beyond the pouch. The ileum was opened on its antimesenteric border and the edges of the adjacent loop were sutured. The two outer edges were then folded together to complete the pouch and were again sutured with continuous stitching. A second layer of continuous stitching was then placed as a seromuscular stitch to reinforce the first layer. In this way a pouch consisting of three segments of ileum, each about 10-15 cm long, was created. Proximally to the ileum entered the pouch at one end and the distal 3-cm spout was situated at the other. No valve mechanism of any kind was made at the exit of the pouch.
The abdominal surgeon closed the terminal ileum with a purse-string suture and passed it down together with the pouch into the denuded rectal remnant. The perineal surgeon removed the purse-string suture and gasped the free edges of the ileum, which was drawn down into the lower anal canal. An anastomosis between the terminal ileum and the mid-anal canal was now performed at the level of the dentate line, using interrupted sutures. Each suture incorporated mucosa of the mid-anal canal, a deep bite of the internal sphincter and the full thickness of the muscle and mucosa of the terminal ileum. Two such sutures were placed anteriorly and posteriorly, after which the retractor was withdrawn and then inserted into the ileum itself to expose the lateral wall of the anal canal as well. This allowed a further four sutures on each side to be inserted, which completed the anastomosis.

Constructing the J-pouch: Fourty cm of distal ileum was folded once; two small enterotomies 5 cm proximal to the apex of the pouch, a GIA stapler was directed distally towards the apex and fired. The septum of tissue remaining at the apex was next divided with a stapler. The stapler was then passed in the opposite direction and fired twice. The enterotomy was closed in two layers. The posterior staple line was examined to ensure continuity. The apex of the pouch was delivered through the rectal muscular cuff to the dentate line. The pouch was next anchored to the puborectalis muscle. The apex of the pouch was then incised, and the pouch was anastomised to the dentate line and underlying internal anal sphincter with absorbable suture as described for the S-pouch construction.

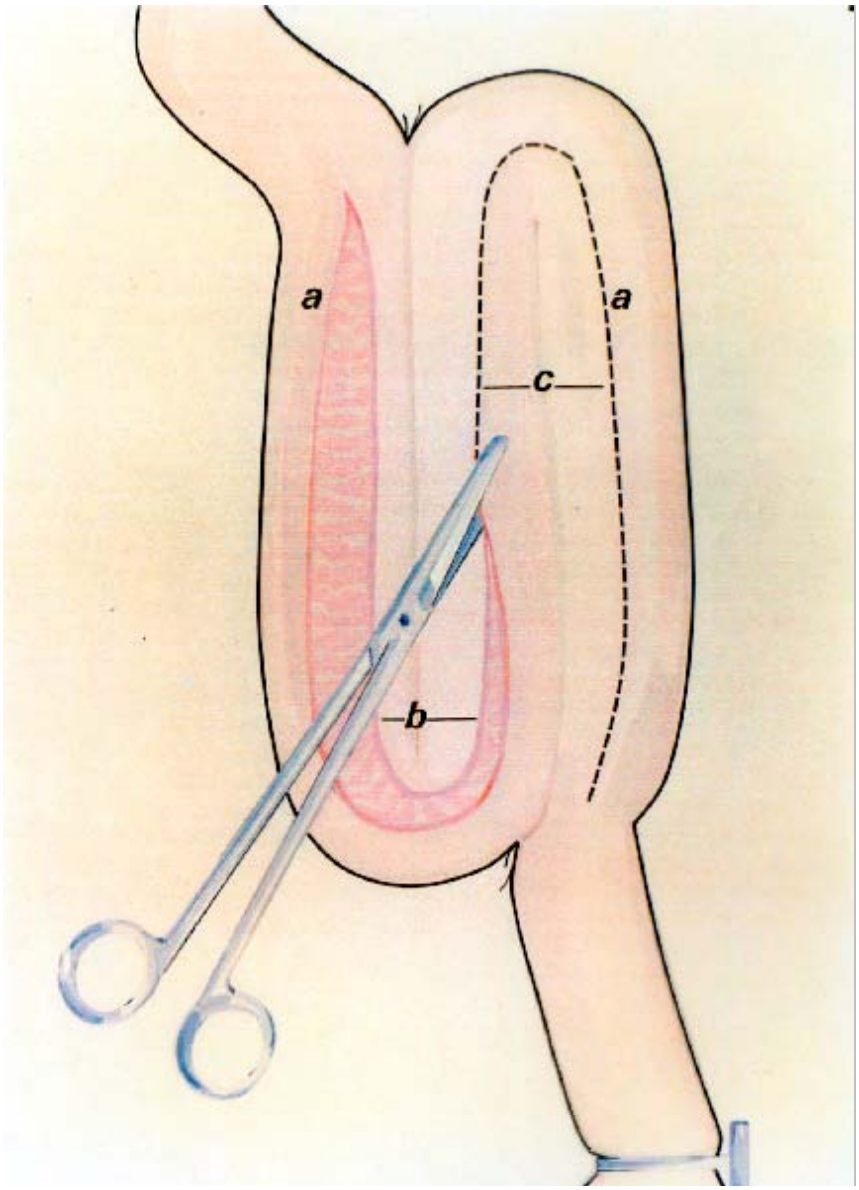
Loop ileostomy: The loop ileostomy was constructed in the right lower quadrant and was formed by exteriorising a loop of the ileum over a plastic rod. The distal

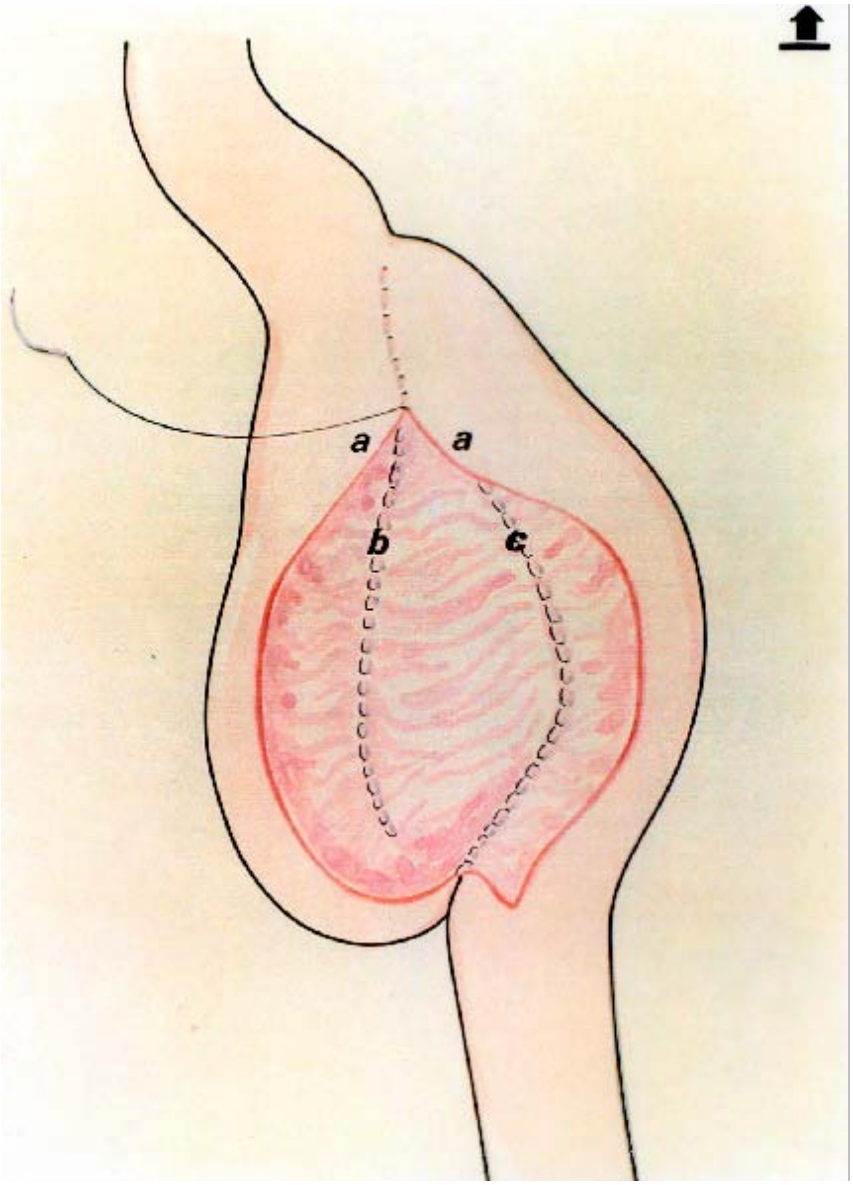
limb of the bowel was opened along four fifths of its circumference, and then the proximal limb was everted and maturated to the skin edge with absorbable suture. The distal end at the skin level was also maturated to the skin. This accomplished faecal diversion to allow healing of the IPAA.
Closure of the stoma was planned 12 weeks after the initial operation. Pouchography was obtained to determine the integrity of the anastomosis and pouch. If a leak or sinus was evident, the closure was delayed 8 to 12 weeks, and pouchography was repeated at that time. Closure was accomplished by either folding over of the stoma or resection and end-to-end anastomosis.

Follow-up routines: Patients were followed up in a prospective fashion by the surgical team at 2, 6, 12, 18, 24 and 36 months after surgery and thereafter, when necessary. A personal interview, different laboratory tests, and a careful clinical examination including pouchoscopy were made at each occasion.

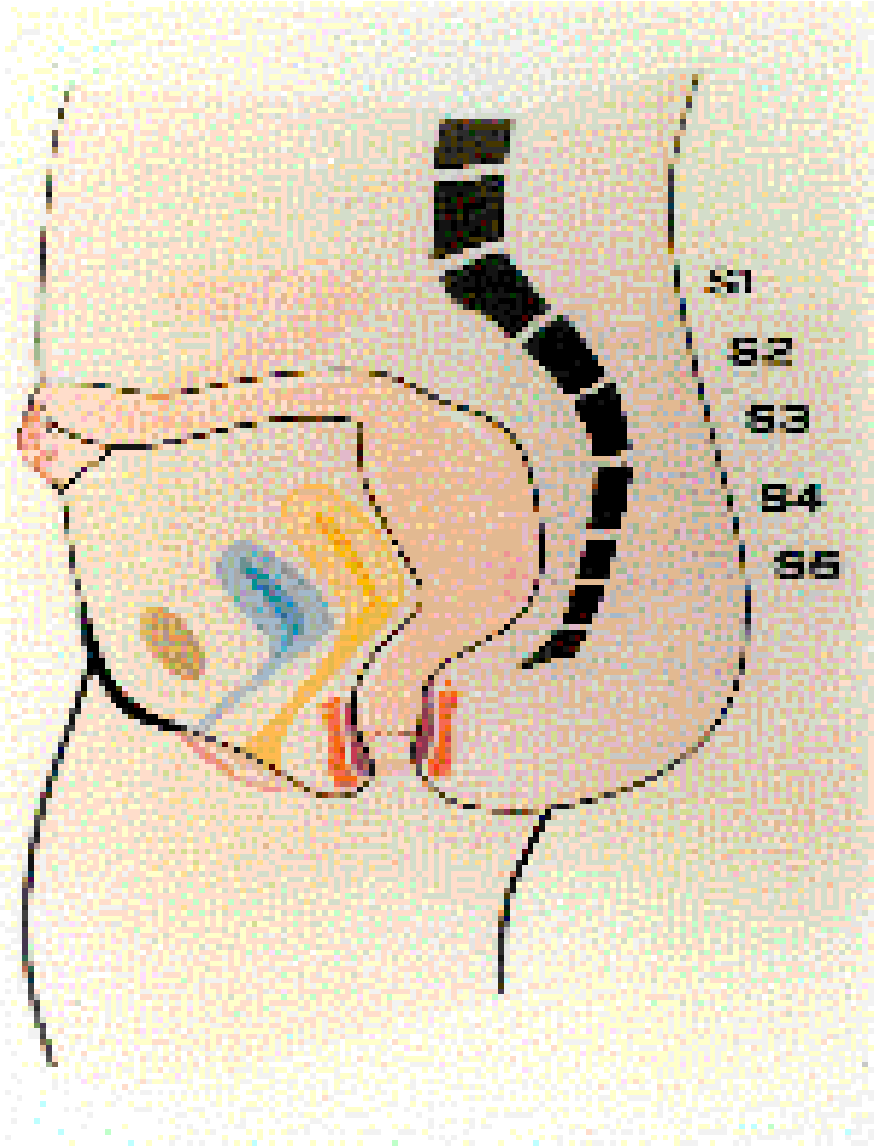
Fig. I

Antimesenteric wall opened. Alignment of the distal ileum for (S) pouch formation. Three limbs of terminal ileum, each 12 to 15 cm length, were aligned side by side. The distal 2 to 3 cm of ileum were to be used for the outlet from the resevoir and anastomosed to the dentate line.

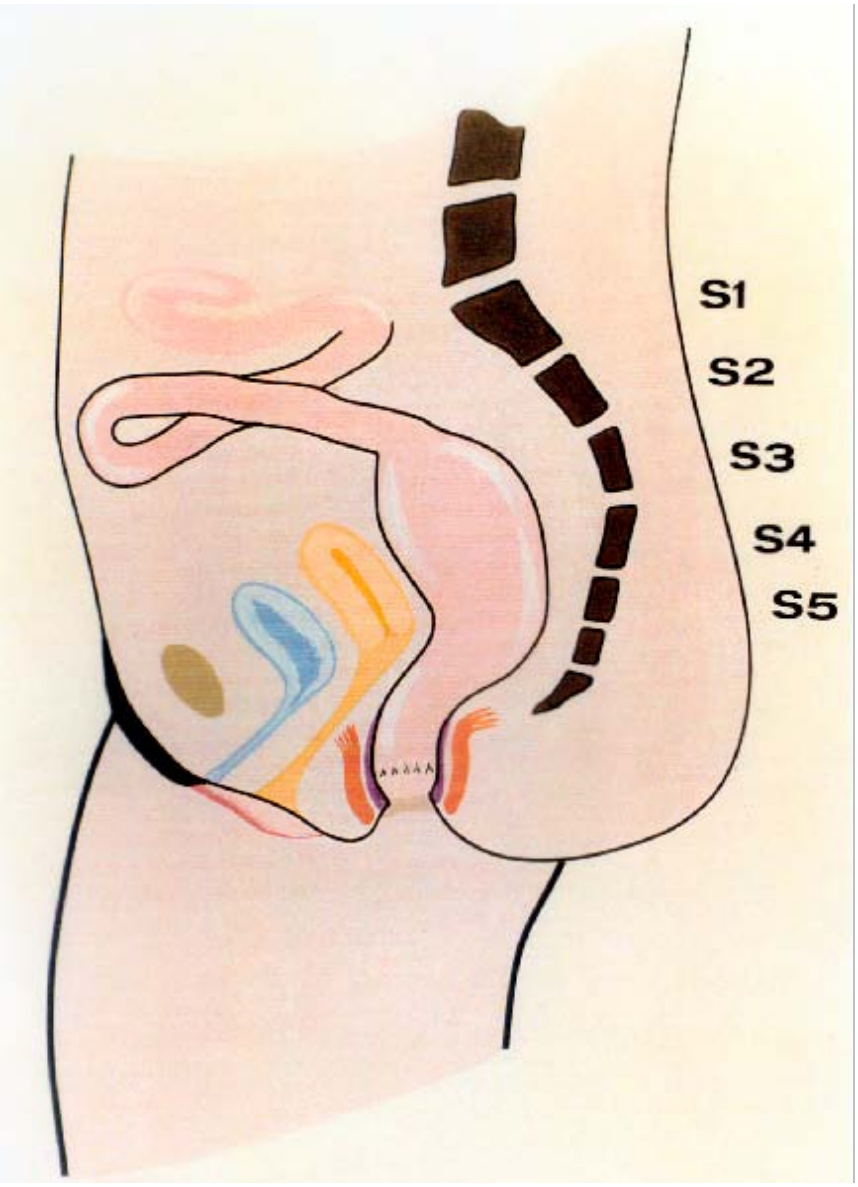



a
a
b
c

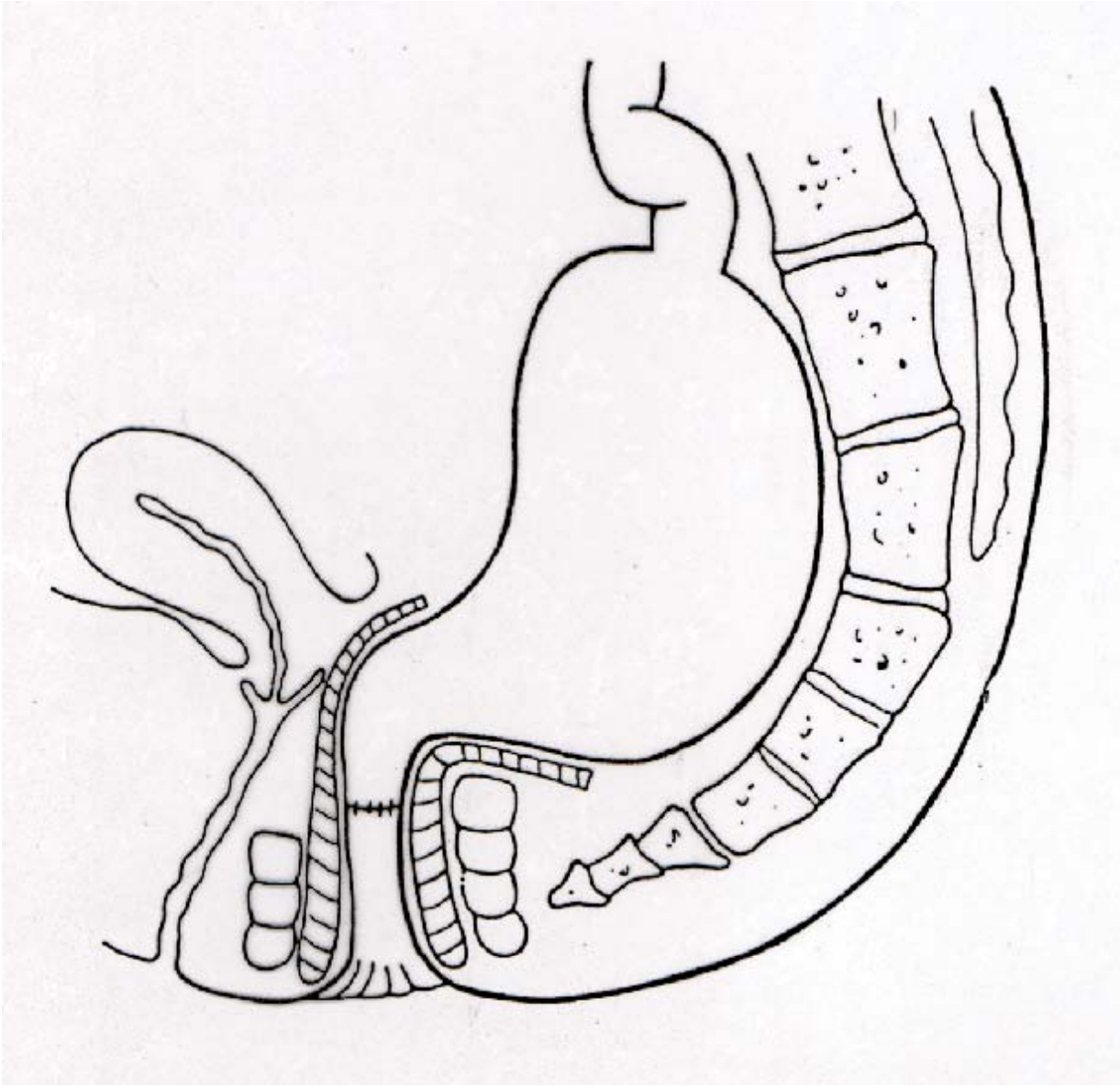
Diverted Loop ileostomy. The loop ileostomy was constructed in the right lower quadrant and was formed by exteriorising a loop of ileum. The distal limb of the bowel was opened along four fifths of its circumference, and then the proximal limb was everted and maturated to the skin edge. The distal end at the skin level was also maturated to the skin.



Loop ileostomy closed. Closure was accomplished by either folding over of the stoma or resection and end-to-end anastomosis.



Completed functional reservoir and IPAA. An ideal was that despite removal of the entire colonic mucosa normal bowel evacuations, continence and fertility were preserved.



9.
BIOCHEMICAL METHODS OF ANALYSIS:

The biochemical laboratory data, aimed to be checked up at each control station, the methods of determination and the number of patients investigated are listed in Table I. Schilling and ^{14}C-Triolein breath tests were determined preoperatively only in the elective cases, and at 12 and 36 months following loop ileostomy closure. The materials were assayed and used routinely for patient's follow-up.
Patients were investigated and were their own control. Besides that we had access to a large reference material at the Karolinska Institute, Department of Clinical Chemistry, Huddinge University Hospital. The reference values are traditionally verified, usually every after two years against the material from 50 – 80 healthy control volunteers.

Study I

Table IX
Normal reference values in serum parameters studied and their methods of determination (Electrolytes, Proteins, Liver enzymes, Hematology, and Lipids)

Parameters	Normal values	Method of analyses
S-Na (sodium)	133-146 mmol/l	Spectrophotometry
S-K (potassium)	3.6-5.1 mmol/l	Spectrophotometry
S-Ca (calcium)	2.20-2.60 mmol/l	Spectrophotometry
S-Mg (magnesium)	0.75-1.25 mmol/l	Spectrophotometry
S-Zn (zinc)	11-20 µmol/l	Spectrophotometry
S-Alb (albumin)	35-46 g/l	Spectrophotometry
P-IgG (immunoglobulin G)	7-15 g/l	Nephelometry
P-IgA (immunoglobulin A)	0.5-3.1 g/l	Nephelometry
P-IgM (immunoglobulin M)	0.3-2.0 g/l	Nephelometry
S-Hapt (haptoglobin)	0.4-2.0 g/l	Nephelometry
S-Oros (orosmucoid)	0.3-1.0 g/l	Nephelometry
S-ASAT (aspartate transaminase)	< 0.7 µkat/l	UV-spectrophotometry
S-ALAT (alanine aminotransferase)	< 0.7 µkat/l	UV-spectrophotometry
S-ALP (alkaline phosphatase)	< 4.2 µkat/l	Spectrophotometry
S-Hb (haemoglobin)	30-165 g/l (men)	Spectrophotometry
	15-145 g/l (Women)	
S-Fe (iron)	9-38 µmol/l	Spectrophotometry
S-Fol (folate)	> 4 nmol/l	Competitive rotein binding isotope

S-B_{12} (cynocobalamin)	40-840 pmol/l	Competitive rotein binding isotope
P-Transferrin	2.1-3.6g/l	Nephelometry
Pt-B_{12} absorption	11-28% without IF	Schilling test
	12-30% with IF	
S-ESR	Males up to 50 yrs < 13 mm	Westergrens Method
	70 yrs < 20 mm	
	Females up to 50 yrs < 21 mm	
	70 yrs < 30 mm.	
S-WBC (white blood cells)	4-10x10^9/l	Coulter-Count model S
S-FFA	< 17 mmol fat acid/d	Spectrophotometry
	Children < 14 mmol/d	
Pt-Triolein test	3,5%/h	Pt-^{14}C-Triolein breath test

Schilling test: Patients fasted and swallowed ^{58}Co Cobalamin and ^{57}Co Cobalamin with intrinsic factor. A Flush dose of nonradioactive Cobalamin 1000µg is given intramuscularly. The urine is collected during 24 hours.
Reference: 11-28% without intrinsic factor and 12-30% with intrinsic factor.

^{14}C-Triolein breath test: Patients are given 30g of fat meal containing 5 µCi ^{14}C-triolein orally. ^{14}Carbon dioxide from expired air is collected hourly for six hours. Expired radioactivity is counted in percent of the given dose to the six periods of specimen collection.
Reference: > 3,5%/h.

Study II

Fasted blood specimens were collected in the mornings. A complete lipid profile, including serum cholesterol, and triglycerides was assayed by enzymatic methods (Boehringer Mannheim, Mannheim, Germany). The tubes were sliced, and the supernatant fraction as well as the infranatant was analysed for cholesterol and triglyceride content. Lipoproteins were analysed by a combination of ultracentrifugation and precipitation. Serum was spun at 35,000 rpm for 18 hours at 4^0C in a Contron Centrikon Y-2060 ultracentrifuge equipment with a 45.6 rotor.

Table X
Normal reference values in serum for total cholesterol, triglycerides, alpha-lipoprotein (HDL), pre-beta-lipoprotein (VLDL) and beta-lipoprotein (LDL).

Parameter	Age (years)	Gender	
		Women	Men
Cholesterol	1-19	< 5,2 mmol/L	< 5,2 mmol/L
	20-29	< 5,7 mmol/L	< 6,0 mmol/L
	30-39	< 6,1 mmol/L	< 6,8 mmol/L
	40-49	< 6,8 mmol/L	< 7,0 mmol/L
	50-59	< 7,7 mmol/L	< 7,2 mmol/L
Triglycerides	16-19	< 1,8 mmol/L	
	20-29	< 2,1 mmol/L	
	>30	< 2,2 mmol/L	
		Of total serum lipoproteins	
Alpha-lipoprotein (HDL)		30-40%	
Pre-beta-lipoprotein (VLDL)		10-35%	
Beta-lipoprotein (LDL)		40-60%	

The tubes were sliced, and the supernatant fraction as well as the infranatant was analysed for cholesterol and triglyceride content. A portion of the infranatant was treated with phosphotungstic acid to precipitate proteins containing lipoprotein and was analysed as described above. The lipoproteins were not analysed in the emergency operated group because these patients had been colectomised in other hospitals. When they were referred to us for pouch operation no precolectomy lipoprotein variables were available. The measurement of the diverted ileum length was always done in the same manner intraoperatively. These analyses were performed before and after colectomy with conventional ileostomy, before loop ileostomy closure and at 12 months following closure of loop ileostomy.
Reference values in accordance to age and gender are presented in Table X.

Study III

Gastric acid determination: After an overnight fasting a nasogastric tube was inserted and the position controlled by fluoroscopy. Fasting stomach gastric content (Retention) was aspirated. Eight 15-minute collection of gastric juice was made four before (Basal secretion) and four after subcutaneous injection of 6-µg pentagastrin (Peptavlon® ICI, Cambridge laboratory Newcastle, United Kingdom) per kg. body weight (Stimulated secretion).

The volume was measured to the nearest ml in all 15-minute collections and acid content was determined by titration with sodium hydrochloride (NaOH) to pH 7.0 by means of an autotitrator TTT (Radiometer, Copenhagen).
Reference values for basal secretion (BAO) were 0 to 5 mmol HCl/hour. Reference values for stimulation secretion (MAO) were 10 to 20 mmol HCl/hour for women and 10 to 25 mmol HCl/hours for men.

Hormones and Enzyme analyses:
Serum gastrin, pentagastrin, and pepsinogen: Blood specimens for determination of fasting serum gastrin concentration were taken before colectomy and 12 months after loop ileostomy closure operation. All samples from each patient were examined at the same time after storage at -20^{C}. Serum gastrin, pepsinogen and pentagastrin were measured by radioimmunoassay.
Reference fasting values were for serum-gastrin: < 120pg/l, serum-pentagastrin: basal secretion 0-5 mmol/h, after stimulation 10 - 20 mmol/h for women and 10 - 25 mmol/h for men and serum-pepsinogen 20 - 80 µg/l.

Study IV

Table XI
Normal reference values in serum for hemoglobin, Iron, Folates, Cynocobalamin, Transferrin, ESR, WBC, Schilling och ^{14}C-Triolein tests

Parameters	Normal values	Method of analyses
S-Hb (haemoglobin)	130-165 g/l (men)	Spectrophotometry
	115-145 g/l (Women)	
S-Fe (iron)	9-38 µmol/l	pectrophotometry
S-Fol (folate)	> 4 nmol/l	Competitive protein binding isotope
S-B_{12} (cynocobalamin)	40-840 pmol/l	Competitive protein binding isotope
P-Transferrin	2.1-3.6g/l	Nephelometry
Pt-B_{12} absorption	11-28% without IF	Schilling test
	12-30% with IF	
Pt-Triolein test	3,5%/h	Pt- ^{14} C-Triolein breath test
S-ESR	Males up to 50 yrs < 13 mm	Westergrens method
	70 yrs < 20 mm	
	Females up to 50 yrs < 21 mm	
	70 yrs < 30 mm.	
S-WBC (white blood cells)	4-10x10^{9}/l	Coulter-Counter modell S

Schilling test: Patients fasted and swallowed ^{58}Co Cobalamin and ^{57}Co Cobalamin with intrinsic factor. Flush dose of nonradioactive Cobalamin 1000µg is given intramuscularly. The urine is collected during 24 hours.
Reference: 11-28% without intrinsic factor and 12-30% with intrinsic factor.

^{14}C-Triolein breath test: Patients are given 30g of fat meal containing 5 µCi ^{14}C-triolein orally. ^{14}Carbon dioxide from expired air is collected hourly for six hours. Expired radioactivity is counted in percent of the given dose to the six periods of specimen collection.
Reference: > 3,5%/h.

Studies V

Table XII
Normal reference values in serum of sodium, potassium, calcium, magnesium, and zinc.

Parameters	Normal values	Method of analyses
S-Na (sodium)	133-146 mmol/l	Spectrophotometry
S-K (potassium)	3.6-5.1 mmol/l	Spectrophotometry
S-Ca (calcium)	2.20-2.60 mmol/l	Spectrophotometry
S-Mg (magnesium)	0.75-1.25 mmol/l	Spectrophotometry
S-Zn (zinc)	11-20 µmol/l	Spectrophotometry

Studies VI

Table XIII
Normal reference values in serum of Immunoglobulin G, Immunoglobulin A, and Immunoglobulin M.

Parameters	Normal values	Method of analyses
P-IgG (immunoglobulin G)	7-15 g/l	Nephelometry
P-IgA (immunoglobulin A)	0.5-3.1 g/l	Nephelometry
P-IgM (immunoglobulin M)	0.3-2.0 g/l	Nephelometry

10.
STATISTICS:

Study I

Data are given as mean ± standard error (of the mean) (M ± SE). Student t-test for paired data and the chi-square analyses were used. Unless stated otherwise differences were regarded as significant for a probability value of less than 0.05.

Study II and Study III

Data are given as mean ± standard deviation (of the mean) (M ± SD). Distributed data were either compared from the values before colectomy and 1) after colectomy with end ileostomy, 2) after ileo-anal pouch anastomosis with a loop ileostomy excluding a considerable part of ileum and/ or 3) 12 months after loop ileostomy closure, during the function of the ileo-anal pouch, by paired or unpaired Student's t-test with Bonferroni´s correction for multiple comparisons [213, 214]. Correlation was calculated as Pearson´s product-moment correlation coefficients [215]. Unless stated otherwise differences were regarded as significant for a probability value of less than 0.05. Correlation of test results to length of excluded ileum was accomplished with linear regression analysis.

Study IV

The results are given as mean value ± standard error of the mean (S.E.M). Paired Student´s t-test and measures of analysis of variance and P-values evaluated the statistical significance of the differences less than 0.05 considered as significant.

Study V

Fisher's exact probability test or chi-square analyses were used for the nominal data. The student's t test for unpaired data was used in the analysis of levels. Significance was claimed when $p< 0.05$.

Study VI

The statistical procedures were performed using the Biomedical Data Processing package, BMDP (Statistical Software Inc. Los Angeles. CA; (1986) [208]. Distributed data were compared from the values before colectomy and i) after colectomy with end ileostomy, ii) after ileo-anal pouch anastomosis with a loop ileostomy excluding part of ileum and iii) 12 months after loop ileostomy closure, by ANOVA method with Bonferroni´s correction for multiple comparisons [213, 214]. Correlation was calculated as Pearson's product-moment correlation coefficient [215]. Comparable test results to length of excluded ileum and plasma variables were accomplished with linear regression analysis. Unless stated otherwise differences were regarded as significant for a probability value of less than 0.05.

11.
ETHICAL CONSIDERATIONS:

This study was conducted in accordance with the second Helsinki Declaration and approved by the Institutional Ethical Committee, Karolinska Institute at Huddinge University Hospital. Informed consent was given, and participation in the study was voluntary.

12.
RESULTS:

CLINICS:

In three patients the pouches were removed because of pelvic sepsis and in one because of chronic pouchitis. One pouch was conveyed to a Kock pouch owing to recurrent anal fistulas. At twelve months follow-up the mean number of evacuations in the 83 patients was 5.0/24 h and 0.5 during the night, 81 percent were continent, 16 percent had minor leakage, and 4 percent had major leakage during daytime. Seventy three percent were continent at night, 10 percent had minor leakage, and 17 percent could often more or less have major leakage. Fifty-three patients had a follow-up of 36 months or more. At 36 months follow-up the mean evacuation rate was 5.2/24 h and 0.5 during the night, 66 percent were

continent, 30 percent had minor leakage, and 4 percent major leakage occasionally or more often during daytime. During the nights 59 percent were continent, 26 percent had staining or soiling, and 15 percent had major leakage occasionally or more often. During the follow-up 34 percent (n = 28) of the patients were treated once or more for pouchitis. Long-standing or chronic pouchitis based upon endoscopic and histologic criteria developed in eight patients. In one patient the pouch was removed after two years and 18 months of continuous successively worse pouchitis, penetrating all layers of the bowel wall. In four of those patients the pouchitis appeared early (0 - 2 months) and were controlled after 10 to 24 months: however in three of them it is still occurring with some activity. In three other patients the pouchitis appeared after 2, 24, and 25 months respectively, and continued after 36, 14, and 14 months, respectively.

Electrolytes (Study I): Parallel data for serum albumin was controlled; in order to make sure that ionised electrolyte values were not available.

Pathologic values of sodium and potassium were rarely seen and the deviations were usually minor. Low values of calcium were found preoperatively in acute patients in relatively high percentages but otherwise pathologic values were seldom recorded. Sixteen percent of the patients with terminal ileostomy had high values of zinc, while 2-5% of the patients had low values during the manipulative and follow-up phases. Magnesium was decreased at all stations in 16-36% of the patients. However, the mean value of magnesium, although decreasing during the manipulative phase, was steadily increasing during the follow-up. At 12 and 36 months of function 6/19 and 2/5 of the patients with low magnesium, respectively, had low values at most stations, while the others had this only occasionally. The patients with repeated low magnesium values were treated with magnesium perorally. However, most patients stopped supplementational medication of magnesium after a short period of time.

Table XIV

Serum- sodium, calcium, zinc, magnesium and potassium before-, during-, and after- restorative proctocolectomy surgery, 36 months follow-up of the functional reservoir.

Point of Control	Parameter	Number of pts Studied	Pathologic values in % Low	High	M ± SEM	*P value*
Precolectomy	Sodium (Na)	60	5	0	138 ± 0.47 mmol/l	
Ileostomy	Sodium (Na)	47	4	0	139.81 ± 0.32 mmol/l	*0.008*
Loop ileostomy	Sodium (Na)	74	0	0	139.07 ± 0.34 mmol/l	*0.08*
6 months	Sodium (Na)	69	0	0	139.93 ± 0.25 mmol/l	*0.01*
12 months	Sodium (Na)	59	0	0	140.46 ± 0.27 mmol/l	*0.0001*
18 months	Sodium (Na)	51	0	2	140.71 ± 0.51 mmol/l	*0.0003*
24 months	Sodium (Na)	46	0	0	140.61 ± 0.33 mmol/l	*0.0003*
36 months	Sodium (Na)	31	2	1	140.68 ± 0.46 mmol/l	*0.01*
Precolectomy	Calcium (Ca)	59	36	0	2.25 ± 0.03 mmol/l	
Ileostomy	Calcium (Ca)	46	15	4	2.38 ± 0.02 mmol/l	*0.04*
Loop ileostomy	Calcium (Ca)	65	5	3	2.41 ± 0.01 mmol/l	*0.0001*
6 months	Calcium (Ca)	69	1	4	2.41± 0.02 mmol/l	*0.0001*
12 months	Calcium (Ca)	62	2	0	2.41± 0.01 mmol/l	*0.0001*
18 months	Calcium (Ca)	50	10	2	2.36 ± 0.03 mmol/l	*0.01*
24 months	Calcium (Ca)	46	4	2	2.30 ± 0.01 mmol/l	*0.0003*
36 months	Calcium (Ca)	32	3	2	2.36 ± 0.18 mmol/l	*0.04*
Precolectomy	Zinc (Zn)	43	5	5	15.30 ± 0.49 µmol/l	
Ileostomy	Zinc (Zn)	44	2	16	16.02 ± 0.63 µmol/l	*0.32*
Loop ileostomy	Zinc (Zn)	63	6	11	16.40 ± 0.62 µmol/l	*0.52*
6 months	Zinc (Zn)	70	4	6	15.59 ± 0.37 µmol/l	*0.73*
12 months	Zinc (Zn)	54	4	7	15.69 ± 0.47 µmol/l	*0.46*
18 months	Zinc (Zn)	54	6	6	15.30 ± 0.45 µmol/l	*0.95*
24 months	Zinc (Zn)	35	6	3	15.11 ± 0.49 µmol/l	*0.77*
36 months	Zinc (Zn)	26	8	4	15.12 ± 0.48 µmol/l	*0.79*
Precolectomy	Magnesium	47	21	0	0.79 ± 0.02 mmol/l	
Ileostomy	Magnesium	42	26	0	0.79 ± 0.01 mmol/l	*0.65*
Loop ileostomy	Magnesium	70	36	0	0.78 ± 0.01 mmol/l	*0.61*
6 months	Magnesium	70	19	0	0.79 ± 0.01 mmol/l	*0.61*
12 months	Magnesium	63	27	0	0.79 ± 0.01 mmol/l	*0.67*
18 months	Magnesium	54	27	0	0.81 ± 0.01 mmol/l	*0.39*
24 months	Magnesium	47	26	0	0.81 ± 0.01 mmol/l	*0.03*
36 months	Magnesium	28	16	0	0.85 ± 0.02 mmol/l	*0.08*
Precolectomy	Potassium	59	0	0	4.22 ± 0.05 mmol/l	
Ileostomy	Potassium	49	2	0	4.19 ± 0.05 mmol/l	*0.30*
Loop ileostomy	Potassium	76	1	0	4.22 ± 0.04 mmol/l	*0.74*
6 months	Potassium	70	3	0	4.28 ± 0.04 mmol/l	*0.31*
12 months	Potassium	63	0	2	4.37 ± 0.05 mmol/l	*0.02*
18 months	Potassium	53	0	2	4.29 ± 0.06 mmol/l	*0.27*
24 months	Potassium	45	0	2	4.36 ± 0.06 mmol/l	*0.10*
36 months	Potassium	30	0	0	4.33 ± 0.05 mmol/l	*0.83*

Proteins (Studies I and VI): Low serum albumin values were seldom seen except in patients who were to be acutely colectomized.

Plasma IgM was found to be above normal in 40% of the patients at time for loop ileostomy closure compared to 6% and 10%, preoperatively, and 12% after 36 months of function. The mean value for IgM at loop ileostomy closure was significantly higher ($p< 0.0005$) than it was preoperatively. The largest share of patients with pathologically increased plasma IgA (26%) was found at 18 months. The mean value was significantly higher than the preoperative value during control at 12 months ($p< 0.05$). The mean value of plasma IgG seemed to rise during the follow-up.

Table XV

Plasma- Immunoglobulin G (IgG), Immunoglobulin M (IgM) and Immunoglobulin A (IgA) before-, during-, and after- restorative proctocolectomy surgery, 36 months follow-up of functional reservoir.

Point of Control	Parameter	Number of pts Studied	Pathologic values in % Low	High	M ± SEM	*P value*
Precolectomy	IgG	44	0	11	10.5 ± 0.47 g/l	
Ileostomy	IgG	38	0	5	10.87 ± 0.82 g/l	*0.62*
Loop ileostomy	IgG	44	0	9	11.86 ± 0.76 g/l	*0.13*
6 months	IgG	51	0	6	11.16 ± 0.36 g/l	*0.36*
12 months	IgG	45	0	16	12.40 ± 0.44 g/l	*0.005*
18 months	IgG	23	0	22	12.70 ± 0.77 g/l	*0.05*
24 months	IgG	21	0	14	11.76 ± 0.76 g/l	*0.38*
36 months	IgG	28	0	18	13 ± 0.65 g/l	*0.07*
Precolectomy	IgM	37	0	8	1.26 ± 0.09 g/l	
Ileostomy	IgM	39	0	18	1.66 ± 0.12 g/l	*0.009*
Loop ileostomy	IgM	40	0	40	1.80 ± 0.09 g/l	*0.0005*
6 months	IgM	49	0	27	1.71 ± 0.12 g/l	*0.008*
12 months	IgM	38	0	26	1.59 ± 0.12 g/l	*0.05*
18 months	IgM	20	0	15	1.46 ± 0.13 g/l	*0.88*
24 months	IgM	8	0	25	2.09 ± 0.57 g/l	*0.56*
36 months	IgM	18	0	12	1.52 ± 0.17 g/l	*0.38*
Precolectomy	IgA	37	0	8	2.05 ± 0.13 g/l	
Ileostomy	IgA	38	0	16	2.04 ± 0.16 g/l	*0.90*
Loop ileostomy	IgA	29	0	14	2.24 ± 0.15 g/l	*0.36*
6 months	IgA	51	0	8	2.20 ± 0.12 g/l	*0.72*
12 months	IgA	40	0	20	2.73 ± 0.33 g/l	*0.04*
18 months	IgA	23	0	26	2.67 ± 0.25 g/l	*0.05*
24 months	IgA	17	0	18	2.36 ± 0.22 g/l	*0.24*
months	IgA	22	0	23	2.37 ± 0.18 g/l	*0.4*

When the emergency operated patients were compared to electively operated, there was a significant difference preoperatively, in plasma immunoglobulin G (P-IgG) ($p< 0.03$). This was the only significant difference between values for the

emergency and elective groups throughout the study. In the emergency patients after colectomy and with terminal ileostomy plasma immunoglobulin A (IgA) and immunoglobulin M (IgM) concentrations in plasma had increased significantly compared to preoperative ($p< 0.03$) and ($p< 0.002$) respectively. During the time with loop ileostomy plasma IgM was still found to be significantly elevated ($p< 0.02$) compared to the level before colectomy.

Table XVI
Comparisons of mean ± Standard Deviation of P-IgG, P-IgA and P-IgM (g/l) between electively *versus* emergency operated patients, Before Proctocolectomy, while having loop ileostomy and After 12 months of Functional Reservoir after Loop ileostomy Closure (P- = Plasma).

Operation Bases	Precolectomy			Loop ileostomy			12 months-IPAA		
	P-IgG g/l	P-IgA g/l	P-IgM g/l	P-IgG g/l	P-IgA g/l	P-IgM g/l	P-IgG g/l	P-IgA g/l	P-IgM g/l
Elective	11.5 ± 3	2.0 ± 0.7	1.5 ± 0.5	11.8 ± 3	2.3 ± 0.8	1.9 ± 0.5	11.9 ± 3	2.3 ± 0.8	1.8 ± 0.6
Emergency	9.6 ± 3	2.0 ± 0.8	1.3 ± 0.5	10.7 ± 3	2.0 ± 0.8	1.6 ± 0.6	11.6 ± 3	2.1 ± 0.8	1.6 ± 0.7
P value	*< 0.03*	*0.87*	*0.69*	*0.15*	*0.35*	*0.29*	*0.95*	*0.80*	*0.61*

In the electively operated patients plasma IgA and IgM were significantly increased after colectomy and pouch construction during the time with diverting loop ileostomy compared to preoperatively ($p< 0.04$) and ($p< 0.0004$). After 12 months with functional pouches the plasma immunoglobulins in both groups were similar to the elective patients preoperatively.

Table XVII

Mean ± standard Deviation in plasma immunoglobulin G, immunoglobulin A and immunoglobulin M in the Emergency operated patients, Before Proctocolectomy, while having terminal and loop ileostomy and After 12 Months of Functional Reservoir After loop ileostomy Closure.

		Precolectomy		Terminal Ileostomy			Loop ileostomy			12 months-IPAA		
Registered Parameter	Number of patients studied	Number of pathologic cases (%)	M ± SD g/l	Number pathologic cases (%)	M ± SD g/l	*P value*	Number of pathologic cases (%)	M ± SD g/l	*P value*	Number of pathologic cases (%)	M ± SD g/l	*P value*
P-IgG	26	2 (8%)	9.9 ± 3	1 (4%)	10.4 ± 3	*0.26*	2 (8%)	10.7 ± 3	*0.19*	3 (16%)	11.6 ± 3	*< 0.002*
P-IgA	26	2 (8%)	2.0 ± 0.8	3 (12%)	2.2 ± 0.8	*< 0.03*	2 (8%)	2.0 ± 0.8	*0.59*	1 (4%)	2.1 ± 0.8	*0.25*
P-IgM	26	4 (15%)	1.3 ± 0.5	5 (19%)	1.7 ± 0.6	*< 0.002*	6 (23%)	1.6 ± 0.6	*< 0.02*	8 (31%)	1.6 ± 0.6	*0.08*

Abbreviations:
M ± SD = mean ± standard Deviation
p = probability value (significances)
P-IgG = plasma immunoglobin G

P-IgA = plasma immunoglobin A
P-IgM= plasma immunoglobin M

Table XVIII

Mean ± standard Deviation in plasma immunoglobulin G, immunoglobulin A and immunoglobulin M in the Electively operated patients, Before Proctocolectomy, while having loop ileostomy and After 12 Months of Functional Reservoir After loop ileostomy Closure.

		Precolectomy		Loop ileostomy			12 months-IPAA		
Registered Parameter	Number of patients studied	Number of pathologic cases (%)	M ± SD g/l	Number pathologic cases (%)	M ± SD g/l	*P value*	Number of pathologic cases (%)	M ± SD g/l	*P value*
P-IgG	19	2 (11%)	11.5 ± 3	2 (11%)	11.8 ± 3	*0.55*	2 (11%)	11.9 ± 3	*0.45*
P-IgA	19	1 (5%)	2.0 ± 0.7	3 (17%)	2.3 ± 0.8	< *0.04*	3 (16%)	2.3 ± 0.8	*0.14*
P-IgM	19	2 (11%)	1.5 ± 0.5	8 (42%)	1.9 ± 0.5	< *0.0004*	4 (21%)	1.8 ± 0.6	*0.06*

Abbreviations:
M ± SD = mean ± standard Deviation

Orosmucoid was found in pathologically high concentrations before colectomy in 60% of the electively and 92% of the acutely operated patients. The corresponding figures for haptoglobin was 40 and 80%, respectively. Throughout the manipulative and functional periods 16% to 37% and 15% to 30% of the patients had increased levels of orosmucoids and haptoglobins. There was no correlation between the increased serum values of orosmucoid and haptoglobin and acute, clinical pouchitis.

Table XIX
Serum- orosomucoid, haptoglobin and albumin before-, during-, and after-restorative proctocolectomy surgery, 36 months follow-up of the functional reservoir.

Point of Control	Parameter	Number of pts Studied	Pathologic values in % Low	High	M ± SEM	*P value*
Precolectomy	Orosomucoid	47	0	72	1.55 ± 0.11 g/l	
Ileostomy	Orosomucoid	43	0	37	1.05 ± 0.07 g/l	*0.0002*
Loop ileostomy	Orosomucoid	60	0	20	0.81 ± 0.04 g/l	*0.0001*
6 months	Orosomucoid	59	0	21	0.86 ± 0.04 g/l	*0.0001*
12 months	Orosomucoid	53	0	16	0.94 ± 0.12 g/l	*0.0004*
18 months	Orosomucoid	27	0	26	0.91 ± 0.07 g/l	*0.0003*
24 months	Orosomucoid	26	0	31	0.89 ± 0.06 g/l	*0.0001*
36 months	Orosomucoid	30	0	21	0.86 ± 0.05 g/l	*0.0001*
Precolectomy	Haptoglobin	49	0	61	2.81 ± 0.20 g/l	
Ileostomy	Haptoglobin	43	0	30	1.66 ± 0.10 g/l	*0.0001*
Loop ileostomy	Haptoglobin	64	0	17	1.38 ± 0.08 g/l	*0.0001*
6 months	Haptoglobin	64	0	20	1.61 ± 0.10 g/l	*0.0001*
12 months	Haptoglobin	62	0	15	1.47 ± 0.08 g/l	*0.0001*
18 months	Haptoglobin	39	0	23	1.61 ± 0.14 g/l	*0.0001*
24 months	Haptoglobin	34	0	29	1.77 ± 0.16 g/l	*0.005*
36 months	Haptoglobin	34	0	35	1.77 ± 0.12 g/l	*0.002*
Precolectomy	Albumin	61	39	8	36 ± 0.89 g/l	
Ileostomy	Albumin	46	7	15	41 ± 0.73 g/l	*0.0006*
Loop ileostomy	Albumin	72	7	13	42 ± 0.58 g/l	*0.0001*
6months	Albumin	73	4	4	41 ± 0.42 g/l	*0.0001*
12 months	Albumin	72	5	1	40 ± 0.37 g/l	*0.0001*
18 months	Albumin	56	4	7	41 ± 0.56 g/l	*0.0001*
24 months	Albumin	60	8	5	40 + 0.57 g/l	*0.0002*
36 months	Albumin	54	9	7	40 ± 0.50 g/l	*0.0005*

Liver enzymes (Study I): There was a high percentage of patients with increased serum ALAT and/ or ALP, 36% and 42% respectively, at the end of the loop ileostomy period compared to a preoperative percentage of 14% and 12% in the elective group, and 13% and 4% in the emergency group.
Fifty percent of the patients with increased ALAT also had increased ALP. A greater part of the patients operated on electively, compared to those operated

on acutely, showed increased levels of ALAT. A certain correlation was seen between the length of excluded bowel and the occurrence of pathologic values. There was a stepwise increase in the percentage of patients with elevated levels of ALP with the length of excluded/-diverted bowel and there were significantly ($p< 0.05$) more patients with high ALAT levels among those with more than 105 cm of diverted bowel. During the functional periods the percentage of patients with increased ALAT and/ or ALP is comparable with the preoperative state and much lower than during the period with loop ileostomy.

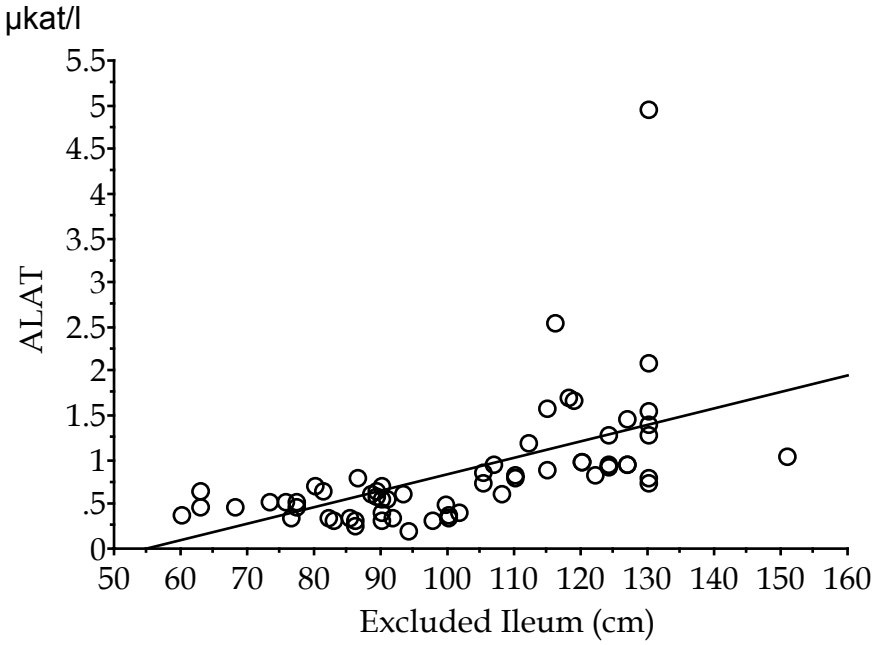
Table XX
Serum- ASAT, ALAT and ALP before-, during-, and after- restorative proctocolectomy surgery, 36 months follow-up of the functional reservoir.

Point of Control	Parameter	Number of pts Studied	Pathologic values in % Low	High	M ± SEM	*P value*
Precolectomy	ASAT	62	0	10	0.40 ± 0.03 µkat/l	
Ileostomy	ASAT	47	0	2	0.38 ± 0.02 µkat/l	*0.40*
Loop ileostomy	ASAT	77	0	9	0.50 ± 0.03 µkat/l	*0.04*
6 months	ASAT	80	0	10	0.46 ± 0.03 µkat/l	*0.17*
12 months	ASAT	73	0	8	0.42 ± 0.03 µkat/l	*0.57*
18 months	ASAT	68	0	9	0.46 ± 0.03 µkat/l	*0.18*
24 months	ASAT	70	0	11	0.49 ± 0.09 µkat/l	*0.12*
36 months	ASAT	64	0	6	0.42 ± 0.02 µkat/l	*0.63*
Precolectomy	ALAT	60	0	15	0.50 ± 0.07 µkat/l	
Ileostomy	ALAT	46	0	15	0.42 ± 0.04 µkat/l	*0.35*
Loop ileostomy	ALAT	77	0	36	0.75 ± 0.07 µkat/l	*0.01*
6 months	ALAT	80	0	19	0.56 ± 0.08 µkat/l	*0.31*
12 months	ALAT	74	0	18	0.55 ± 0.08 µkat/l	*0.51*
18 months	ALAT	70	0	21	0.59 ± 0.08 µkat/l	*0.39*
24 months	ALAT	72	0	20	0.59 ± 0.09 µkat/l	*0.25*
36 months	ALAT	65	0	18	0.52 ± 0.06 µkat/l	*0.70*
Precolectomy	ALP	53	0	8	3.06 ± 0.27 µkat/l	
Ileostomy	ALP	40	0	11	3.18 ± 0.20 µkat/l	*0.10*
Loop ileostomy	ALP	71	0	42	4.17 ± 0.20 µkat/l	*0.001*
6 months	ALP	78	0	13	3.08 ± 0.10 µkat/l	*0.51*
12 months	ALP	73	0	8	3.04 ± 0.20 µkat/l	*0.83*
18 months	ALP	69	0	13	3.11 ± 0.20 µkat/l	*0.87*
24 months	ALP	72	0	8	2.99 ± 0.20 µkat/l	*0.74*
36 months	ALP	65	0	12	3.08 ± 0.20 µkat/l	*0.84*

No correlation was found between the mean postoperative levels of serum ALAT and ALP versus drugs, anaesthesia time and blood transfusion given during the operation (Annex I - III). A lower incidence of elevated ALAT was found after enfluran than isofluran anaesthesia ($p< 0.05$). A definite explanation

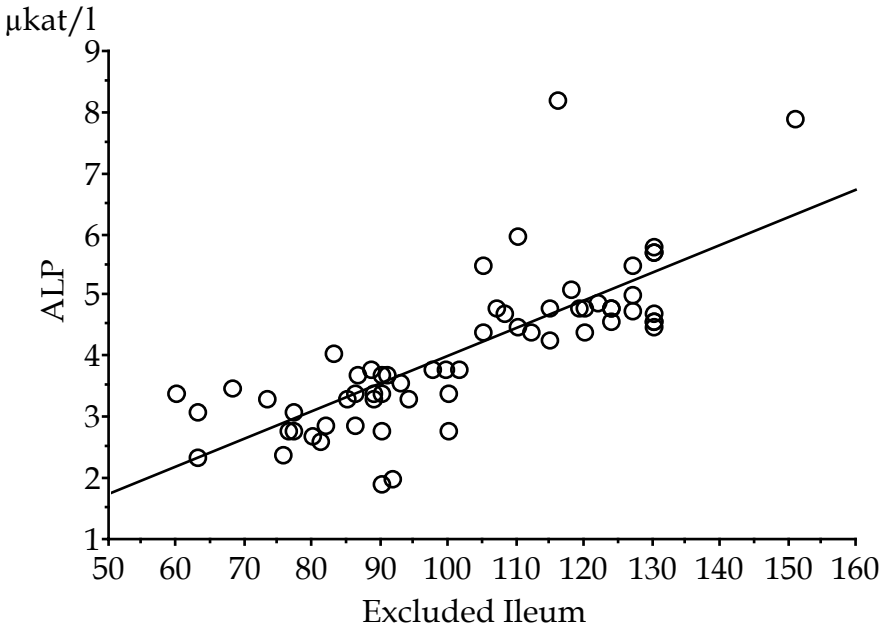
Fig. II

The Correlation between the fraction of serum ALAT levels and the length of the diverted ileum during the period with loop ileostomy.



Pearson´s correlation coefficient

Fig. III
The Correlation between the fraction of serum ALP levels and the length of the diverted ileum during the period with loop ileostomy.



Pearson´s correlation coefficient

for the rise of quantitative measurements of liver enzymes after pouch operation could not be ascertained but the loop ileostomy seemed to delay the normalization of the values.

Haematology (Study I): More patients with high [1] or low [2] pathologic values were found among the patients operated on an emergency basis compared with those operated on electively. This is most obvious for erythrocyte sedimentation rate (ESR) [1], white blood cell (WBC) [1] haemoglobin (Hb), [2] and iron (Fe) [2]. However, there is a considerable share of the elective patients who have low haemoglobin and iron. Of the total precolectomy material, 19 of 34 with low haemoglobin also had low iron. More than 30 percent of the investigated elective patients had impaired uptake of vitamin B_{12}.

At the time of the pouch operation and 2 to 12 months after the operation with subtotal colectomy and ileostomy, the percentage of patients with low haemoglobin and iron as well as increased ESR and WBC diminished. No certain correlation between time with terminal or loop ileostomy and the occurrence of pathologic values was found. At the end of the period with loop ileostomy compared to earlier phases was that there were fewer patients with pathologic ESR, WBC, and haemoglobin and iron in serum. There was no significant correlation between the length of the excluded/ diverted bowel and the occurrence of pathologic values. During the functional period the number of patients with elevated ESR and WBC were comparable to the elective patients preoperatively. The percentage of patients with low haemoglobin and iron was lower for the elective or acute preoperatively. Around 30 percent of the patients with low haemoglobin during the follow-up also had low iron. The share of patients with a low vitamin B_{12} was low both during the stoma and during functional period. However, the percentage of patients with low Schilling test and low ^{14}C-Triolein breath test was similar to the percentage preoperatively, and between 30 and 40 percent in patients having the pouch for 12 and 36 months.

Table XXI

Serum- haemoglobin, iron, transferrin and folates data before-, during-, and after- restorative proctocolectomy surgery, 36 months follow-up of the functional reservoir.

Point of Control	Parameter	Number of pts Studied	Pathologic values in % Low	High	M ± SEM	*P value*
Precolectomy	Haemoglobin	63	44	5	123.46 ± 2.85 g/l	
Ileostomy	Haemoglobin	48	18	4	137.96 ± 2.34 g/l	*0.004*
Loop ileostomy	Haemoglobin	76	12	5	138.84 ± 1.56 g/l	*0.0001*
6 months	Hemoglobin	75	11	5	139.27 ± 1.85 g/l	*0.0001*
12 months	Haemoglobin	65	11	9	141.74 ± 1.77 g/l	*0.0001*
18 months	Haemoglobin	55	7	5,5	140.16 ± 2.0 g/l	*0.0001*
24 months	Haemoglobin	50	12	2	140.6 ± 2.09 g/l	*0.0001*
36 months	Haemoglobin	30	14	7	140.2 ± 3.01 g/l	*0.001*
Precolectomy	Iron (Fe)	55	49	0	10.78 ± 0.99 µmol/l	
Ileostomy	Iron (Fe)	37	23	0	12.95 ± 1.03 µmol/l	*0.33*
Loop ileostomy	Iron (Fe)	57	16	4	17.54 ± 1.53 µmol/l	*0.0003*
6 months	Iron (Fe)	68	15	0	15.57 ± 1.05 µmol/l	*0.005*
12 months	Iron (Fe)	61	11	0	16.34 ± 1.04 µmol/l	*0.0005*
18 months	Iron (Fe)	49	21	0	15.47 ± 1.04 µmol/l	*0.005*
24 months	Iron (Fe)	46	18	0	15.07 ± 1.11 µmol/l	*0.01*
36 months	Iron (Fe)	31	16	0	17.45 ± 1.40 µmol/l	*0.01*
Precolectomy	Transferrin	15	0	0	2.53 ± 0.35 g/l	
Ileostomy	Transferrin	16	0	6	2.9 ± 0.26 g/l	*0.34*
Loop ileostomy	Transferrin	14	0	14	3.55 ± 0.41 g/l	*0.66*
6months	Transferrin	14	0	0	2.58 ± 0.48 g/l	*0.34*
12 months	Transferrin	16	0	0	2.3± 0.32 g/l	*0.32*
18 months	Transferrin	15	0	0	2.82 ± 0.16 g/l	*0.33*
24 months	Transferrin	12	0	0	3.0 ± 0.6 g/l	*0.70*
36 months	Transferrin	11	0	0	2.4 ± 0.25 g/l	*0.35*
Precolectomy	Folates	42	12	0	14.99 ± 1.83 nmol/l	
Ileostomy	Folates	43	0	0	16.16 ± 1.71 nmol/l	*0.01*
Loop ileostomy	Folates	61	0	0	16.78 ± 1.76 nmol/l	*0.01*
6 months	Folates	66	0	0	16.20 ± 1.13 nmol/l	*0.01*
12 months	Folates	56	0	0	16.10 ± 1.40 nmol/l	*0.002*
18 months	Folates	51	0	0	16.90 ± 1.67 nmol/l	*0.001*
24 months	Folates	44	0	0	16.51 ± 1.77 nmol/l	*0.005*
36 months	Folates	25	0	0	19.22 ± 2.44 nmol/l	*0.001*

Table XXII

Serum- vitamin B_{12} before-, during-, and after- restorative proctocolectomy surgery, 36 months follow-up of the functional reservoir

Point of Control	Parameter	Number of pts Studied	Pathologic values in % Low	High	M ± SEM	*P value*
Precolectomy	B_{12}	41	8	10	433 ± 31.45 pmol/l	
Ileostomy	B_{12}	43	7	2	353 ± 32.27 pmol/l	*0.17*
Loop ileostomy	B_{12}	61	8	3	326 ± 30.78 pmol/l	*0.28*
6 months	B_{12}	69	7	3	335 ± 26.81 pmol/l	*0.33*
12 months	B_{12}	58	3	5	349 ± 27.73 pmol/l	*0.19*
18 months	B_{12}	53	6	2	319 ± 23.24 pmol/l	*0.03*
24 months	B_{12}	51	6	4	380 ± 36.1 pmol/l	*0.50*
36 months	B_{12}	28	11	0	350 ± 27.22 pmol/l	*0.09*

Table XXIII

Vitamin B_{12} absorption tests by Schilling test before-, and after- restorative proctocolectomy surgery during 12 and 36 months control of the functional reservoir.

Point of Control	Parameter	Number of pts Studied	Pathologic values in % Low	High	M ± SEM	*P value*
Precolectomy	Schl-w-IF	16	38	12	17 ± 2.48 %	
	Schl-wt-IF	17	35	12	16 ± 2.41 %	
12 months	Schl-w-IF	67	30	6	16 ± 1.09 %	*0.87*
	Schl-wt-IF	67	31	6	15 ± 0.99 %	*0.42*
36 months	Schl-w-IF	35	37	0	15 ± 1.22 %	*0.23*
	Schlwt-IF	36	36	0	15 ± 1.23 %	*0.13*

Abreviations:

Schl-w-IF Schilling test with intrinsic factor (-IF)

Schl-wt-IF Schilling test without intrinsic factor (+IF)

Table XXIV
Erythocyte sedimentation rate (ESR) and White blood count/cells (WBC) before-, during- and after- restorative proctocolectomy surgery, 36 months of functional reservoir.

Point of Control	Parameter	Number of pts Studied	Pathologic values in % Low	High	M ± SEM	*P value*
Precolectomy	ESR	57	0	43	29 ± 3.61 mm	
Ileostomy	ESR	44	0	26	13 ± 2.44 mm	*0.003*
Loop ileostomy	ESR	69	0	7	8 ± 0.85 mm	*0.0001*
6 months	ESR	72	0	11	10 ± 1.07 mm	*0.0001*
12 months	ESR	60	0	15	12 ± 2.31 mm	*0.0001*
18 months	ESR	53	0	15	12 ± 1.87 mm	*0.0001*
24 months	ESR	45	0	21	12 ± 1.62 mm	*0.002*
36 months	ESR	31	0	13	11± 2.44 mm	*0.05*
Precolectomy	WBC	59	0	27	8 ± 0.47 10^9/l	
Ileostomy	WBC	44	0	12	7 ± 0.27 10^9/l	*0.01*
Loop ileostomy	WBC	69	0	6	6 ± 0.24 10^9/l	*0.0001*
6 months	WBC	73	0	5	6 ± 0.21 10^9/l	*0.0001*
12 months	WBC	62	0	3	6 ± 0.20 10^9/l	*0.0001*
18 months	WBC	55	0	7	6 ± 0.29 10^9/l	*0.0003*
24 months	WBC	50	0	8	6 ± 0.24 10^9/l	*0.001*
36 months	WBC	32	0	10	6 ± 0.37 10^9/l	*0.11*

Table XXV
Free fat acids (FFA) in serum preoperatively and after restorative proctocolectomy surgery during 12 and 36 months controls of the functional reservoir.

Point of Control	Parameter	Number of pts Studied	Pathologic values in % Low	High	M ± SEM	*P value*
Precolectomy	FFA	15	0	0	0.60 ± 0.02 mmol/d	
12 months	FFA	15	0	0	0.50 ± 0.02 mmol/d	*0.69*
36 months	FFA	15	0	0	0.96 ± 0.04 mmol/d	*0.78*

Table XXVI
Fat absorption tests by ^{14}C-Triolein breath tests preoperatively and after restorative proctocolectomy surgery during 12 and 36 months controls of the functional reservoir.

Point of Control	Parameter	Number of pts Studied	Pathologic values in % Low	High	M ± SEM %/hour	*P value*
Precolectomy	^{14}C-Breath test	9	33	0	3.88 ± 0.89 %/h	
12 months	^{14}C- Breath test	46	35	0	3.71 ± 0.24 %/h	*0.70*
36 months	^{14}C- Breath test	32	41	0	3.63 ± 0.32 %/h	*0.98*

In all, 8 patients have or have had substitution therapy with vitamin B_{12}. In five patients low values were found during the first six months of pouch functions in two patients after one year, and in one patient after two years.
Before colectomy surgery 14 percent from the acute group and 5 percent from elective group had low serum folic acid. After colectomy and during other stations the levels were normal.

Lipids (Study II): There was a significant difference of mean total serum cholesterol preoperatively between patients who were operated on electively versus on an emergency basis (5.4 ± 1.1 *Vs* 3.8 ± 1.4 mmol/l) ($p< 0.01$). The cholesterol levels between patients who have had a long *versus* short duration loop ileostomy after its closure had a similar rise in cholesterol fraction occurring over time (p = NS)

In electively operated patients there was no statistical significant difference (p= 0.45) in total serum cholesterol levels between patients who received corticosteroids and those who did not. These patients (Table XXVII) had serum levels of cholesterol decreased from preoperative values of 5.4 ± 1.1 mmol/l to 3.9 ± 0.6 mmol/l ($p< 0.0001$) (M ± SD) when they had loop ileostomy. The decrease was significantly correlated to the length of the diverted ileum (r^2 = 0.75, $p< 0.0002$) (Fig. 3) but not the time duration with loop ileostomy. During the same period, total serum triglyceride was increased from preoperative level of 1.1 ± 0.4 mmol/l to 2.2 ± 0.6 mmol/l ($p< 0.0001$) (M ± SD), but there was no relation to the length of the excluded ileum. There was also a changed pattern of lipoproteins in serum. Serum alpha-lipoprotein (HDL) decreased from the preoperative values of 35 ± 2.6 per cent to 23.8 ± 1.4 per cent ($p< 0.0001$) (M ± SD) during the period with loop ileostomy. There was no significant correlation between the diverted ileum and share of serum alpha-lipoprotein. The changes of pre-beta-lipoprotein (VLDL) and beta-lipoprotein (LDL) were not significant ($p = 0.22$ and $p = 0.11$). At 12 months after loop ileostomy closure, serum cholesterol, triglyceride and alpha-lipoprotein (HDL), pre-beta-lipoprotein (VLDL) and beta-lipoprotein (LDL) levels were not significantly changed compared to precolectomy time.

Table XXVII

Electively operated patients: Serum- Cholesterol, Triglycerides, Alpha-, Pre-beta-, and Beta-lipoprotein before-, during-, and after resorative proctocolectomy surgery, 12 months fellow-up of the functional reservoir.

Point of Control	Paramete	Number of Patients Studied	M ± SEM	*P value*
Precolectomy	Cholesterol	15	5.4 ± 1.1 mmol/l	
Loop ileostomy	Cholesterol	15	3.9 ± 0.6 mmol/l	*0.0001*
12 months	Cholesterol	15	5.0 ± 0.9 mmol/l	*0.13*
Precolectomy	Triglycerides	14	1.1 ± 0.4 mmol/l	
Loop ileostomy	Triglycerides	14	2.2 ± 0.6 mmol/l	*0.0001*
12 months	Triglycerides	14	1.3 ± 0.6 mmol/l	*0.25*
Precolectomy	Alpha-lipoprotein (HDL)	12	35.0 ± 8.5 %	
Loop ileostomy	Alpha-lipoprotein (HDL)	12	23.8 ± 5.0 %	*0.0001*
12 months	Alpha-lipoprotein (HDL)	7	34.0 ± 4.5 %	*0.28*
Precolectomy	Pre-beta-lipoprotein (VLDL)	12	33.2 ± 20.5 %	
Loop ileostomy	Pre-beta-lipoprotein (VLDL)	12	36.8 ± 16.4 %	*0.22*
12 months	Pre-beta-lipoprotein (VLDL)	7	33.1 ± 16.5 %	*0.43*
Precolectomy	Beta-lipoprotein (LDL)	12	31.8 ± 21.7 %	
Loop ileostomy	Beta-lipoprotein (LDL)	12	39.3 ± 17.9 %	*0.41*
12 months	Pre-beta-lipoprotein (LDL)	7	32.9 ± 15.2 %	*0.41*

Fig. IV

The correlation between the length of the diverted ileum during loop ileostomy and the total serum cholesterol in the **electively** operated patients. There was a significant negative correlation between the diverted ileum and serum-cholesterol level (p< 0.0002) (***Pearson´s correlation coefficien)***.

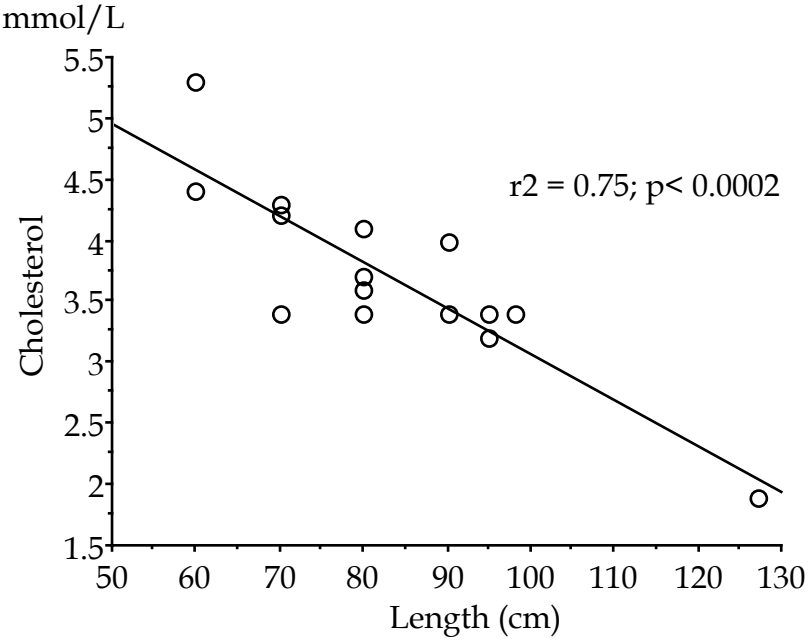


Table XXVIII

Emergency operated patients: Serum Cholesterol and Triglycerides preoperatively, during and after restorative proctocolectomy surgery, 12 months follow-up of the functional reservoir.

Point of Control	Parameter	Number of Patients' Studied	M ± SEM mmol/L	*P value*
Precolectomy	Cholesterol	19	3.8 ± 1.4 mmol/l	
Ileostomy	Cholesterol	19	4.6 ± 1.3 mmol/l	*0.07*
Loop ileostomy	Cholesterol	19	4.3 ± 0.7 mmol/l	*0.12*
12 months	Cholesterol	19	4.8 ± 0.7 mmol/l	*0.07*
Precolectomy	Triglycerides	13	1.2 ± 0.9 mmol/l	
Ileostomy	Triglycerides	13	1.4 ± 0.7 mmol/l	*0.33*
Loop ileostomy	Triglycerides	13	2.0 ± 0.7 mmol/l	*0.02*
12 months	Triglycerides	13	0.9 ± 0.5 mmol/l	*0.47*

In the emergency patients (Table XXVIII) there was a tendency to increased serum cholesterol after colectomy with terminal ileostomy. After construction of the pouch and diverting loop ileostomy, serum cholesterol was not significantly changed while mean total serum triglyceride was significantly increased ($p < 0.02$) compared to values prior to colectomy.

Gastric acids, GI-enzyme and -hormones (Study III):

Pre- and postoperative retention and basal and volume are given below in Table XXIX. Pentagastrin stimulated gastric acid secretion values are given in Table XXX. The observation on GI-hormones is presented on Table XXXI.

Mean retention and basal gastric secretion (HCl) and secretion after pentagastrin stimulation at 12 months after IPAA operation were significantly increased ($p < 0.001$ and $p < 0.01$ and $p < 0.001$) respectively, compared with the preoperative values (Table XXIX). After pentagastrin stimulation the acid (mmol HCl, volume (ml) was not only increased but also seemed to appear earlier than at the precolectomy control (Table XXX).

The mean concentration of serum gastrin, pentagastrin and pepsinogen did not change (Table XXXI).

Table XXIX

Mean ± Standard Deviation of the mean of Hydrochloric acid (HCl) secretion and the volume of gastric fluid before and after restorative proctocolectomy surgery, 12 months follow-up of the functional reservoir.

Point of Control	Number of Stidied patients	Retention		Basal secretion	
		mmol HCl	Volume (ml)	mmol HCl	Vol (ml)
Precolectomy 28.6± 8.90	7	1.6 ± 0.53	64.3 ± 15.17	1.15 ± 0.17	
12 months ± 38.93	7	3.05 ± 2.15	65.2 ± 38.91	2.64 ± 2.42	62
P value		*< 0.001*	*0.93*	*< 0.01*	*< 0.001*

p value = probability value (significances)
P-IgG = plasma immunoglobin G
P-IgA = plasma immunoglobin A
P-IgM = plasma immunoglobin M

Table XXX

Pentagastrin Stimulation

Mean ± standard deviation of Hydrochloric acid (HCl) Secretion and Volume of Gastric Fluid After Pentagastrin Stimulation, Before Proctocolectomy and After 12 Months of Functional Reservoir After Loop ileostomy Closure.

Control Point	No. of patients	0 to 15 Minutes		16 to 30 Minutes		31 to 45 Minutes		46 to 60 Minutes		During 60 Minutes	
		mmol **HCl**	Vol (ml)	mmol **HCl**	Vol (ml)	mmol **HCl**	Vol (ml)	mmol **HCl**	Vol (m)	mmol **HCl**	Vol (ml)
Preproctocolectomy	10	**2.5 ± 0.47**	10 ± 3	**4.8 ± 1.1**	50 ± 6	**5.5 ± 0.92**	36 ± 6	**7.4 ± 1.11**	60 ± 8	**20.2 ± 2**	156 ± 3
12 Months	10	**4.2 ± 2.8**	49 ± 34	**9.5 ± 4.6**	54 ± 26	**9.9 ± 4.1**	50 ± 38	**7.5 ± 2.8**	60 ± 22	**31.1 ± 12.8**	213 ± 8
P value		***0.13*** *< 0.05*	*< 0.01*	***< 0.03***		*0.16*	***< 0.03***	*< 0.01*	***0.89***	*0.18*	***< 0.001***

Table XXXI

Mean ± Standard Deviation of S-.Gastrin, S-Pentagastrin and S-Pepsinogen, Before Proctocolectomy and After 12 Months of Functional Reservoir After Loop ileostomy Closure.

Control Point	Gastrin/S pg/L	No. of Patients Studied	Patients with Increased values (%)	Pentagastrin/S mmol/h	No. of Patients Studied	% Patients with Increased values (%)	Pepsinogen/S µg/L	No. of Patients Studied	Patients with Pathologic values (%)
Preproctocolectomy	29.0 ± 17	11	0	21.0 ± 13.0	11	23	69.1 ± 26	10	0
12 Months	31.6 ± 15.7	11	0	21.0 ± 13.4	11	9	70.4 ± 28.2	10	0
P value	*0.18*			*0.90*			*0.98*		

13.
GENERAL DISCUSSION

A new organ instead of diseased or lost organs is a dream for patients and doctors since long. First, during the 20th centuary this has become a possibility. The way to replace organs has followed three lines so far.
i/ Use of artificial organ, extra-corporeal or intra-corporeal ii/ Transplantation of organs from other humans iii/ Construction of new organ by use of sources from the patient´s own body.
One of the most extensive procedures following the thirds way, is the restorative proctocolectomy, which means replacement of the colon and rectum by a pouch formed from the ileum and sutured to the anal canal preserving the anal sphincters. The reconstruction gives a continuous gastrointestinal tract, defecation, deferral and discrimination in an almost normal way in spite of the loss of 150 cm of bowel. Sir Alan Parks gave the first presentation of this procedure in 1978 [9]. During the following years the construction was regarded more as a mere experiment but is now the procedure of choice in surgical treatment of ulcerative colitis and familial polyposis coli.
In 1980 the first restorative proctocolectomy in Sweden was undertaken at Huddinge University Hospital. During the following 2 years plans for necessary prospective follow-up studies were realized. One of the plans was to follow the patients closely and continuously for evaluation of the procedure and its clinical results in order to give feedback for modification of the operative procedure [7, 13, 57, 58, 216]. The second plan was to regularly investigate the pouch mucosa macro- and microscopically [17, 22, 217-219]. The third plan was to evaluate how the personality of the patients influenced the outcome and how the patient valued the pouch compared to ileostomy [54, 220). The fourth prospective evaluation aimed to study the impact on homeostasis of different operative procedures (ileostomy, loop ileostomy and pouch) compared to preoperative and normal [24, 25, 28, 29, 32]. The plans have been fulfilled and the results of the fourth study constitute the present thesis.
ELECTROLYTES: -

In previous studies on electrolytes for patients with ileostomy [73, 75-77], Kock pouches [73, 75], ileal pouch-anal anastomosis (IAP) [78] and ileoanal anastomosis (IAA) [8, 11], no disturbances were reported. Nicholls [78] had six patients who developed electrolyte depletion postoperatively before closure of the ileostomy. The present thesis, with its thorough penetration of electrolyte data during the different steps of restorative proctocolectomy and during follow-up, has revealed a more detailed picture [28].

Magnesium: Before and after restorative proctocolectomy, few patients had continuously low serum-magnesium concentrations but no one developed clinical signs of hypomagnesemia [28]. Substitutes were however moderately given when serum values developed below 0,71 (normal 0,75-1,1 mmol/1). Magnesium deficiency has been described in patients with ulcerative colitis [8, 11, 95, 102], Crohn´s disease [82, 83] and ileostomy [77, 84, 221]. The depletion is common in patients who undergo ileal resections [221] and in patients with chronic diarrhoeas [75, 78, 86]. Presuming a normal magnesium intake in the reservoir operated patients; the low s-magnesium will reflect malabsorption of magnesium. If magnesium is given parenterally to healthy volunteers, an amount similar to the parenteral load will be excreted where as magnesium-depleted patients will retain magnesium [222]. Following surgery, since colectomy and loop ileostomy leaves part of the intestine defunctionalized, magnesium abnormalities may develop because of deprivation in intestinal surface [78, 223]. Other causes for hypomagnesemia include high stoma output [78], (chronic) diarrhoea, steatorrhea and malabsorption [78, 89].

Zinc: Increased serum-zinc was found more often than decreased values (I) [28]. The reason for this is not clear and needs further study. The decreased values may be explained as due to impaired intestinal absorption of zinc [96], increased losses associated with intestinal malabsorption and/ or losses of zinc into the intestinal lumen, with inflammatory exudates [82, 90, 96-99]. Following postrestorative proctocolectomy, changes in the reservoir mucosal morphology have been observed [17-20, 22, 23, 75, 223]. A reduced zinc uptake from an oral test doses in patients with atrophic mucosal (villi) has been reported [95].

Calcium: Over 35 per cent of the UC, mostly emergency patients (I) were observed to have pathologically low serum calcium at precolectomy control (28). After colectomy the number of patients with hypocalcaemia diminished considerably. Low serum levels of Calcium have been shown to characterise patients with ulcerative colitis, before and after surgery [95]. It has been verified

that patients with inflammatory bowel disease (ulcerative colitis) are significantly protein depleted [11, 52, 95, 100-103] before surgery and that calcium depletion has to do with the state of ulcerative colitis. Hypocalcemia often reflects hypoproteinemia [100]. Moreover, calcium absorption may be decreased by corticosteroid treatment [104, 105]. In our material, sixty-seven patients received cortisone therapy.

Sodium and Potassium: Very few abnormally low s-sodium and potassium cases were seen at precolectomy and at 12, 18 and 24 months of IPAA function. Depletions may be caused by diarrhoea and / or vomiting. Hypokalemia and hyponatremia can also be seen during parenteral hyperalimentation with inadequate sodium and potassium replacement [79, 93], in patients left with ileostomies after total colectomy [84] and in loss of gastrointestinal secretions.

PROTEINS:

Immunoglobulin(s): There is a report that patients with ulcerative colitis had increased IgG [165]. There is no study about serum IgG, IgA and IgM after restorative proctocolectomy and/ or during reservoirs in function. In our observations (I and VI), we noted an elevation of serum IgG and IgA with time during the functioning pouches after loop ileostomy closure and with serum IgM during the period with loop ileostomy, than preoperatively. These changes may be associated with an increased bacterial flora (antigen) in ileostomies and pouches [19-21] that may stimulate lymphocytes to produce more immunoglobulins (antibody molecules).

Increased numbers of IgG-producing cells and IgG immune complexes are found in the human intestinal mucosa in celiac disease and inflammatory bowel disease [165-168]. Such observations support that IgG may contribute to indicate pathogenesis of inflammatory reaction and tissue injury in certain intestinal diseases. What cause(s) increase in IgG following colectomy and later in the course during functioning pouches needs further investigation to be explained. However, this could be seen to indicate patient´s signs of rehabilitation.

IgA [167] is a major immunoglobulin class in the intestinal secretions. It can enter the lymphatic draining of the intestines and subsequently the circulation. There is much evidence that there is a hepatobiliary clearance of IgA immune complexes [167].

IgM is also produced in the intestinal lymphoid tissue but in a less concentration and is normally degraded in the intestine. In IgA-deficient

individuals an increase in IgM producing cells is found [96, 174-177, 224-231]. While IgA and IgM producing cells are common in the intestinal lamina propria there are relatively few IgG producing cells. IgM is degraded in the intestine by proteolytic enzymes [177, 232, 233]. A marked increase in secretory IgM-producing cells in the lamina propria is found in some individuals with IgA deficiency [180]. This suggests that secretory IgM may be playing a protective role in the intestinal mucosa.

Orosomucoid: Ninety two percent of patients who underwent emergency surgery and 61% electively had increased serum orosomucoid concentration before colectomy (I). After colectomy, the number of patients with high serum orosomucoid reduced, but was still remarkably high up to more than 36 months of functional reservoir. Orosomucoid is described as an acute [234-239] sensitive marker with 100% specificity of inflammatory disease that may increase four to five folds in severe disease [235, 236]. Its role in inflammatory bowel disease is of value [181, 182] in monitoring the response to treatment [234-236] and correlates the disease activity [182, 240].

Haptoglobin: Serum haptoglobin was noted increased in 61% (n=49) in patients with ulcerative colitis [24]. After surgical treatment with restorative proctocolectomy, both the patients with elevations and mean values were significantly reduced. Human haptoglobin is a glycoprotein, which forms a specific, irreversible and non-covalent complex with haemoglobin released from the erythrocytes [241]. The principal function is to transport free haemoglobin from destroyed red blood cells to the liver. Haptoglobin concentration in serum, if decreased, reflects hepatocellular disease. Conversely, synthesis is enhanced in inflammatory states. Haptoglobin, like alpha 1-antitrypsin, and orosomucoid, is an acute phase reactant [183]. It also reflects hemolysis, with increased values. The precise nature of haptoglobin abnormality that occurs in ulcerative colitis is not understood. In this presentation, neither the persisted elevation of orosomucoid nor haptoglobin could be directly bound to acute pouchitis (I). However, the increased values could be correlated to subclinical pouch inflammation, which has been found in 87% of pouch patients [166].

LIVER ENZYMES: -

Hepatobiliary disease has been reported in ulcerative colitis [127, 239, 240, 242, 243]. Patients with ulcerative colitis have a higher frequency of primary sclerosing cholangitis [243-245] than healthy controls [128, 237-239]. In ulcerative colitis also liver cirrhosis has been reported [246-248]. In non-fulminate ulcerative colitis cases, about 4% to 5% are reported to have pathologic high ASAT, ALAT and ALP values [241, 249]. After colectomy, rapid normalisations of markedly elevated transaminases have been reported [130].

In pouch surgery the distal part of the small bowel is used [9, 50-52]. The use of loop ileostomy is to bypass temporarily part of the terminal ileum so as to allow healing of the anastomosis [9]. The terminal ileum is preserved but out of absorptive function. Therefore, there is a loss of bile salts [192] and as a result a compensatory bile salts synthesis by the liver is increased. Findings that a considerable number of patients had increased liver enzymes before loop ileostomy closure [14, 23, 26] encouraged further investigations of the liver function before, during and after that phase.

The present study revealed that before loop ileostomy closure, there were more patients with increased liver values compared to pre and post closure. Thirty six percent of the patients had elevated ALAT and 42% had increased ALP. The liver function alterations may be associated with the deprived supply in enterohepatic circulation. With this dissertation one is unable to prove if loop ileostomy could cause hepatic dysfunction. However, patients with loop ileostomy who had had their bowel excluded more that 105 cm, had a significant ($p < 0.05$) increase in ALAT and stepwise increase in the percentage of patients with elevated levels of ALP (I). When patients had their loop ileostomy closed, values indicating alterations in the hepatic function turned direction towards stabilising [14-16, 24], when new steady bowel continence was achieved, and remained so throughout the remainder of the follow-up.

Similarly, changes are reported by Max et al. [26] in his patients during the defunctionalised stage after ileal pouch anal anastomosis. Other researchers in pelvic and Kocks pouches [15, 16] report few patients with such alterations during the follow-up. However, patients with intestinal shunt are reported to develop hepatic function disorders. About 95% of postbypass patients for obesity [113] are reported to have hepatic dysfunction. The fact that the pouch and defunctionized loop, favours bacterial growth has been pointed out [12, 19-21]. Bacterial toxins have been noted to induce hepatic alternations by the elaboration of unidentified toxins [120, 121].

HAEMATOLOGY: -

In case of an intact and healthy ileum, colectomy plus ileostomy alone rarely causes haematological impairments [114, 119]. Removal of the terminal ileum segment or/and mucosa damage of the remaining ileum may create haematology threat [119]. This study was performed in order to evaluate the absorptive alterations of the distal ileum and the adaptive changes for haematology parameters in patients before and after ilealanal pouches. The study shows that prior and after the completed operative concerns, during the stoma time and the follow-up, some patients had pathologic serum haemoglobin, iron, vitamin B_{12}, erythrocyte sedimentation rate, white blood count pt. B_{12} and pt. fat absorption. There was no patient with low serum folic acid or transferrin.

Twenty two percent of the electively and 67 percent of the acutely operated patients (I) had decreased haemoglobin preoperatively [25]. At the 12 months follow-up only 4 percent patients had low values. The number of patients with low serum haemoglobin or/and iron was higher before colectomy. This is due to blood loss (hematochezia). In patients with low serum haemoglobin or/and low iron following ileal pouch anal anastomosis, the low values are possibly due to defective digestion and decreased absorption. Significant chronic iron deficiency anaemia was noted in one patient with chronic pouchitis. The possible factor leading to iron deficiency is secondary to insufficient iron intake (in the diet), impaired absorption, increased requirements or loss of blood. In many instances, more that one of these factors could be responsible for the resulting deficiency [107, 110, 250]. Decreased serum iron was found in 58 percent of the acutely operated patients preoperatively and only in 10 percent at the follow-up. Further analysis of the decreased values during the controls at 6, 12, 18, 24 and 36 months follow-up showed that, one patient had low values in all the investigations, four at 3 occasions, two at 2 occasions and 14 at one occasion.

Schilling test revealed low values in 4 of 13 patients' (I) investigated preoperatively [25]. At the 12 and 36 month's follow-up of the IAP patients not less than a third had low values. Still only 5 percent of the patients had low vitamin B_{12} values and only 35 percent had substitution therapy [25].

When constructing an ileal pouch, the distal party of the ileum is used. The distal ileum is an active part for the absorption for vitamin B_{12} [111]. Vitamin B_{12} is absorbed in the distal ileum in man [112]. The question whether the surface of the defunctionalized intestinal segment is or is not sufficient for the

cause of malabsorption of vitamin B_{12} has been discussed [8, 112-115]. It has been repeatedly confirmed that vitamin B_{12} in sufficient amount cannot be absorbed in the absence of the terminal ileum [114, 115]. A reversible absorptive loss of small intestinal capacity was demonstrated in case of vitamin B_{12} deficiency and it was suggested that a depletion of vitamin B_{12} further impairs the absorption of vitamin B_{12} [117, 250].

Jejunocolic shunt in obese patients was invariably followed by lack of vitamin B_{12} [117-126, 251]. Payne and De Wind [113] claim that a 13 cm long portion of the distal ileum was sufficient for the absorption of vitamin B_{12} in adequate amount. Dano [121] suggests 36 cm. On the other hand, Clark and Booth [122], Booth and Mollin [111], Coylet et al. [115], Booth [119] and Juhl et al. [124] failed to demonstrate this and instead noted gradual deficiency of vitamin B_{12} in their patients. This confirms that in such patients megaloblastic anaemia may result. Reduced vitamin B_{12} absorption has been reported after colectomy [72].

In a previous study, Philipson [21] found that despite the morphologic changes in the intestinal mucosa and microbial flora, the reservoir retains a stable absorptive capacity [21, 114]. The fact that the pouch and defunctionilized loop, favours bacteria growths has been realised [19-21]. The abnormal growth of the bacterial flora [21, 134] possibly associated with changes in the intrinsic factors (IF), the ileal receptor for the IF- B_{12} complex, bacteria utilising vitamin B_{12} and decreased transit time due to anatomic constrain, might interfere with vitamin B_{12} absorption. Diarrhoea/steatorrhea and low vitamin B_{12} intake, or a combination of the causes above may cause vitamin B_{12} malabsorption. Stagnant loop syndrome associated with steatorrhea may play part in causing malabsorption of vitamin B_{12}. The malabsorption is frequently improved by the use of antibiotics or/and by correcting the loop surgically.

In patients with ulcerative colitis, folic acid was elevated in 12 percent of the acutely operated patients' [24] and all were normal after colectomy. Folacin is absorbed in the proximal part of the small intestines but must be converted to the free form by an intestinal enzyme conjugase. The liver contains about half of the body's storage and limited amounts (20 mg) are stored in the body. In this case folacin deficiency may occur in intestinal malabsorption secondary to a low dietary intake or disturbed intestinal absorption. The use of medicine, which has a folacin antagonistic effect, i.e. anticonceptional pills, antiepileptic pills, antimalaria preparation, may result in folacin deficiency.

LIPIDS:

There was a significant difference of mean serum cholesterol preoperatively between patients who were operated on electively versus on emergency basis ($p< 0.01$) (pp II). In electively operated patients, serum levels of cholesterol decreased ($p< 0.0001$) (M ± SD) when they had loop ileostomy. The decrease was significantly correlated to the length of the diverted ileum ($r^2 = 0.75$, $p< 0.0002$). During the same period, serum triglyceride was increased ($p< 0.0001$) (M ± SD), but there was no relation to the length of the excluded ileum. After 12 months with a functioning ileoanal pouch the serum cholesterol, triglyceride and lipoprotein pattern was the same as preoperatively in the elective patients. This is in contrary to the findings by Hakala et al. [186] in his patients with functional ileal pouch anastomosis (IPA) for 16 ± 5 months (M ± SE) without loop ileostomy, noted a significantly decrease of total serum cholesterol and triglyceride, compared to controls.

In a study of patients with defunctional loop ileostomy after ileal pouch-anal anastomosis Max et al. [26] and Åkerlund et al. [187] in patients with ileal exclusion, also found significantly decreased levels of serum cholesterol and significantly increased serum triglyceride levels. Ileal exclusion leads to decreased cholesterol [26, 187, 192, 250]. Lipid and lipoprotein reductions after ileal bypass have been previously described [188, 189], as well as analyses of the causes of the changes in total serum cholesterol and LDL cholesterol levels [193, 253].

Buchwald and Vareo [197] have demonstrated that surgical exclusion of the ileum produces a significant reduction in plasma cholesterol concentrations in many patients with hypercholesterolemia. Although Buchwald [197, 253] presented evidence that this lowering was associated with a decreased absorption of dietary cholesterol, it seems likely that alterations in reabsorption of bile acids also play a major role [197, 199, 254-256].

Bile acid absorption takes place at the distal ileum [110, 257-259]. Ileal dysfunction (loop ileostomy) or resection of the distal ileum leads to deprivation in distal ileum surface [190, 191, 260]. This may causes bile acid malabsorption and an increased faecal loss of bile acids [187, 195, 196, 261]. Bile acid malabsorption affects the micelles solubilisation of cholesterol, thus resulting in impaired cholesterol absorption and decreased serum cholesterol, triglyceride and alpha-lipoprotein absorption from the intestine [196, 262]. Malabsorption of cholesterol can be expected to lead to a similar increase in the activity of the rate-limiting enzyme in cholesterol biosynthesis. Ileum resection

leads to increased bile acid biosynthesis as well as increased cholesterol synthesis and increased expression of receptors [193]. This is in accordance with Åkerlund et al. [187], who conclude that patients with terminal ileum exclusion had apparent selective malabsorption of bile acids. The malabsorption of bile acids leads to a condition similar to that occurring after cholestyramine treatment with increased synthesis of both cholesterol and bile acids and decreased concentration of circulating cholesterol.
Not only the distal ileum but also part of the proximal ileum must be resected before a significant malabsorption of cholesterol occurs [188, 189, 200]. Grundy et al. [190] studied four patients with resection of terminal ileum. Only two of these patients had a slight malabsorption of cholesterol. Buchwald et al. [199] showed that hyperlipidemic patients subjected to removal of 200 cm of the distal bowel had malabsorption of both bile acids and cholesterol. Åkerlund et al. [187] found in his patients with 95 cm of distal ileal exclusion, malabsorption of both bile acids and cholesterol.

Compared to precolectomy values in the present study, in patients who were operated on an emergency basis, serum triglyceride levels remained unchanged during the period with terminal ileostomy. In both electively and acutely operated groups, a significant increase was noted during loop ileostomy ($p< 0.0001$ and $p< 0.02$). Scott et al. [263] in his patients during a metabolic "steady state" compared them before and after ileal exclusion, 3 of 4 patients showed no difference. Max et al. [26] in his 14 patients with defunctionalized loop ileostomy, found significantly increased plasma triglycerides. Similarly, Åkerlund et al. [187], in patients with 95 cm ileal exclusion found that the plasma concentration of total triglyceride and VLDL triglyceride increased significantly. Fiorentini et al. [23] and Angelin [200] discussed that increased VLDL as a consequence of the increased cholesterol synthesis causes the increase in triglyceride with a common pool for bile acid synthesis and VLDL secretion. Another explanation could be the direct stimulation of phospholipids and triglyceride synthesis sharing early steps in their biosynthesis [190, 264].
There was significantly decreased serum alpha-lipoprotein during control at defunctionalised loop ileostomy, compared to precolectomy values. Serum pre-beta-lipoprotein and beta-lipoprotein remained unchanged. Färkkilä et al. [196] reported low serum lipoprotein in his patients with gut exclusion and emphasised that, levels of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol are regulated more effectively by cholesterol than bile acid malabsorption.

GASTRIC ACID SECRETION:

In our observations we found a significant increase in both the mean retention and basal gastric secretion and secretion after pentagastrin stimulation at 12 months of functional IPAA. Serum gastrin, pentagastrin and pepsinogen did not change.

Clinical investigations in humans [202-210] have demonstrated increased gastric acid secretion following small intestinal resection or exclusions. Recent results [209-212] consider colon an endocrine organ, producing regulatory peptides. Colon resection exerts an influence on remnant bowel including proliferate adaptive phenomena [209], resulting in a significant decrease in plasma somatostatin, neurotension and cholecystokinin postsurgery [210]. However, Gastrin/s and peptide YY (PYY) are elevated [209-212].

Glucagon-like peptide-1 7-36 amide (GLP-1) and peptide YY (PYY) have an important role in the physiologic control of gastric acid secretion [210].

In animal experiments [205, 265-270] it was observed that there was an increase in the gastric secretion after small intestine exclusion. It was not clear whether the cause was mechanically, chemically or caused by the intestinal humoral stimulation of the gastric secretion. Gregory and Ivy [269] urged however that, it was not a secretagogue derived from the food, but a GI hormone. Westerheide et al. [266] demonstrated in animals that removal of the distal bowel half of the small bowel from the intestinal stream caused a hypersecretion, which was only half of the hypersecretion, caused by diversion of the proximal half of the small intestine. Grundberg et al. [268] demonstrated increased gastric secretion after reversal of a small bowel segment in dog. The mechanism whereby reversal segments increase secretion is because of intestinal dilatation as shown by Sircus [201].

The sites responsible for the catabolism of gastrin are not known. In animal experiments [270-272], however, the small intestine has been found to be of importance in the inactivation of gastrin. Svendsen et al. [273] compared 36 patients with familial adenomatous polyposis (FAP) who were colectomised or got ileorectal anastomosis (IRA) with non-operated patients. He found no difference in serum gastrin values between these groups. Kikendall et al. [274] argue that serum gastrin is not higher in subject with colonic neoplasm but a large part of his patients with high gastrin values had other clinical disorders, e.g., severe atrophic gastritis, a disease with higher incidence in the older population.

14.
CONCLUSIONS:

Concerning the biochemical laboratory data following restorative proctocolectomy (RPC) and ileal-pouch anal anastomosis (IPAA), patients will most likely enjoy normal body composition after loop ileostomy closure. Since some patients developed pathologic disturbances, demanding intervention, the main impression is that some analyses have to be performed on a regular basis, postoperatively.

There lays therefore, an obligation with those who check these patients before and after surgery, to follow their postoperative serum levels of magnesium (Mg), iron (Fe) and cynocobalamin (vitamin B_{12}) and to be alert on symptoms due to deficiency of these substances that (may) require substitution therapy.

Concerning a normo-gastrinemia associated significant increase in gastric acid secretion noted in our observations; this may contribute to an abnormal frequency of looser stools in pouch patients. It is known that hypersecretion of gastric acid leads to diarrhoea. In case of frequent stooling without other explanations, antacids or H_2-receptor blockers or inhibitors may be tried. Pouchitis, with its unknown aetiology, is the main cause of a temporary increased number of bowel movement and the fact that metronidazole often cures this event, implies a possible microbial aetiology. However, there are patients that respond less well to metronidazole. Therefore, more extensive gastric acid as well as microbial studies in pouch patients with and without pouchitis should be carried out if the hypothesis is to be verified or ruled out.

Patients developed signs of liver cells damage following RPC surgery. The ALAT and ALP alterations normalized quicker in patients who got no loop ileostomy. In patients who received loop ileostomy, stable normalization of these liver enzymes was delayed until closure of the loop ileostomy. No correlation was found between the mean postoperative levels of serum ALAT and ALP and drugs, anaesthesia time and blood transfusion in contrast to length of diverted bowel. A definite explanation for the rise of quantitative measurements of liver enzymes after pouch operation could not be ascertained but the loop ileostomy seemed to delay the normalization of the values. This is intriguing and a good hypothesis for future studies using liver function test (LFT) abnormal data to length of diverted bowel. However, without liver biopsies at the time of the original pouch procedure, like in our case, it is

uncertain to ensure that no patients had early PSC, unsuspected IBD-associated hepatitis, or other liver abnormalities.

Although there were changes in the lipid pattern during some phases before and after the restorative proctocolectomy with loop ileostomy (manipulative period), completed end results showed that patients with functional ileoanal pouches have the same blood lipid profile as preoperatively, where the only difference to a normal reference material was a subnormal ßeta-lipoprotein fraction.

Immunoglobulin G (IgG) in plasma was found to be significantly lower in-patients with acute severe ulcerative colitis that demanded emergency operation than in elective patients. Most likely this is due to increased losses and affected production of IgG in fulminate UC. The increase in plasma IgG later in the course could then be seen as a sign of the patient´s rehabilitation.
Contrary to IgG; IgA and IgM, increased significantly after colectomy with ileostomy. The increase of IgA and IgM is most probably due to the changed microflora in the ileum, but the excision of the colon may also be of importance.

On long-term observations, minor morbidity and late complications are common after RPC. Regular surveillance is therefore important because some patients seem to run risk of secondary pouchitis and secondary anaemia. Check-up should therefore, include monitoring of homeostasis, especially in case of recurrent bleeding from the pelvic pouch and/ or chronic primary pouchitis.

The presented metabolic observations are well documented and describe the findings in order to obtain a reference with basic data so that it can rationally support future estimation of risk of homeostatic changes in the long-term follow-up after RPC surgery.

15.

ACKNOWLEDGEMENTS

This thesis was made possible by the encouragement and support of many persons and institutions. For this reason it will not be possible to enumerate them all. However, the following deserve special acknowledgements.

I wish to express my sincere gratitude to **Dag Hallberg** †, the late professor. He made it possible for me to join this outstanding institution. I remember his last words as an advice: not to take for granted assumption of another's discipline escapes assault, but requires a justifying and convincing argument in order to be accepted. He is not with us in sight but in mind forever.

I am particularly grateful to Associate professor **Lars Liljeqvist** and Dr. **Kerstin Lindquist** for their dedication, influence and supervisory roles in surgery and research, starting from scratch with clinical practice guidelines at the ward examining and counselling UC patients for surgery, during operations, and for data sample formulations and for arousing my interest to register for a PhD program with Karolinska Institute. As co-authors of the papers in this thesis they have been highly motivating and instrumental. They have taken much trouble and a lot of their private time for my sake by going through the countless number of manuscript drafts in order to bring the thesis to what it has become. Their expertise has shaped my own. Without their interactions over the years this work would not have reached here.

Jörgen Larsson, my Supervisor, Professor and Head of the Department of surgery for providing all necessary measures and support facilities that anabled maturity of this thesis accomplished.

Associate professor **Li Fällander Tsai**, my Co-supervisor, for her inspiration, fundamental humanity, guidance, time, support and interest shown to find solutions when probation questions were inevitable. And for her objective and faultless efforts before the administration of KARO-Institution have been very rewarding indeed.

Dr. **Mats Bergström**, **MD, PhD**, from the Department of Clinical Chemistry for his inestimable collaboration and guidance in the laboratory methodological aspects that made the project interdisciplinary. Over years he was able to answer all my questions regarding variables when it was not clear to us. His interest shown in proof reading offered valuable suggestions for improvement.

Dr. **Jan-Erik Åkerlund, MD, PhD,** an excellent colleague and eminent teacher in colorectal surgery. His skilled scientific views have always guided mine in understanding the risks that pouch patients might face regarding homeostasis.

Dr. **Staffan Ekblom, PhD** and Dr. **Joana Tyrcha**, **PhD**, University of Stockholm, Institute of actuarial and statistic mathematics (statistiska forskningsgruppen) for time shown in offering statistic guidelines.

All members of the IBD-research team at Huddinge University Hospital, in particular professor **Kurt Einarsson**, associate professor **Dagny Ståhlberg** and associate professor **Robert Löfberg** for their hospitality during my frequent visits at their department hunting for their scientific expertise and knowledge of IBD and pouch patients.

My sincere gratitude to all staff from the Department of Clinical Chemistry, Karolinska Institute at Huddinge University Hospital for carrying out all the patients analyses. I wish to express my special acknowledgements to Dr. **Per Bjellerup**, **MD**, Ms **Elisabeth Fransson**, Mr. **Anders Bergman** and Dr. **Christian Löwbeer**, **MD**, for the excellent guidelines regarding biochemical laboratory analytical methodologies.

Ms **Héléne Jansson**, Ms **Marjalena Kiljander**, Ms **Berit Lecomte**, Ms **Inger Janninger**, Ms **Ann-Charlott Nordström**, Ms **Monica Ritzling**, Ms **Astrid Ericson,** Ms **Irene Crouthon** and Ms **Rita Berg** for their unfailing administrative, secretarial and archive aid.

My brother, **Abia** and my sisters, **Celia** and **Palamilanji** for unfailing and constant support. They have never understood as to why my research training took this long. Despite that, their support has even gone beyond that by making me equally enjoyable inspite of the long distance and has been the hidden rock behind this work.

Lastly, I wish to convey my everlasting love to my family, my wife **Veneranda**, my children, **Jennifer** and **Samuel** for without whose sacrifices this work could never have been accomplished.

This study was supported by research grants from the Karolinska Institute.

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Table XXXII.
General overview for electrolytes, haematology, proteins, liver enzymes, lipids, gastrointestinal hormones and enzyme and Gastric acid secretion during and after restorative proctocolectomy

Point of Control	Parameter	Number of patients studied	Percentage Low values	Percentage High values	M±SEM	*P value*
Precolectomy	Sodium	60	0	0	138 ± 0.47 mmol/l	
Ileostomy	Sodium	47	0	0	139.81± 0.32	*0.008*
Loop ileostomy	Sodium	74	0	0	139.07 ± 0.34	*0.08*
6 months	Sodium	69	0	0	139.93 ± 0.25	*0.01*
12 months	Sodium	59	0	0	140.46 ± 0.27	*0.0001*
18 months	Sodium	51	0	0	140.71 ± 0.51	*0.0003*
24 months	Sodium	46	0	0	140.61 ± 0.33	*0.0003*
36 months	Sodium	31	0	1	140.68 ± 0.46	*0.01*
Precolectomy	Calcium	59	36	0	2.25 ± 0.03 mmol/l	
Ileostomy	Calcium	46	15	4	2.38 ± 0.02	*0.0004*
Loop ileostomy	Calcium	65	5	3	2.41 ± 0.01	*0.0001*
6 months	Calcium	69	1	4	2.41 ± 0.02	*0.0001*
12 months	Calcium	62	2	0	2.41 ± 0.01	*0.0001*
18 months	Calcium	50	10	2	2.36 ± 0.03	*0.01*
24 months	Calcium	46	4	2	2.39 ± 0.01	*0.0003*
36 months	Calcium	32	3	2	2.36 ± 0.18	*0.04*
Precolectomy	Zinc	43	5	5	15.30 ± 0.49 µmol/l	
Ileostomy	Zinc	44	2	16	16.02 ± 0.63	*0.32*
Loop ileostomy	Zinc	63	6	11	16.40 ± 0.62	*0.52*
6 months	Zinc	70	4	6	15.59 ± 0.37	*0.73*
12 months	Zinc	54	4	7	15.69 ± 0.47	*0.46*
18 months	Zinc	54	6	6	15.30 ± 0.45	*0.95*
24 months	Zinc	35	6	3	15.11 ± 0.49	*0.77*
36 months	Zinc	26	8	4	15.12 ± 0.48	*0.79*
Precolectomy	Magnesium	47	21	0	0.79 ± 0.02 mmol/l	
Ileostomy	Magnesium	42	26	0	0.79 ± 0.01	*0.65*
Loop ileostomy	Magnesium	70	36	0	0.78 ± 0.01	*0.61*
6 months	Magnesium	70	19	0	0.79 ± 0.01	*0.61*
12 months	Magnesium	63	27	0	0.79 ± 0.01	*0.67*
18 months	Magnesium	54	27	0	0.81 ± 0.01	*0.39*
24 months	Magnesium	47	26	0	0.81 ± 0.01	*0.03*
36 months	Magnesium	28	16	0	0.85 ± 0.02	*0.08*
Precolectomy	Potassium	59	0	0	4.22 ± 0.05 mmol/l	
Ileostomy	Potassium	49	2	0	4.19 ± 0.05	*0.30*
Loop ileostomy	Potassium	76	1	0	4.22 ± 0.04	*0.74*
6 months	Potassium	70	3	0	4.28 ± 0.04	*0.31*
12 months	Potassium	63	0	2	4.37 ± 0.05	*0.02*
18 months	Potassium	53	0	2	4.29 ± 0.06	*0.27*
24 months	Potassium	45	0	2	4.36 ± 0.06	*0.10*
36 months	Potassium	30	0	0	4.33 ±0.05	*0.83*

Precolectomy	Hemoglobin	63	44	5	123.46 ± 2.85 g/l	
Ileostomy	Hemoglobin	48	18	4	137.96 ± 2.34	*0.004*
Loop ileostomy	Hemoglobin	76	12	5	138.84 ± 1.56	*0.0001*
6 months	Hemoglobin	75	11	5	139.27 ± 1.85	*0.0001*
12 months	Hemoglobin	65	11	9	141.74 ± 1.77	*0.0001*
18 months	Hemoglobin	55	7	5,5	140.16 ± 2.0	*0.0001*
24 months	Hemoglobin	50	12	2	140.6 ± 2.09	*0.0001*
36 months	Hemoglobin	30	14	7	140.2 ± 3.01	*0.001*
Precolectomy	Iron	55	49	0	10.78 ± 0.992 µmol/l	
Ileostomy	Iron	37	23	0	12.95 ± 1.03	*0.33*
Loop ileostomy	Iron	57	16	4	17.54 ± 1.53	*0.0003*
6 months	Iron	68	15	0	15.57 ± 1.05	*0.005*
12 months	Iron	61	11	0	16.34 ± 1.04	*0.0005*
18 months	Iron	49	21	0	15.47 ± 1.04	*0.005*
24 months	Iron	46	18	0	15.07 ± 1.11	*0.001*
36 months	Iron	31	16	0	17.45 ± 1.40	*0.01*
Precolectomy	Transferrin	15	0	0	2.53 ± 0.35 g/l	
Ileostomy	Transferrin	16	0	6	2.9 ± 0.26	*0.34*
Loop ileostomy	Transferrin	14	0	14	3.55 ± 0.41	*0.66*
6months	Transferrin	14	0	0	2.58 ± 0.48	*0.33*
12 months	Transferrin	16	0	0	2.3 ± 0.32	*0.31*
18 months	Transferrin	15	0	0	2.82 ± 0.16	*0.32*
24 months	Transferrin	12	0	0	3.0 ± 0.6	*0.69*
36 months	ransferrin	11	0	0	2.4 ± 0.25	*0.34*
Precolectomy	B_{12}	41	8	10	433 ± 31.45 pmol/l	
Ileostomy	B_{12}	43	7	2	353 ± 32.27	*0.17*
Loop ileostomy	B_{12}	61	8	3	326 ± 30.78	*0.28*
6 months	B_{12}	69	7	3	335 ± 26.81	*0.33*
12 months	B_{12}	58	3	5	349 ± 27.73	*0.19*
18 months	B_{12}	53	6	2	319 ± 23.24	*0.03*
24 months	B_{12}	51	6	4	380 ± 36.1	*0.50*
36 months	B_{12}	28	11	0	350± 27.22	*0.09*
Precolectomy	Folates	42	12	0	14.99 ± 1.83 nmol/l	
Ileostomy	Folates	43	0	0	16.16 ± 1.713	*0.01*
Loop ileostomy	Folates	61	0	0	16.78 ± 1.757	*0.01*
6 months	Folates	66	0	0	16.20 ± 1.127	*0.01*
12 months	Folates	56	0	0	16.10 ± 1.402	*0.002*
18 months	Folates	51	0	0	16.90 ± 1.673	*0.001*
24 months	Folates	44	0	0	16.51 ± 1.77	*0.005*
36 months	Folates	25	0	0	19.22 ± 2.44	*0.001*
Precolectomy	ESR	57	0	43	29 ±3.61 mm/hour	
Ileostomy	ESR	44	0	26	13 ±2.44	*0.003*
Loop ileostomy	ESR	69	0	7	8 ± 0.85	*0.0001*
6 months	ESR	72	0	11	10 ±1.07	*0.0001*
12 months	ESR	60	0	15	12 ±2.31	*0.0001*
18 months	ESR	53	0	15	12 ±1.87	*0.0001*
24 months	ESR	45	0	21	12 ±1.62	*0.002*
36 months	ESR	31	0	13	11±2.44	*0.05*

Precolectomy	WBC	59	0	27	8 ± 0.47 10^9/l	
Ileostomy	WBC	44	0	12	7 ± 0.274	*0.01*
Loop ileostomy	WBC	69	0	6	6 ± 0.214	*0.0001*
6 months	WBC	73	0	5	6 ± 0.209	*0.0001*
12 months	WBC	62	0	3	6 ± 0.202	*0.0001*
18 months	WBC	55	0	7	6 ± 0.293	*0.0003*
24 months	WBC	50	0	8	6 ± 0.24	*0.001*
36 months	WBC	32	0	10	6 ± 0.37	*0.11*
Precolectomy	Sch t +IF	16	38	12	17 ± 2.48 %	
	Sch t -IF17	35	12	16 ± 2.41		
12 months	Sch t +IF	67	30	6	16 ± 1.09	*0.87*
	Sch t -IF67	31	6	15 ± 0.99	*0.42*	
36 months	Sch t +IF	35	37	0	15 ± 1.22	*0.23*
	Sch t -IF36	36	0	15 ± 1.23	*0.13*	
Precolectomy	IgG	44	0	11	10.5 ± 0.47 g/l	
Ileostomy	IgG	38	0	5	10.87 ± 0.82	*0.62*
Loop ileostomy	IgG	44	0	9	11.86 ± 0.76	*0.13*
6 months	IgG	51	0	6	11.16 ± 0.36	*0.36*
12 months	IgG	45	0	16	12.4 ± 0.44	*0.005*
18 months	IgG	23	0	22	12.70 ± 0.77	*0.05*
24 months	IgG	21	0	14	11.76 ± 0.76	*0.38*
36 months	IgG	28	0	18	13 ± 0.65	*0.07*
Precolectomy	IgM	37	0	8	1.26 ± 0.09 g/l	
Ileostomy	IgM	39	0	18	1.66 ± 0.12	*0.009*
Loop ileostomy	IgM	40	0	40	1.80 ± 0.09	*0.0005*
6 months	IgM	49	0	27	1.71 ± 0.12	*0.008*
12 months	IgM	38	0	26	1.59 ± 0.12	*0.05*
18 months	IgM	20	0	15	1.46 ± 0.13	*0.88*
24 months	IgM	8	0	25	2.09 ± 0.57	*0.56*
36 months	IgM	18	0	12	1.52 ± 0.17	*0.38*
Precolectomy	IgA	37	0	8	2.05 ± 0.134 g/l	
Ileostomy	IgA	38	0	16	2.04 ± 0.158	0.90
Loop ileostomy	IgA	29	0	14	2.24 ± 0.148	0.36
6 months	IgA	51	0	8	2.20 ± 0.116	0.72
12 months	IgA	40	0	20	2.73 ± 0.332	0.04
18 months	IgA	23	0	26	2.67 ± 0.249	0.05
24 months	IgA	17	0	18	2.36 ± 0.221	0.24
36 months	IgA	22	0	23	2.37 ± 0.181	0.41
Precolectomy	Orosomucoid	47	0	72	1.55 ± 0.11 g/l	
Ileostomy	Orosomucoid	43	0	37	1.05 ± 0.07	*0.0002*
Loop ileostomy	Orosomucoid	60	0	20	0.81 ± 0.04	*0.0001*
6 months	Orosomucoid	59	0	21	0.86 ± 0.04	*0.0001*
12 months	Orosomucoid	53	0	16	0.94 ± 0.12	*0.0004*
18 months	Orosomucoid	27	0	26	0.91 ± 0.07	*0.0003*
24 months	Orosomucoid	26	0	31	0.89 ± 0.06	*0.0001*
36 months	Orosomucoid	30	0	21	0.86 ± 0.05	*0.0001*
Precolectomy	Haptoglobin	49	0	61	2.81 ± 0.20 g/l	
Ileostomy	Haptoglobin	43	0	30	1.66 ± 0.10	*0.0001*
Loop ileostomy	Haptoglobin	64	0	17	1.38 ± 0.08	*0.0001*
6 months	Haptoglobin	64	0	20	1.61 ± 0.10	*0.0001*
12 months	Haptoglobin	62	0	15	1.47 ± 0.08	*0.0001*
18 months	Haptoglobin	39	0	23	1.61 ± 0.14	*0.0001*
24 months	Haptoglobin	34	0	29	1.77 ± 0.16	*0.005*
36 months	Haptoglobin	34	0	35	1.77 ± 0.12	*0.002*
Precolectomy	Albumin	61	39	8	36 ± 0.89 g/l	

Ileostomy	Albumin	46	7	15	41 ± 0.73	*0.0006*
Loop ileostomy	Albumin	72	7	13	42 ± 0.58	*0.0001*
6months	Albumin	73	4	4	41 ± 0.42	*0.0001*
12 months	Albumin	72	5	1	40 ± 0.37	*0.0001*
18 months	Albumin	56	4	7	41 ± 0.56	*0.0001*
24 months	Albumin	60	8	5	40 + 0.57	*0.0002*
36 months	Albumin	54	9	7	40 ± 0.50	*0.0005*
Precolectomy	ASAT	62	0	10	0.40 ± 0.03 µkat/l	
Ileostomy	ASAT	47	0	2	0.38 ± 0.02	*0.40*
Loop ileostomy	ASAT	77	0	9	0.50 ± 0.03	*0.04*
6 months	ASAT	80	0	10	0.46 ± 0.03	*0.17*
12 months	ASAT	73	0	8	0.42 ± 0.03	*0.57*
18 months	ASAT	68	0	9	0.46 ± 0.03	*0.18*
24 months	ASAT	70	0	11	0.49 ± 0.09	*0.12*
36 months	ASAT	64	0	6	0.42 ± 0.02	*0.63*
Precolectomy	ALAT	60	0	15	0.50 ± 0.07 µkat/l	
Ileostomy	ALAT	46	0	15	0.42 ± 0.04	*0.35*
Loop ileostomy	ALAT	77	0	36	0.75 ± 0.07	*0.006*
6 months	ALAT	80	0	19	0.56 ± 0.08	*0.31*
12 months	ALAT	74	0	18	0.55 ± 0.08	*0.51*
18 months	ALAT	70	0	21	0.59 ± 0.08	*0.39*
24 months	ALAT	72	0	20	0.59 ± 0.09	*0.25*
36 months	ALAT	65	0	18	0.52 ± 0.06	*0.70*
Precolectomy	ALP	53	0	8	3.06 ± 0.27 µkat/l	
Ileostomy	ALP	40	0	11	3.18 ± 0.20	*0.10*
Loop ileostomy	ALP	71	0	42	4.17 ± 0.20	*0.001*
6 months	ALP	78	0	13	3.08 ± 0.10	*0.51*
12 months	ALP	73	0	8	3.04 ± 0.20	*0.83*
18 months	ALP	69	0	13	3.11 ± 0.20	*0.87*
24 months	ALP	72	0	8	2.99 ± 0.20	*0.74*
36 months	ALP	65	0	12	3.08 ± 0.20	*0.84*
Precolectomy	Cholesterol	25	0	5	5.26 ± 0.29 mmol/l	
Ileostomy	Cholesterol	31	0	0	4.74 ± 0.18	*0.90*
Loop ileostomy	Cholesterol	36	0	0	3.81 ± 0.15	*0.01*
6 months	Cholesterol	10	0	0	3.85 ± 0.24	*0.01*
12 months	Cholesterol	40	0	0	4.41 ± 0.18	*0.47*
18 months	Cholesterol	17	0	0	4.33 ± 0.30	*0.59*
24 months	Cholesterol	10	0	0	4.89 ± 0.312	*0.38*
36 months	Cholesterol	10	0	0	4.77 ± 0.561	*0.54*
Precolectomy	Triglycerides	24	0	11	1.11 ± 0.121 mmol/l	
Ileostomy	Triglycerides	17	0	7	1.58 ± 0.267	*0.64*
Loop ileostomy	Triglycerides	21	0	18	2.55 ± 0.429	*0.05*
6 months	Triglycerides	8	0	0	1.27 ± 0.128	*0.63*
12 months	Triglycerides	35	0	6	1.23 ± 0.124	*0.33*
18 months	Triglycerides	16	0	6	1.24 ± 0.312	*0.62*
24 months	Triglycerides	19	0	1	1.23 ± 0.062	*0.65*
36 months	Triglycerides	16	0	0	1.23 ± 0.122	*0.64*
Precolectomy	Pre-beta-lipop	15	0	0	14.38 ± 2.5 %	
Ileostomy	Pre-beta-lipop	-	-	-	-	-
Loop ileostomy	Pre-beta-lipop	16	0	0	10.17 ± 3.9	*0.05*
12 months	Pre-beta-lipop	18	5	6	16.0 ± 1.8	*0.87*
18 months	Pre-beta-lipop	16	0	0	12.0 ± 3.2	*0.86*
24 months	Pre-beta-lipop	16	2	2	13.38 ± 2.9	*0.83*
36 months	Pre-beta-lipop	16	0	0	17.0 ± 5.0	*0.85*
Precolectom	Beta-lipop	15	0	0	53.31 ±3.043 %	

Ileostomy	Beta -lipop	-	-	-	-	-
Loop ileostomy	Beta -lipop	14	0	0	55.0 ± 7.84	*0.99*
6 months	Beta -lipop	16	0	0	45.67 ± 2.50	*0.05*
12 months	Beta -lipop	16	0	12	46.63 ± 2.30	*0.05*
18 months	Beta -lipop	13	0	0	47.50 ± 3.54	*0.05*
24 months	Beta -lipop	16	0	0	49.0 ± 4.28	*0.05*
36 months	Beta -lipop	16	0	0	43.5 ± 2.5	*0.05*
Precolectomy	Alpha-lipop	15	0	0	32.77 ± 2.547 %	
Ileostomy	Alpha-lipop	-	-	-	-	-
Loop ileostomy	Alpha-lipop	10	0	0	16.96 ± 4.65	*0.001*
6 months	Alpha-lipop	10	0	0	20.65 ± 3.24	*0.05*
12 months	Alpha-lipop	18	0	7	38.89 ± 2.44	*0.03*
18 months	Alpha-lipop	10	0	0	37.3 ± 3.347	*0.03*
24 months	Alpha-lipop	10	0	7	39.0 ± 3.35	*0.01*
36 months	Alpha-lipop	10	0	0	37.33 ± 8.41	*0.03*
Precolectomy	FFA	15	0	0	0.60 ± 0.02 mmol/l	
12 months	FFA	15	0	0	0.50 ± 0.02	*0.69*
36 months	FFA	15	0	0	0.96 ± 0.04	*0.79*
Precolectomy	^{14}C-bt	9	33	0	3.88 ± 0.89 %/h	
12 months	^{14}C-bt	46	35	0	3.71 ± 0.24	*0.70*
36 months	^{14}C-bt	32	41	0	3.63 ± 0.32	*0.98*

GASTRIC SECRETION

Retention

Precolectomy	HCl conc.	7	-	-	1.6 ± 0.53 mmol/l	
12 months / IPAA	HCl conc.	7	-	-	3.05 ± 2.15	*0.001*
Precolectomy	HCl volume	7	-	-	64.3 ± 15.17 ml	
12 months / IPAA	HCl volume	7	-	-	65.2 ± 38.91	*0.93*

Basal secretion

Precolectomy	HCl conc.	7	-	-	1.15 ± 0.17 mmol/l	
12 months / IPAA	HCl conc.	7	-	-	2.64 ± 2.42	*0.01*
Precolectomy	HCl volume	7	-	-	28.6 ± 8.90 ml	
12 months / IPAA	HCl volume	7	-	-	62 ± 38.93	*0001*

After pentagastrin stimulation /sc

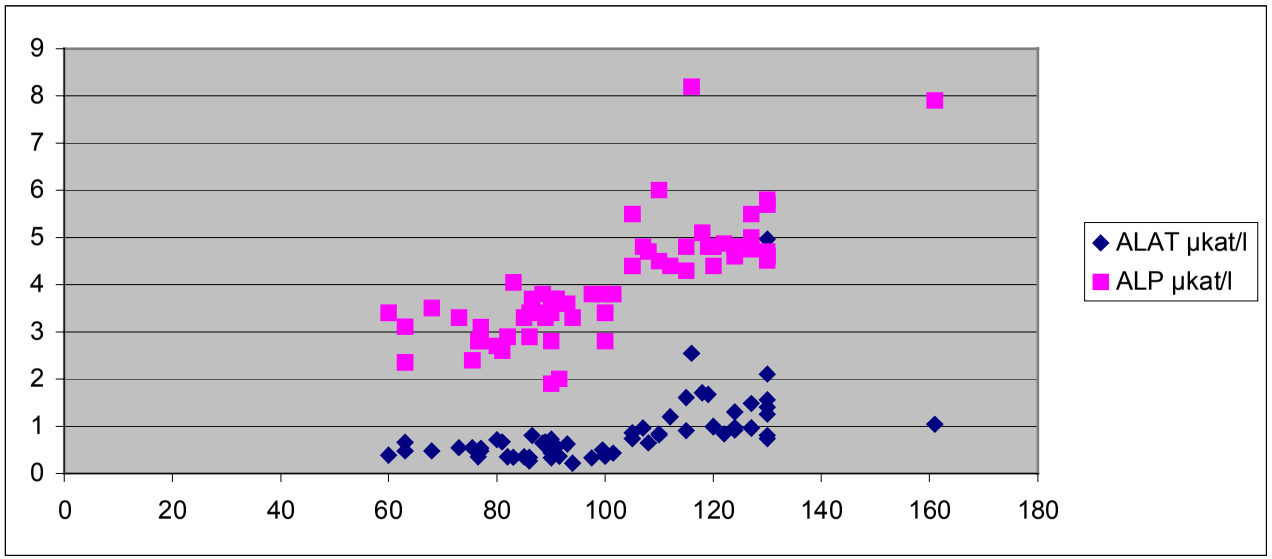
Precolectomy	0-15 min HCl conc	10	-	-	2.5 ± 0.01 mmol	
12 months	0-15 min HCl	10	-	-	4.2 ± 2.8	*0.13*
Precolectomy	16-30 min		-	-	4.8 ± 1.1	
12 months	16-30 min		-	-	9.5 ± 4.6	*0.03*
Precolectomy	31-45 min		-	-	5.5 ± 0.92	
12 months	31-45 min		-	-	9.9 ±4.1	*0.03*
Precolectomy	46-60 min		-	-	7.4 ± 1.11	
12 months	46-60 min		-	-	7.5 ± 2.8	*0.89*
Precolectomy	During 60 minutes		-	-	20.2 ± 2	
12 months	During 60		-	-	31.1 ±12.8	*0.011*
Precolectomy	0-15 min HCl volume	10	-	-	10 ± 3 ml	
12 months	0-15 min HCl		-	-	49 ± 34	*0.01*

Precolectomy	16-30 min		-	-	50 ± 5	
12 months	16-30 min		-	-	54 ± 26	*0.16*
Precolectomy	31-45 min		-	-	36 ± 6	
12 months	31-45 min		-	-	50 ± 38	*0.01*
Precolectomy	46-60 min		-	-	60 ± 8	
12 months	46-60 min		-	-	60 ± 22	*0.18*
Precolectomy	During 60 minutes		-	-	156 ± 3	
12 months	During 60		-	-	213 ± 8	*0.05*
Gastrointestinal hormone and enzyme						
Precolectomy	S-gastrin	11	0	0	28.98 ± 5.89	
12 months	S-gastrin	21	0	0	32.57 ± 4.16	*0.56*
36 months	S-gastrin	5	0	0	26.56 ± 5.41	*0.18*
Precolectomy	S-pepsinogen	10	0	0	69.1 ± 5.212	
12 months	S-pepsinogen	20	0	0	70.45 ± 5.79	*0.88*
36 months	S-pepsinogen	5	0	0	70.4 ± 12.43	*0.98*
Precolectomy	S-pentagastrin	22	0	23	21 ± 2.99	
12 months	S-pentagastrin	44	0	9	21 ± 1.74	*0.51*
36 months	S-pentagastrin	10	0	0	21 ± 4.03	*0.90*

Annexes

Overviews – annex I – VII

Annex I



Pearson´s correlation coefficient

The correlation between serum ALAT and ALP versus diverted length of the small bowel (cm) during manipulative period with loop ileostomy period. Patients had pathologic high values when the diverted bowel was not less than 105 cm long ($p< 0.05$).

Reference:
ALAT = < 0.70 µkat/l
ALP = < 4.2 µkat/l

Annex II

Total mean anaesthesia time and mean transfused blood, mean isofluran and enfluran time (hours) in two different pelvic pouch procedures (Elective and Emergency operations).

Group	Mean total anesthesia. Time in hours (number of patients)	Use of Isofluran anesthesia. Mean time in hours (number of patients)	Use of Enflurane anesthesia. Mean time in hours (number of patients)	Mean (ml) transfused concentrated blood (number of patients)
Elective OP	6.7 ± 0.2 (n = 92)	6.8 ± 0.3 (n = 64)	6.6 ± 0.3 (n = 28)	995 ± 28 (n = 92/92)
Emergency OP	4.3 ± 0.3 (n = 42)	4.3 ± 0.3 (n = 42)	0	420 ± 55 (n = 6/42)

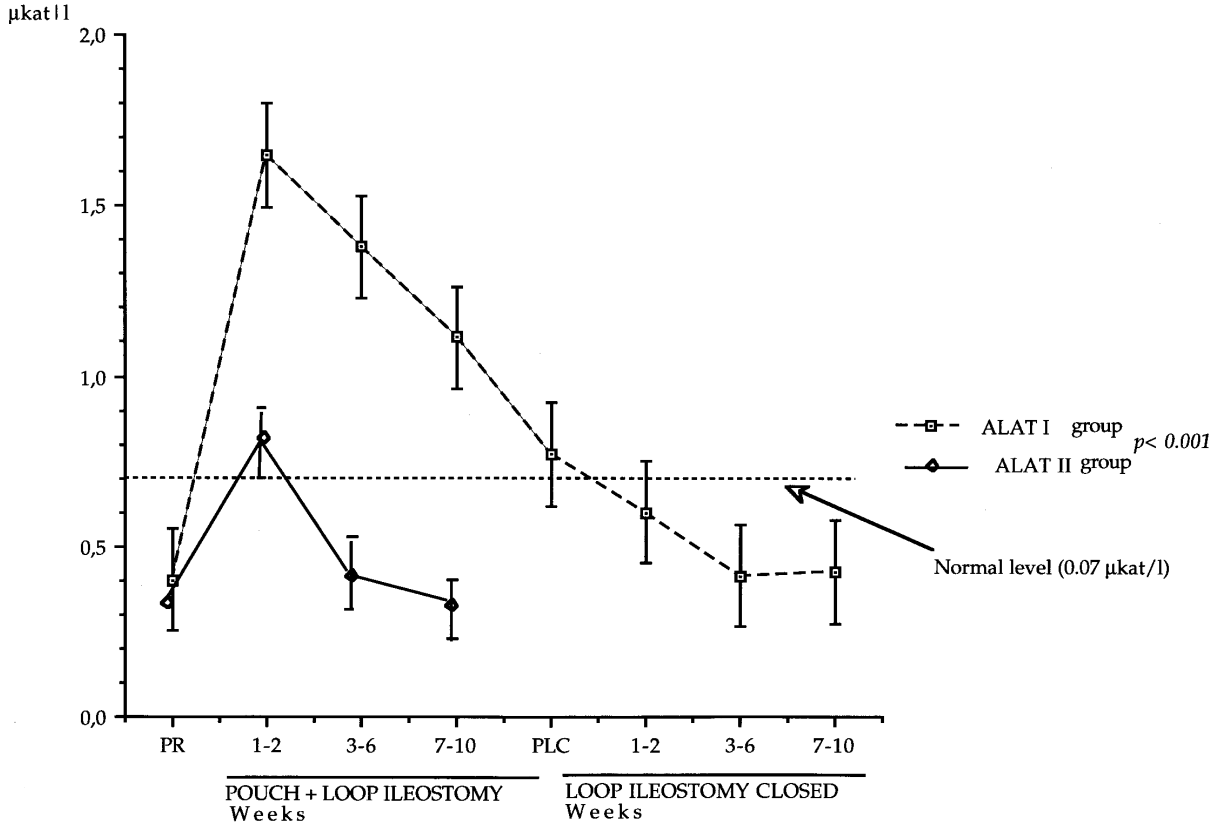
Annex III

The number of patients who obtained different drugs and the percentage of who obtained elevation of ALAT and ALP in serum in two different pelvic pouch procedures (Elective and Emergency operations).

	Elective OP (Number of patients = 92)			Emergency OP (Number of patients = 42)		
		ALAT	**ALP**		ALAT	ALP
MEDICATIONS	**TOTAL**	**> 0.70 µkat/l**	**> 4.2 µkat/l**	TOTAL	> 0.70 µkat/l	< 4.2 µkat/l
ISOFLURAN	**64**	**54 (84%)**	**41 (64%)**	42	14 (33%)	13 (31%)
ENFLURAN	**28**	**9 (32%)**	**16 (57%)**	-	-	-
CEFAXITIN	**92**	**63 (68%)**	**57 (62%)**	20	9 (45%)	9 (45%)
METRONIDAZOL	**92**	**63 (68%)**	**57 (62%)**	36	12 (33%)	10 (28%)
BACTRIM®	**25**	**18 (72%)**	**9 (36%)**	14	8 (57%)	7 (50%)
HEPARIN	**92**	**63 (68%)**	**57 (62%)**	42	31 (74%)	30 (71%)
DIAZEPAM	**92**	**63 (68%)**	**57 (62%)**	36	23 (64%)	20 (58%)
TIOPENTAL	**92**	**63 (68%)**	**57 (62%)**	21	18 (86%)	16 (76%)
SCOPOLAMIN	**68**	**51 (75%)**	**39 (57%)**	42	33 (79%)	30 (71%)
OXICON	**68**	**51 (75%)**	**39 (57%)**	42	33 (71%)	30 (71%)
CORTICOSTEROID	**71**	**50 (70%)**	**43 (61%)**	13	9 (69%)	9 (69%)
NO BLOOD TRANS	**2**	**1 (50%)**	**0 (0%)**	5	1 (20%)	2 (40%)
BLOOD TRANSF	**90**	**62 (69%)**	**57 (63%)**	37	32 (91%)	29 (78%)
ATROPINE	**87**	**59 (69%)**	**56 (64%)**	12	9 (75%)	1 (75%)

Annex IV

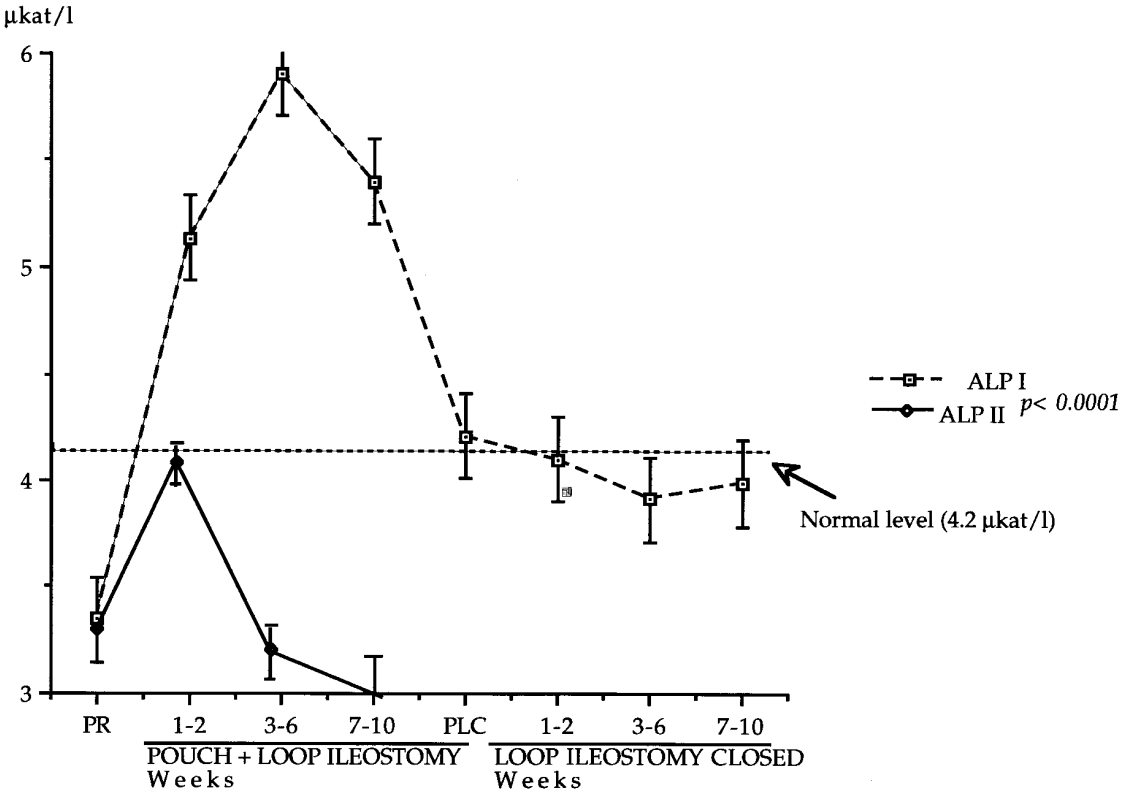
The M ± SD of S-ALAT in groups I with loop and II without loop (PR: Prior to colectomy, PLC: Prior to loop ileostomy closure)



Abreviations: PR=pre-colectomy; PLC=pre-loop ileostomy closure

Annex V

The M ± SD of S-ALP in groups I with loop and II without loop (PR: Prior to colectomy, PLC: Prior to loop ileostomy closure)



Abbreviations: PR=precolectomy; PLC=pre-loop ileostomy closure

ALAT=alanine aminotransferase; ALP=alkaline phosphates

Abbreviation: ALAT=alanine aminotransferase; ALP=alkaline phosphates

Annex VI

Social activities after IPAA surgery

		Tn	En	Enp
Work:				
Normal capacity to work	83	70	84.3	
Some interference to work		83	6	7.2
50% sick leave		83	4	4.8
100% sick leave		83	3	3.6
Diet restriction:				
No diet restriction		83	35	42.2
Avoid gas producing food		83	26	31.3
Avoid some products		83	12	14.5
More pronounced food restriction		83	10	12.0
Social life:				
No restriction		83	47	56.6
Few restrictions		83	20	24.1
Some restriction planning		83	7	8.4
Definite social restriction		83	6	7.2
Low activities		83	2	2.4
Home bounded		83	1	1.2

Abbreviation

Tn = Total number of patients studied

En = Effected number of patients

Enp= Effected number of patient in percentage

Annex VII

Number of patients who participated in different studies for papers I to VI, a total of 99 patients was recorded.

Patients Op number	Paper I	Paper II	Paper III	Paper IV	Paper V	Paper VI
1	X			X	X	
2	X			X	X	
3	X			X	X	
4	X			X	X	X
5	X			X	X	
6	X			X	X	
7	X			X	X	
8	X			X	X	
9	X			X	X	X
10	X	X		X	X	X
11	X	X		X	X	X
12	X			X	X	X
13	X			X	X	X
14	X			X	X	
15	X			X	X	X
16	X			X	X	
17	X			X	X	X
18	X	X		X	X	X
19	X			X	X	X
20	X			X	X	X
21	X			X	X	X
22	X	X		X	X	X
23	X			X	X	X
24	X	X		X	X	X
25	X			X	X	X
26	X			X	X	X
27	X	X		X	X	
28	X	X		X	X	X
29	X	X		X	X	X
30	X			X	X	
31	X	X		X	X	X
32	X			X	X	
33	X			X	X	
34	X			X	X	
35	X	X		X	X	X
36	X	X		X	X	X
37	X			X	X	X
38	X			X	X	X
39	X	X		X	X	X
40	X		X	X	X	X
41	X		X	X	X	X
42	X			X	X	X
43	X			X	X	X
44	X			X	X	
45	X			X	X	

I

II

III

IV

V

VI