

Faecal retention: A common cause in functional bowel disorders, appendicitis and haemorrhoids

– with medical and surgical therapy

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This review has been accepted as a thesis together with seven original papers by University of Copenhagen 13th of June 2014 and defended on 6th of October 2014.

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Dan Med J 2015;62(3):B5031

ARTICLES INCLUDED IN THE THESIS:

1. Raahave D, Loud FB. Additional faecal reservoirs or hidden constipation: a link between functional and organic bowel disease. *Dan Med Bull* 2004;51:422-5.
2. Raahave D, Christensen E, Loud FB, Knudsen LL. Correlation of bowel symptoms with colonic transit, length, and faecal load in functional faecal retention. *Dan Med Bull* 2009;56:83-8.
3. Raahave D, Loud FB, Christensen E, Knudsen LL. Colectomy for refractory constipation. *Scand J Gastroenterol* 2010;45:592-602.
4. Raahave D, Christensen E, Moeller HE, Kirkeby LT, Knudsen LT, Loud FB. Origin of acute appendicitis: faecal retention in colonic reservoirs: a case control study. *Surg Infect* 2007;8:55-61.
5. Raahave D. Stapled anorectomy for prolapsed haemorrhoids: a new operation. *Ugeskr Laeg* 2002;164:3862-5.
6. Raahave D, Jepsen LV, Pedersen IK. Primary and repeated stapled hemorrhoidectomy for prolapsing hemorrhoids: follow-up to five years. *Dis Colon Rectum* 2008;51:334-41.
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BACKGROUND

Patients with abdominal symptoms are among the most frequent to seek health care. The symptoms are difficult to attribute to a specific intra-abdominal organ; for example right iliac fossa pain could be referred to groin hernia, appendicitis, a caecum tumour, ureterolithiasis or, in females gynaecological disease. Consequently, many patients go through several investigative procedures, including upper and lower endoscopies (eventual pill camera endoscopy), ultrasound and CT or other scanning, and blood tests, to establish a diagnosis. However, a number of these patients will end up not having an organic, but a functional, diagnosis. Functional gastrointestinal disorders are identified by symptoms that differentiate between the upper and lower gastrointestinal tract. Thus, functional bowel disorders include irritable bowel syndrome (IBS) and functional constipation. In industrialized countries, IBS afflicts 10-20 % of the population (8,9) and affects the quality of life (10) and work productivity (11). In addition, constipation is a burden to many people in the western world, ranging from 2 to 27 %, reducing their

quality of life and work (12,13). Currently, IBS is subdivided into IBS-C (constipation dominant), IBS-D (diarrhoea dominant), IBS-M (mixed) and IBS-A (alternating), but does not have a clear aetiology. Constipation has many causes, including metabolic, endocrine, neurogenic, pharmacologic, mechanical, psychological, and idiopathic, but only a few studies have focussed on the length of the colon as a cause of constipation (14,15,16, 17). Both constipation and IBS sufferers constantly seek care because of persisting symptoms in spite of many investigative procedures and therapeutic efforts, incurring high health care costs (12).

When physically examining such a patient, two observations are evident. Frequently a soft mass in the right iliac fossa is palpated with tenderness (suspicious of a faecal reservoir in the right colon) and immediate ano-rectoscopy is often impossible because of faecal retention in the rectum. Other parts of the colon are then suspected of being filled with faeces, and a somatic disturbance could be behind the abdominal and defaecatory complaints. The major functions of the colon are to conserve water, to allow bacteria to split dietary fibre into absorbable nutrients (with gas production), and to store, propel, and expel faeces. Thus, the nature of faecal content is in turn dependent on the food eaten.

I was inspired to focus on the faecal content of the colon by Denis Burkitt (1911-1993), who searched for a common cause of colorectal diseases, such as diverticula, polyps, malignancy, appendicitis and haemorrhoids (18,19). The occurrence of haemorrhoids has been linked to constipation (20,21). Thus, the ultimate aim was to identify a cause of the persisting abdominal symptoms and defecation disorders in order to treat these patients with medical and/or surgical therapies.

THESIS TOPICS AND OBJECTIVES

- Explore whether abdominal and anorectal symptoms and physical signs co-exist in patients with bowel complaints (1).
- Explore whether abdominal and anorectal symptoms correlate with the physiological parameters, colon transit time (CTT), and faecal loading (faecal retention) (2).
- Determine the impact of colon length on CTT and faecal load (2).
- Explore whether clusters of gastrointestinal symptoms and signs may belong to the same underlying disease dimension (1,2).
- Explore whether dietetic and medical interventions reduce CTT

and faecal load, eliminate abdominal symptoms and restore normal defecation patterns (1,2).

- Compare CTT, faecal load, and colon length between operated and non-operated patients refractory to conservative treatment by assessing the type of colectomy, complications, functional results, and patient satisfaction (3).
- Explore whether patients with acute appendicitis have prolonged CTT or faecal retention, and whether these observations are associated with the occurrence of a faecalith in the appendix (4).
- A novel surgical procedure, stapled haemorrhoidopexy, is introduced for curing haemorrhoids linked with faecal retention and the results are assessed, including complications, reasons for failure, need for repeated procedures, and the durability of the operation to 5 years of follow-up (5,6,7).
- Explore whether faecal retention is “a common cause” underlying functional bowel disorders, acute appendicitis, and haemorrhoids (1,2,3,4,5,6).

MATERIAL AND METHODS

PATIENTS, CONTROLS, AND STUDY DESIGN

A random sample of 251 patients was selected from 645 patients between September 12, 1988 and January 19, 1999 (1). The patients had been referred for abdominal symptoms, such as bloating and pain, and defecation disorders and physical signs, such as abdominal distension and haemorrhoids. A second cohort of 281 patients was studied between June 19, 1997 and August 31, 2004, including objective physiological measures of colorectal function (2). The criteria for inclusion were a suspicion of constipation with abdominal symptoms and defecation disorders. Both studies had observational and interventional components. A new study was derived from the latter study, consisting of 35 patients refractory to conservative treatment for constipation, who underwent surgery (3). A case-control study was carried out parallel to the second study between October 11, 1999 and December 18, 2002, including 68 patients scheduled for appendectomy (4).

A cohort of 372 persons over 18 years of age was selected at random from the National Civil Register to serve as a control group. The control subjects were free of gastrointestinal complaints, not taking laxatives or strong analgesics, and had no history of abdominal surgery, including appendectomy. A total of 44 persons, equal numbers of females and males and equally distributed in 10-year age groups from 20 to 50+ years, fulfilled the criteria and underwent the same marker study as the patients, serving as a reference group (2,3,4).

Many patients in the cohort studies also suffered from haemorrhoids, and the surgical treatment of this disease was renewed after introducing stapled haemorrhoidopexy. Thus, between June 8, 1999 and March 21, 2004, 258 consecutive patients were included in outcome studies of the procedure for prolapsed haemorrhoids (PPH) (5,6), after we participated in the international randomized trial of haemorrhoid excision and stapling (22). Finally, one case reported a serious complication after stapled haemorrhoidopexy (7).

The studies were conducted according to the Declaration of Helsinki.

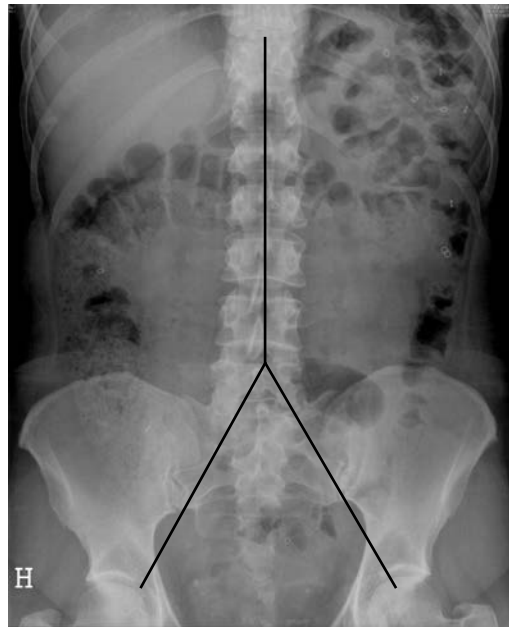
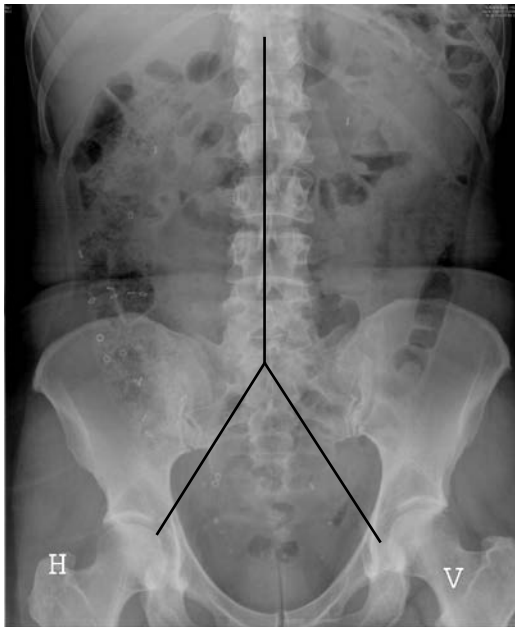
METHODS

Symptoms and physical signs

A standardized questionnaire covering 19 selected abdominal and anorectal symptoms (Figure 1, (1, 2)) was completed for each patient to report the presence or absence of a symptom. A symptom had certain dominance if the patients responded affirmatively. Anamnestic data included chronic diseases, profession and employment status, and any previous abdominal, genital, or anal operations. The presence or absence of familiar colorectal cancer was also recorded. Each patient underwent a physical examination, including ano-rectoscopy to observe possible rectal constipation. The patients with haemorrhoids were asked to strain while the anoscope was withdrawn to observe sliding mucosa through the anus. A surgical anatomy score was developed on a visual analogue scale (VAS) to describe the appearance of the anus (5,6). A score of 1 indicated a normal anus without visible mucosa or skin tags and a score of 7 was used for the worst prolapsing haemorrhoids. Anal anatomy scores were obtained pre- and postoperatively and at follow-up. The anal tonus and squeeze of the anal sphincter was assessed digitally.

Colon transit time (CTT)

After the first mostly clinical study (1), physiological and anatomic colonic measures were applied in the studies that followed (2,3,4). Most authors have supported the use of these measures, especially for defining pathophysiological subtypes of chronic constipation (23,24). The best information about colorectal function in constipation has been obtained from colonic transit studies using bismuth as a tracer substance (25), coloured glass beads (26), carmine (27), radioactive chromium (28), or radioopaque polyethylene pellets (29). Ingested radio-opaque markers are counted in the stools (29) or on plain films of the abdomen (30); the latter has been shown to be a reproducible method (30,31). Because radio-opaque markers are not absorbed, do not alter gut metabolism, and have a specific gravity to gut content, they can be assumed to travel at the same rate as faeces (29). Transit studies can include either single marker ingestion with multiple X-ray or multiple marker ingestion with single X-ray (30,32). Single marker ingestion was preferred for better compliance and depicting the faecal load on separate days (2), whereas multiple marker ingestion was chosen for reduced radio exposure in control subjects and for the patients in one study (2,4). Patients refrained from using laxatives, enemas, or suppositories for one week prior to the study. A capsule containing 24 radio-opaque markers (Sitzmarks, Konsyl Pharmaceutical Inc., Fort Worth, Texas, U.S.) was ingested by each patient and abdominal X-rays taken 48 h and 96 h after the markers were ingested. The abdominal X-ray was divided into three segments in a reversed Y-design, formed by the vertebral column and two imaginary lines from the fifth lumbar vertebra to the right and left pelvic brim, pointing towards the femoral head, which is a modification from earlier studies (33,34).



Colon transit study after the ingestion of 24 markers by a 50-year-old female patient.
 Left X-ray at 48 h: $16 + 1 + 3 = 20$ markers, faecal load: $3 + 3 + 2 = 8$.
 Right X-ray at 96 h: $2 + 9 + 1 = 12$ markers, faecal load: $3 + 3 + 1 = 7$.
 CTT = 64 h.

The localized and counted markers were assigned to the right, left, and distal part of the colon, with the latter including the rectum. This method of determining the marker count in each of the three segments was used irrespective of bowel outlines that may suggest some other placement of a part of the colon. The total number (n) of markers was counted in each segment, and CTT was calculated using the following equation:

$$\text{CTT (hours)} = (48/n) \times (n48 + n96),$$

where n48 and n96 are the number of markers detected at 48 h and 96 h after the ingestion of $n = 24$ markers. This approach is a variant of the original technique of following the markers by daily X-rays until they were completely defecated and under the assumption that all markers would have been expelled after another 48h (totally 144h) (30,32, Bouchoucha personal communication); segmental CTT was calculated as well (2,3). The sum of the markers is equal to the mean transit time of a single marker. The CTT study was repeated after interventional therapy.

Multiple marker ingestion at the same time for 6 days followed by an abdominal X-ray on day 7, was used in the case-control study with fewer patients and control subjects (4), because we assumed that it would be difficult to obtain two abdominal radiographs, especially on control subjects, and to avoid unnecessary radiation. The mean value of the mean transit times of different boluses of ingested markers is measured by this technique. The number of markers on the film is the segmental or total transit time in hours (32). This method is analogous to a bolus ingestion of markers visible on successive daily abdominal X-rays, and the two techniques have been shown to correlate significantly (30).

Both methodologies used here give the CTT in hours, in contrast to a more widely used, but simplistic, method of counting the num-

ber of residual markers on the abdominal X-ray day 5 after ingestion, when at least 80% of markers have been excreted in subjects with grossly normal colonic transit and the others are constipated (35). Under the assumption of a linear excretion of 24 markers after ingestion, and using the formula developed for the present studies, the cut-off for constipation will be $(16 + 9) \times 2 = 50$ h. However, in heavily constipated patients, colonic inertia was defined as the presence of 80 % of the transit markers on the 5th day after ingestion (36). This will equate with $(22 + 20) \times 2 = 84$ h, using the present formula. The patients in the study on the origin of appendicitis underwent the colon transit study 6 weeks post-operatively (4).



Colon transit study in a 20-year-old female control. The number of markers on the film is the segmental and total transit time in hours
 CTT = $14 + 2 + 5 = 21$ h.
 Faecal load: $2 + 1 + 2 = 5$.

Colon faecal load

A plain abdominal radiograph has been used for many years in clinical practice to assess colonic faecal loading (coprostasis). However, a more exact assessment of the degree of faecal loading for scientific purposes has been exclusively described in children, when the present studies were initiated. Several systems have been developed to score both the amount of faeces and its localisation in different colon segments (37,38,39). The Leech-score has been shown to be a highly reproducible tool for assessing constipation in children with high intra- and inter-observer agreement (39,40). The Leech-score details the increasing faecal loading from 0 to 5, which was modified in the present studies from 0 to 3 with the hope to see it later used in clinical practice.

Thus, the presence of faeces (load) in each colon segment (delineated by the reversed Y) was scored as follows: 0 = no faeces visible, 1 = mild faecal loading, 2 = moderate faecal loading, and 3 = severe faecal loading. A segmental score of 0 to 3 and a total score of 0 to 9 was obtained for each radiograph (2,3,4). Faecal loading scores were also estimated for the controls. The X-ray images were examined by observers who were unaware of the clinical course of the patient.

Colon anatomy

Hirschsprung's disease with a lack of ganglia cells is well known to cause constipation, but it is less known that a long redundant colon (dolichocolon or colon elongatum) may be a significant factor in developing constipation. The concept of a redundant colon is attributed to Kantor (41), who found an incidence of 16.0% in 1,614 roentgenography patients. This anomaly was also demonstrated to occur with a clinical picture of constipation, gas distress, and abdominal pain and tenderness (16,17,41,42). When performing colectomy for colonic inertia, a majority of colon specimens have been found to be significantly redundant (43,44). The redundant parts were most often localized to the sigmoid or transverse colon or as extra loops on the left and right flexure (45).

Barium enema to visualize dolichocolon in a 56-year-old male patient.



A radiographic barium enema of the colon was used to picture the anatomy and detect morphological changes, such as inflammation, diverticula or neoplasia (2,3). Colonic redundancies were determined according to the following criteria: a sigmoid loop rising over a line between the iliac crests, a transverse colon below the same line, and extra loops at the hepatic and spleniflexure. A fully developed dolichocolon (elongated colon) occurs when all redundancies are present simultaneously (41,42,45).

Lower endoscopy was used only when alarm symptoms occurred, such as haematochezia or occult bleeding.

Physiological anorectal testing

Anorectal exams were performed with the patient in the left lateral position with flexed knees and hips. A 120 ml enema was given 2 hours prior to the procedure. A saline perfused polyvinyl catheter with four channels and pressure transducers was connected to a computer recording system (Medical Equipment, Jyllinge, Denmark). The fourth channel was in line with a rectal balloon at the tip of the catheter and could be insufflated with a syringe. After positioning, the catheter was left to accommodate for several minutes. The patient was then asked to push and to squeeze in order to record maximum pressures at 6, 5, 4, 3 and 2 cm from the anal verge. Subsequently, the rectoanal inhibitory reflex (RAIR) was tested by infusing saline into the balloon with a syringe. Sensation thresholds for rectal filling were measured using a steady fill rate of 30ml saline/min. The volumes that stimulated the first sensation and a modest urge to defecate were recorded, as well as the maximum tolerable volume. Finally, the patient was asked to expel the 50 ml balloon.

Ultrasonography

An abdominal ultrasound was performed on all patients, except on those who had had a previous cholecystectomy.

Clinical biochemistry

To identify possible metabolic and endocrine factors that might contribute to eventual colonic disturbances, blood samples were analysed for P-glucose, calcium, orosomuroid, C-reactive protein (CRP), cholesterol (HDL, LDL, VDL), triglycerides, coeliac antibodies, and thyroid parameters. The faeces was analyzed for occult bleeding.

INTERVENTION

The studies (1, 2) were not a priori planned for testing the efficacy of therapeutic regimens, but they were interventional for studying the aetiology of faecal retention in the colon. After completing the evaluation, the patients were treated in a step-wise fashion, beginning with daily meal planning by a dietician who recommended a diet low in fat and rich in fibre as advocated by the Danish Nutritional Council. The diet was supplemented with 10-20 g/day of ispagula HUSK (Ratje Frøskaller, Kastrup, Denmark), because a high intake accelerates transit time (46). The patients were also encouraged to engage in physical activity. In addition, the patients received



Milligan-Morgan haemorrhoidectomy for prolapsing haemorrhoids leaving open wounds in the anal canal.

an established bowel stimulatory treatment with cisapride (47,48). When cisapride was withdrawn from the market because of cardiac risks, the patient were treated with domperidone instead (49). Individual treatment continued until the patients reported relief from abdominal and/or anorectal symptoms. At that time, the patient's CTT, faecal loading, and symptoms were reassessed.

Patient satisfaction

Quality of life was defined as the patient's perception of the actual influence of the bowel disorder on daily life. Thus, a great influence meant a low quality and vice versa, which was measured on a VAS from 0 to 10, at entrance to the study and after intervention (2,3). Patient satisfaction was recorded on the same scale at the follow-up after surgery for refractory constipation (3), and rated at every follow-up after stapled haemorrhoidopexy as 4 (excellent), 3 (good), 2 (fair), or 1 (poor) (6).

SURGERY

Surgery for refractory constipation

Unlike surgery for other colonic diseases, the main objective of surgical treatment for constipation is the resolution of abdominal symptoms and defecation disorders. However, complications have to be few, because the surgical intervention is for a benign disease. Historically, the most common surgical procedure for slow transit constipation (STC) has been subtotal colectomy with an ileorectal anastomosis (IRA). Success rates based on different criteria have ranged from 33% to 100% in rather small series of patients (36,50, 51,52). A frightening post-operative sequela is uncontrolled diarrhoea (50,53). Because of this unwarranted situation, other surgeons have preferred an ileosigmoidal anastomosis (ISA) (43,54) or segmental resections, most often a left hemicolectomy (17,55,56). Another option, depending on anal physiological tests is a permanent stoma.

Consequently, we preferred the subtotal colectomy with ISA, and in a few young patients segmental resection (3). When counselling the patients, we told them that they could expect relief from abdominal pain, bloating, and distension, and would have one to four semi-liquid or soft defecations daily with ease. A certain but small risk of infectious complications and anastomotic dehiscence, which could lead to a temporary stoma, was present.

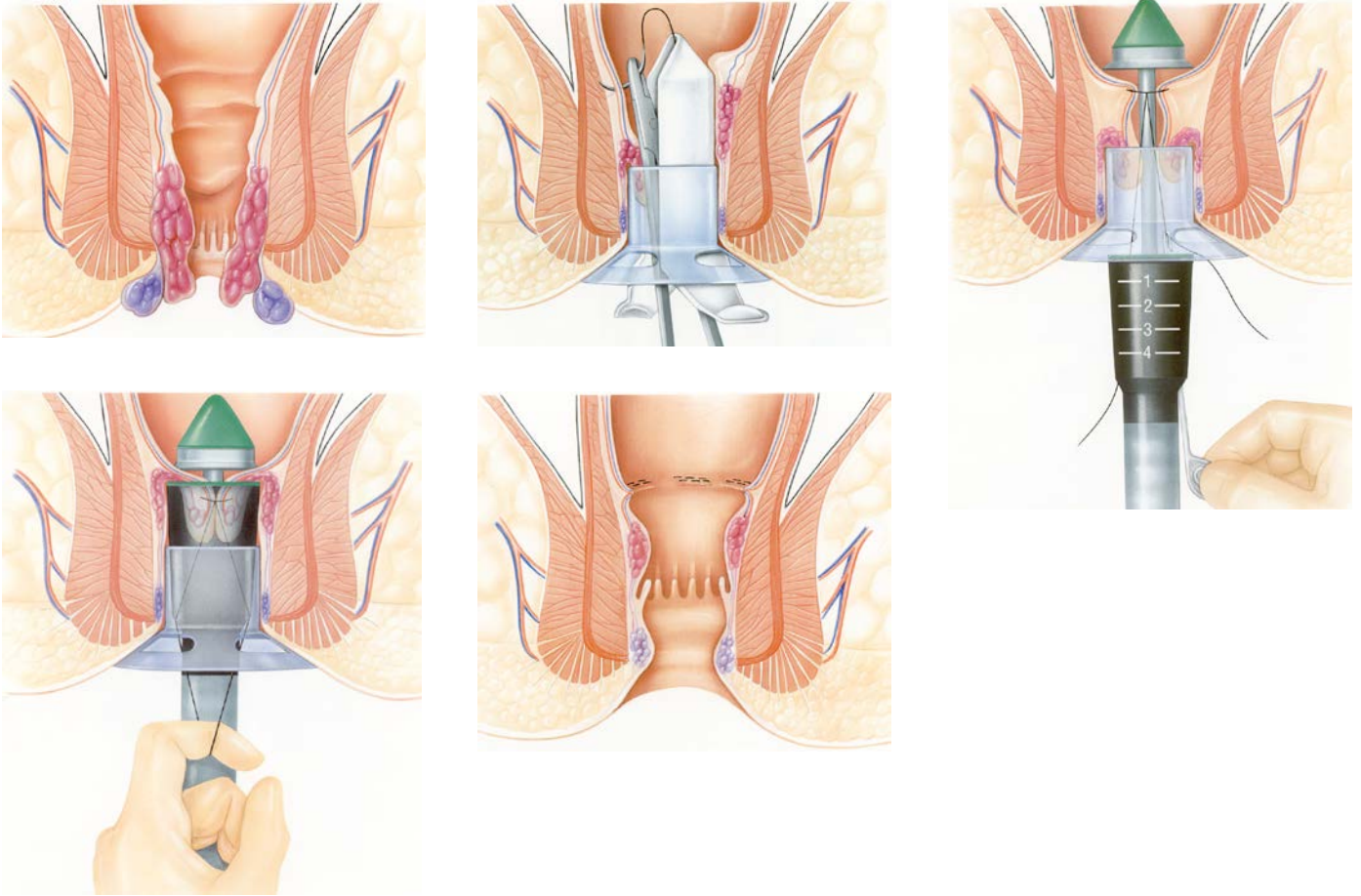
The surgical procedure began with a left paramedian incision of the abdominal wall. The terminal ileum was divided by stapling approximately 5 cm before the caecum, and the colon was divided, leaving 15-20 cm of the sigmoid. Reconstruction was achieved with a hand-sewn double-layer anastomosis using a resorbable suture. In the extended left hemicolectomies, the anastomosis was performed between the mid-transverse colon and the sigmoid at the same level. In the case of an additional rectal prolapse, the rectum was mobilized and straightened before the anastomosis was performed. The rectum was not anchored to the promontorium by stitches or meshes. Before wound closure, suction drainage was placed in the left abdominal cavity and positioned in the pouch of Douglas. In patients with pelvic floor dysfunction (PFD), an end-ileostomy was performed. The patients received a pre-operative bolus of gentamicin, metronidazole, and penicillin. Epidural analgesia and oxygen by mask (6-10 l/min for 3 days) was standard. The patients were fed enterally through a naso-duodenal tube for 3 days, which was put into place at the end of the surgical procedure. In addition, the patients were allowed to take liquids and food orally.

Appendectomy

Conventional open surgery, not laparoscopic was used (4). The surgeon recorded the degree of appendix inflammation as inflamed, gangrenous or perforated, and noted the presence or absence of a faecalith. Antibiotics were given during the operation to combat bacterial contamination (57). Postoperative complications were recorded.

Stapled haemorrhoidopexy

Haemorrhoids (piles) are a prolapse of the anal mucosa because of disruption of the supporting and anchoring tissues of the anal cushions. Classifying haemorrhoids by degree is customary: first degree, only bleeding announces their presence; second degree, spontaneously reducing prolapse at defecation; third degree, prolapse requiring manual replacement; fourth degree, permanent prolapse (58). Additional symptoms are pain, soiling, itching, and rectal dysfunction. The anal cushions are disrupted by the forces of defecation and passage of hard stools (59). A significant association between constipation and haemorrhoids has been shown (20), which is in line with the observations in the present studies (1,2).



Procedure for Prolapse and Haemorrhoids (PPH): After repositioning the prolapsed haemorrhoidal tissue, a pursestring suture is placed in the deep submucosa and knotted under the head of the stapler. The stapler is then closed, fired, and withdrawn, leaving a staple line proximal to the dentate line.

Patients with third and fourth degree haemorrhoids are generally advised to undergo surgical treatment, which traditionally meant extirpation, in this country by the Milligan-Morgan haemorrhoidectomy (60). This operation causes much pain and open wounds that heal for many weeks post-operatively. However, in 1998 A. Longo described a novel technique using a circular stapling device, presumably with less pain and quicker recovery (61). A year later, I performed the first case (5,6).

An enema was given prior to the operation; patients were positioned in the lithotomy and light Trendelenburg positions and given spinal, general, or local analgesia. The prolapsed haemorrhoidal tissue was initially repositioned using two curved anal specula to withhold the anal sphincter. More recently, a circular anoscope was used as part of a special PPH kit (Procedure Prolapsed Haemorrhoids, Ethicon Endo-Surgery, Inc., Cincinnati, Ohio, US). After stretching the anorectal mucosa with forceps, a monocryl 2-0 pursestring suture was placed in the deep submucosa, approximately 3 cm above the dentate line, starting at the 8 o'clock position and taking the suture anoscope in and out clockwise for each stitch. A lubricated, fully open circular stapling instrument was then introduced into the rectum, after which the purse string suture was knotted tightly under

the head of the stapler. As with the anal specula, the circular anoscope was withdrawn from its position when the stapler had passed the sphincter. After final closure, the stapling gun was fired and compressed for 2 min. In females, the posterior wall of the vagina was checked immediately before firing the stapler. The stapler was then opened and rotated free and withdrawn, and the ring-shaped doughnut was inspected. The stapler was the EEA (Tyco Healthcare, New Haven, Connecticut, US) in 12.7% of patients, and the HCS 33 and PPH01 (Ethicon Endo-Surgery, Inc., Cincinnati, Ohio, US), in 87.3% of patients. The staple line was inspected for continuity and bleeding after completing the stapling, using only the suture anoscope in an anterior, posterior, and lateral position of the anus. Electrocoagulation and haemostatic sutures were used as needed. The external components were removed when necessary to plane the anus. The location of the staple line proximal to the dentate line was recorded in centimetres, along with the surgical anatomy score obtained after the PPH (Fig. 2 (5), Fig. 1A-B (6)). All technical difficulties were noted. Finally, a cylindrical haemostatic sponge (Spongostan, Ferrosan, Copenhagen, Denmark) was placed relative to the staple line, and the total operation time was recorded. Antibiotics were only administered in cases of severe contamination.

A recurrent or persistent and symmetric prolapse is most suitable for a second PPH. Thus, the initial surgical steps are the same, but with placement of the purse string suture below the previous staple line which is visible as a white circular fibrous line included in the resected tissue. The mean position of the new staple line was then 1.5 cm proximal to the dentate line, significantly lower than the staple line at the first PPH. As with the first PPH, the purse string suture was placed deep in the submucosa for better fibrous healing and anchoring. We inform a patient with massive grade IV haemorrhoids that we may anticipate having to perform PPH twice at an interval of 6 months. In a few cases, we have re-stapled a patient immediately after completing the first PPH with no complications and good results.

Postoperative analgesia began with 50 mg intravenous diclofenac and continued with 400 mg ibuprofen three times daily together with 1g paracetamol four times daily for a week. The patients were discharged from the hospital the same day as the procedure and asked to return if problems occurred. Patients were not prescribed laxatives. The patients were instructed to avoid straining during defecation and to follow a fluid-rich and fibre-rich diet. The patients returned a self-reported VAS scorecard for pain (using a 1-10 scale, with 10 being the most severe pain) to determine a daily average and peak pain for 14 post-operative days. Patients also recorded their general condition, i.e. whether they felt sick or normal, and their return to normal activities, including work.

Histology

All removed specimens (appendix, colon, or haemorrhoidal tissue) were examined macro- and microscopically.

STATISTICAL ANALYSIS

All data were compiled in a separate database for each study (1,2,3,4,6), prepared in cooperation with Uni-C, the Danish IT Centre for Research and Education (statistician Jesper Lund), who carried out the statistical analyses. The frequencies of symptoms, physical signs, and investigations were defined as the percentage of all patients with symptoms, who responded affirmatively. A Mann-Whitney U-test was used to compare CTT and faecal loadings between patients and controls (2,3,4). A p-value ≤ 0.05 was considered significant. Correlations between CTT and faecal loading scores and between the abdominal and anal symptoms were measured using Spearman's rho (r). Important symptoms, signs, and investigations were also cross-tabulated. In the study of faecal retention associated with acute appendicitis, analyses were carried out for correlations between pre-operative faecal load and the presence of a faecalith and the status of the appendix (4). Multiple statistical testing could imply a risk of mass significance. However, the present studies tested specific hypotheses or explored possible coexistence. The statistical tests were performed with different variables and were not multiple comparisons of overlapping groups. In order to further minimize the risk, the actual p-values have been provided for all tests performed, and the results are interpreted with caution in cases when it is close to the chosen level of significance.

Principal component analysis (factor or cluster analysis) was used to explore correlations. Although factor analysis is not primarily designed for binary variables, it can be used in this context. The method analyses the pattern of correlation coefficients between the variables and combines groups of highly correlated variables into a smaller number of new independent (uncorrelated) variables (factors) that explain a major portion of the variation (62,63). Thus, the correlation of a variable (symptom, sign, or investigation) with an individual factor is expressed as a factor loading or correlation coefficient, with a value between -1 and +1; the greater the numeric correlation, the greater the association with the factor. A factor loading less than 0.3 was considered insignificant. Factor analysis can at best indicate if certain symptoms and signs (abdominal and rectoanal) correlate in a way that shows that they belong to the same underlying disease dimension. In general, the numbers of patients for follow-up declined in the studies (1,2,3,6), mainly because they did not attend the scheduled investigations, did not want to adhere to the prescribed diet or to take medication, or they moved away; this has been seen regularly in other clinical studies (64).

After intervention, the changes in major abdominal and defaecatory symptoms were compared using the McNemar test. The proportional decline in colonic markers was determined between 48 h and 96 h in order to estimate the marker elimination rate (2). The elimination rates were then related to the efficiency of the treatment intervention. The elimination rate was calculated for each patient as follows:

$$\text{Elimination rate} = (n_{48} - n_{96})/n_{48}$$

where n_{48} and n_{96} were the numbers of markers detected on the X-ray film taken at 48 h and 96 h after ingestion, respectively. The elimination rate was correlated with abdominal and anorectal symptoms.

The influence of the removal of a part of the colon was studied (3) using the following equations:

Subtotal colectomy (with ISA): $\text{CTT total} - (\text{CTT right} + \text{CTT left})$

Left hemicolectomy: $\text{CTT total} - \text{CTT left}$

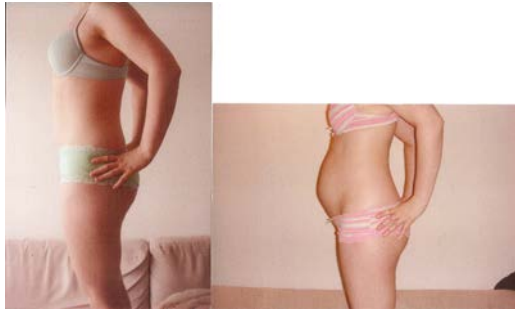
Right hemicolectomy: $\text{CTT total} - \text{CTT right}$

These adjusted CTT values were tested for a null hypothesis of not differing from the values for the control group or from values for the group of patients receiving conservative treatment. Faecal loading scores were adjusted and tested simultaneously.

Differences between pain-scores and VAS anatomy scores for the anus after stapled haemorrhoidopexy at follow-up were tested using non-parametric tests (6). A Kaplan-Meier plot was used to show the cumulative risk of a re-operation. A statistical model explored the predictability of the outcome after stapled haemorrhoidopexy (6). Patient satisfaction scores were analysed by a Wilcoxon signed rank test (2,3,6).

If needed in a present context, the data from the databases was further analysed (ad hoc data).

Abdominal bloating and distension in a 32-year-old female (with permission).



CONSTIPATION DISORDERS

SYMPTOMS AND PHYSICAL SIGNS

The definition of constipation has varied over time. A symptom is a subjective experience and not a sign i.e. a measurable observation (65). Aspects of constipation include hardness of the stool, difficulty of evacuation, and reduced frequency. Patients will often also complain of abdominal pain, bloating, distension and fullness. Bloating is the sensation of increased abdominal pressure, whereas distension is an actual change in abdominal circumference (girth). During the last few decades, a definition that encompasses a broad range of complaints has been attempted, ending up with the so-called Rome I, II and III criteria (66,67). The criteria include two or more of the following 25% of the time for at least 12 weeks in the preceding 12 months: a) straining, b) lumpy hard stools, c) incomplete evacuation, d) blocking sensation, and e) fewer than three defecations per week. Abdominal symptoms, such as pain and bloating, are not included in these criteria, which is in contradiction to other reports (65,68) and a constipation scoring system (69) that includes abdominal pain in the evaluation of patients with the most severe type of constipation, slow transit constipation, in which both abdominal pain and bloating occur (70,71,72). Systematic reviews have concluded that no single definition of constipation can be considered as a gold standard (12,13,73).

The diagnostic criteria for irritable bowel syndrome (IBS) are abdominal pain or discomfort (pressure) at least three days per month in the last three months with symptom onset at least six months prior to diagnosis and associated with two or more of the following: a) improvement with defecation, b) change in frequency of stool, c) change in form (appearance) of stool. IBS has been further subtyped into IBS with predominant constipation (IBS-C), diarrhoea (IBS-D), mixed (IBS-M) or alternating (IBS-A) (67). However, the Rome criteria are infrequently used in primary care (74), where more pragmatic definitions are used instead (75). Recently, IBS was defined as abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least three months (76). Also, the differentiation between functional constipation and IBS-C has been suggested to be artificial (77).

The aim of the present studies was to investigate consecutive patients with a broad spectrum of both abdominal and defaecatory symptoms and to analyse the data without an a priori assumption of grouping (1,2). An affirmative answer of yes to the presence of a

symptom meant that the symptom occurred with a high frequency and was disabling in daily life. Patient answers could be, for example, yes to solid faeces and yes to liquid faeces, meaning that it was sometimes solid, sometimes liquid, or sometimes mixed.

The two studies of patients with gastrointestinal and defecation disorders differed in that in the cohort in the first (1) was 63% females, compared to 86% females in the the second (2), but the cohorts had similar mean ages, (females 49.9 yr vs 50.4 yr; males 51.7 yr v. 52.0 yr). In the first study, female patients experienced bloating and abdominal tenderness significantly more often than males (1). In the second study, key-symptoms, such as abdominal pain and bloating, occurred significantly more often compared to the first study, as well as defaecatory symptoms such as difficult and incomplete evacuation for years, halitosis, and feverish attacks. It all points to a more heavily burdened population of patients in the second study. A similar complex of symptoms was recently reported in patients with functional constipation and IBS-C (78). It was shown previously in a Danish study that abdominal symptoms occur frequently and recurrently in the general population. Thus, a combination of abdominal pain and distension and, additionally, either borborygmi or altered stool consistency occurred with a prevalence of 7.5 % among women and 3.2 % among men (79). With regard to the presence of physical signs, meteorism and left iliac fossa tenderness were more frequently found in the second study, whereas a right fossa palpable mass (faeces) with tenderness and a mass in the left fossa occurred with equally high frequency in the two studies. The presence of a faecal mass in the right fossa significantly correlated with tenderness ($r = 0.508$, $p = 0.000$, $n = 260$) and infrequent defecations for years, and with a mass in the left fossa and fever episodes (ad hoc data). A palpable and tender colon was early recognized in patients with constipation (41,80) and inheres the right fossa squelsh sign (81), which is rarely found in other disorders. Recently, patients with functional constipation reported pain in the right hypochondrium, while IBS-patients and patients with functional abdominal pain syndrome reported the right flank as predominant pain site (82).

In retrospect, one must conclude that constipation is as old as human civilisation. In ancient Egypt, faeces was thought to be harmful to the body, giving rise to pain and illness, which is why regular cleaning of the bowel with laxatives was advocated (83). This compelling intuition that disease is a process of putrefaction initiated by the content of the colon shaped medical theory for more than three millennia. From the late 1700s onward, European and American physicians were convinced that constipation was becoming even more common because of changes in diet, exercise levels, and the pace of life associated with urbanisation (84). When the modern germ theory of disease was put forth during the last quarter of the 19th century, a new theory of intestinal stasis and autointoxication was formulated (80,85,86). Self-poisoning from one's own retained wastes was to occur from bacterial toxins absorbed from a bowel with stasis. However, there was a little proof of bacterial toxin production and the theory was discredited although the absence of any demonstrable or unidentified toxin absorbed from the bowel does not exclude autointoxication (87). Non-specific symptoms attributed to autoin-

toxication in constipated persons include lassitude, headache, and feeling sick with short flue-like episodes (80,85). Such non-gastrointestinal symptoms were shown to co-exist in patients with IBS (88). In the present studies, 10 % (1) and 49 % (2) of the patients experienced flue-like episodes, which is in concordance with the second study encompassing patients with the worst constipation. The co-existence of specific and non-specific constipation symptoms was also revealed by the cluster analysis (1,2), which at its best indicates whether certain symptoms and signs group together more than expected by chance, suggesting that they belong to the same underlying disease dimension. Here, the fever episodes co-existed (in symptom factors) with abdominal pain and meteorism (factor F, Table 4 (1)), and these together with a right iliac fossa palpable mass and tenderness (factor D, Table 4, (1)). The fever episodes co-existed also with seldom, difficult, and incomplete defecation (factor D, Table 4 (1)), as well as with epigastric discomfort and halitosis with faecal odour (factor V, Table 2 (2)). Bad breath (halitosis) is mostly caused by the endogenously produced intestinal gas, which contains bad smelling sulphur compounds. When the partial pressure of any intestinal gas component is higher than its partial pressure in the blood, it enters the blood stream by diffusion and is later expired via the lungs. The later prokinetic intervention significantly reduced the feverish episodes from 10 % to 1 % (1) and from 49 % to 13 % (2) (ad hoc data). Halitosis, reported previously in patients with IBS (88) was actually reduced from 30 % to 6 % (2).

Recent studies revealed significant changes in the composition of the faecal microflora among constipated patients. Suppression of the major species of the obligate microflora was paralleled by an increased pool of potentially pathogenic microorganisms, including *Escherichia coli*, *Staphylococcus aureus*, and enterobacteria (89). The changes were most pronounced among those who were most severely constipated with the slowest colonic transit, and the concentrations of *E. coli* and *Candida* were increased by 10 to 100-folds in more than half of the patients. After treatment with bisacodyl, increased counts of obligate microflora (*Bifidobacteria*, *Bacteroides*, *Streptococcus faecalis*) and decreased counts of potentially pathogenic microorganisms (*E. coli*, fungi) were observed. Following the discontinuation of therapy, prior abnormalities returned, suggesting that the changes in the microflora are secondary to constipation. Antigens and toxins derived from microorganisms constantly interact with the mucosal immune system of the large bowel to induce a state of "controlled physiological inflammation". Immune activation is detected in constipated patients by elevated levels of CD 3+, CD 4+, CD 8+, and CD 25+ T-cells and by spontaneous proliferation of lymphocytes. T-cell activation, elevated levels of antibacterial antibodies, and a tendency towards elevated concentration of IgG, IgM, and circulating immune complexes, provide evidence of the stimulation of systemic cellular and humoral immunity in chronic constipation (89). Thus, delayed transit through the colon promotes changes in the colonic flora, leading to an accumulation of bacterial antigenic products in the large bowel that, either through direct interactions with the gut-associated lymphoid tissue or following translocation across the gut wall induces hyperactivation of the immune system

(89). An increased density of inflammatory cells has been documented in biopsies from the proximal colon of constipated patients with IBS (89,90). The ongoing interaction between lumenally derived bacterial antigen and the mucosal immune system in patients with chronic constipation, results in not only the stimulation of the immune system, but also its suppression, as manifested by the depletion of T- and B-cell pools and the suppression of phagocytosis and elements of humoral immunity (89). Bisacodyl therapy leads to a normalisation of the major parameters of cellular and systemic immunity. Thus, accumulating evidence shows that the gut microbiota influences the sensory, motor and immune system of the gut and interact with higher brain centers (91).

Although gut microbes are confined predominantly to the colon, they have been shown to expand proximally into the small intestine. The prevalence of bacterial overgrowth in the small intestine, as demonstrated by the lactulose hydrogen breath test, was 34.5% in IBS patients (92), and as high as 54 % (93). Also, mildly increased bacterial counts were more common in patients with IBS than controls (94). Some patients with IBS have an increased number of inflammatory cells in the colonic and ileal mucosa (95). A potential role for bacterial overgrowth has been suggested in some patients with IBS, who obtained amelioration of bloating and flatulence following curative treatment with a poorly absorbed antibiotic (96). Other risk factors for the development of bacterial overgrowth include disorders of the immune system, Crohn's disease (with fistulae), and medication, such as proton pump inhibitors. However, new studies do not support an important role for bacterial overgrowth in IBS (93,97). Bacterial overgrowth was also demonstrated in healthy controls, though to a lesser degree. In the present studies (1,2,3,4), permanent faecal reservoirs were shown in controls and found to be significantly heavier in patients with or without prolonged CTT. Faecal bacteria likely have the opportunity to move proximal into the ileum, despite the ileo-cecal valve. Thus, the overall interpretation of available data, including the present studies, suggests that constipation and IBS may cause disabling extra-colonic symptoms in a relatively large proportion of patients (98).

DEFECATION

The defaecatory mechanism is complex and not fully understood. The emptying process is, in many ways, similar to emptying the bladder, which is mostly an automatic function of short duration. Movements of the colorectal contents during defecation can be assessed by colorectal scintigraphy after the oral ingestion of isotopes (99). In healthy young volunteers, median colorectal emptying was shown to be 99 % of the rectosigmoid with no differences between the sexes. The antegrade colorectal transport, as a median percent of activity during defecation, was 11 % from the ascending colon, 46 % from the transverse colon, 53 % from the descending colon and 99 % from the rectosigmoid. Retrograde transport was mainly from the transverse and descending colon with large inter- and intra-individual variations. If the volunteers rated their defecation as small, antegrade and retrograde colorectal transport was significantly diminished. These findings could be parallel in

patients with constipation, for which a similar study does not seem to have been conducted. Colorectal transport is not a continuous process as it mainly occurs during the colonic mass movements generated a few times each day and often initiating defecation (100,101). Physiologists state that the rectum remains empty until the act of defecation is about to occur, and then it acts more as a pathway (102). However, in a radiographic study of 18 volunteers, all but one had faeces in the rectum with no urge to defecate (102). They also found that the colon from the splenic flexure downwards was evacuated in some subjects, whereas even the rectum was not completely emptied in other subjects. Along these lines, a reservoir of faeces was found in 62 % (1) and 41 % (2) of our patients, independent of age or sex. Faeces in the rectum occurred with bloating in 62 % of patients, and faeces, bloating and an abdominal mass co-existed in 50 % of the patients ($p = 0.071$) (1).

In the first study, faeces in the rectum was loaded negatively in a factor with meteorism and abdominal pain (factor F, Table 4 (1)), whereas in the second study solid faeces was loaded significantly in one factor with bloating, proctalgia, and infrequent defecation (factor I, Table 2 (2)), and in another factor with infrequent, but also incomplete, repetitive, liquid and easy defecations (factor II, Table 2 (2)), and finally was solid faeces loaded with bloating and variable defecation frequency (factor III, Table 2 (2)). These figures demonstrate again that the patients in the second study had more severe constipation symptoms compared to the patients in the first study. Also, in many patients, and probably normal persons as well, the rectum may serve more as a permanent reservoir for faeces than a temporary reservoir before defecation. The median number of bowel movements a week was seven for both sexes in a population-based investigation (103).

Other studies have shown an increased risk of faecal impaction in individuals with constipation (104). Thus, rectal constipation may also be responsible for proctalgia, as it was significantly loaded in the same factor with bloating, infrequent and difficult defecation for years, soiling and bleeding (factor I, Table 2, (2)). This conclusion seems to be further confirmed by the fact that proctalgia was significantly reduced after a prokinetic intervention in both study populations (1,2). Thus, the severe pain attacks in the anorectal region, called proctalgia fugax (105), and described by patients as being stabbed suddenly with a spear in the rectum, may be explained by an unconscious forceful emptying manoeuvre of a fully loaded rectum against closed anal sphincters. The prevalence of proctalgia was found to be as high as 6.5 % in a recent population-based study (106).

Grade II haemorrhoids or higher were found in every second patient and significantly more often in the oldest patients, but without any sex difference (1,2). In the earlier mentioned symptom factor with infrequent and difficult defecation (factor I, Table 2 (2)), the simultaneous occurrence of bleeding indicated the presence of haemorrhoids. Other studies have shown a significant association between constipation and haemorrhoids (20,104,107,108), whereas older studies have shown the opposite (109). Additional studies have documented an association between haemorrhoids and constipation

symptoms, such as straining (21). The relationship between constipation and haemorrhoids has been indirectly demonstrated in intervention studies, in which dietary modifications and laxatives to minimize constipation were associated with the prevention of recurrent symptomatic haemorrhoids (110). Chronic straining and the passage of hard stools is still primarily thought to result in the degeneration of the supportive tissue of the anal canal, as well as a distal displacement of the anal cushions, thus leading to the development of haemorrhoids (19,59).

TRANSIT TIME, FAECAL LOAD, AND HIDDEN CONSTIPATION IN THE COLON

The content of a meal takes 2-4 h to pass from the pylorus to the ileocolonic junction (ca. 500 cm) and 12-72 h to transit 100-150 cm of colon (111). A main objective of the present studies was to measure CTT and assess faecal load in the colon to correlate these parameters with patient symptoms. In clinical practice, the CTT is exclusively used to evaluate patients with severe constipation for surgery and seldom applied to patients with functional bowel diseases. A screening method is used when evaluating patients for surgery, in which the number of residual markers is counted on the abdominal X-ray 5 days after ingestion. Thus, colonic inertia is defined as the presence of 80 % of the transit markers (36). This will equate 84 h using the formula developed for the present studies with the assumption of linear excretion of the markers. In subjects with grossly normal CTT, 80 % of the markers have been excreted at that time (35,51,112), equating a CTT of 50 h with the present formula.

Faecal load does not seem to have been previously estimated in this context, but was very recently brought to attention in the evaluation of childhood constipation (113). The present marker study showed that the mean CTT is significantly longer in patients (40.71 h) compared to controls (24.75 h), and that female patients and controls tend to have longer CTTs than males, though the difference was not significant (2). Others have shown this CTT difference between males and females for control subjects and IBS patients in larger sample sizes (111,114,115). When grouping patients according to the Rome criteria, patients with functional constipation had a mean total CTT of 52.2 h, which was not significantly different from the 41.2 h in patients with IBS-C (78).

The method of ingesting radioopaque markers for 6 days and obtaining an X-ray on the seventh day corresponds to the mean of six CTT measurements using the daily films methods (116). However, the calculations performed here may have some limitations that have to be taken into account: a) after a bolus ingestion the markers were not followed by daily X-rays until all had been expelled, b) a limited number of marker ingestions (six) was used, thus the steady state assumption may not be fulfilled at the time of X-ray (seventh day), c) the formula (equation) is only strictly applicable to a continuous ingestion of markers, but the markers were actually ingested in an bolus once a day (116) and d) omission of marker ingestion from non-compliance (117). Thus, the CTT may have been underestimated in control subjects and patients, especially when transit was delayed.



Colon transit study after the ingestion of 24 markers by a 45-year-old female patient.

Left X-ray at 48 h: $0 + 3 + 8 = 11$ markers, faecal load: $3 + 3 + 2 = 8$
 Right X-ray at 96 h: $0 + 0 + 0 = 0$ markers, faecal load: $3 + 3 + 3 = 9$.
 CTT = 22 h (normal), but with heavy faecal load: *Hidden constipation*.

In addition, the obtained measurements are actually mouth-to-anus time unless the markers are delivered directly to the ileum or caecum, but it does not disqualify the CTT measurements from being used for comparisons in the present studies (2,3,4) or comparisons with the work of other researchers within this field. The present technique also relied on the reversed Y-design on the abdominal radiograph, which was used to picture the right, left and distal colonic segments for counting the markers. This approach may not take into account the origin of a redundant colon loop, which may be localized elsewhere.

The faecal loading scores did not differ significantly between females and males in the control group. The patients' loading scores were significantly greater than those of the controls in all colonic segments and were unchanged between 48 h and 96 h, depicting a permanent condition and emphasizing the importance of taking two radiographs. Overall, the CTT was positively correlated with the segmental and total faecal loading scores at 48 h and 96 h. This is in accordance with a new study evaluating plain abdominal radiographs in bowel dysfunction, where significant correlations were found between CTT and Leech scores (118).

Defining a normal CTT is rather difficult. The mean CTT was 24.75 h (range 0-71 h) for control subjects in this study (2,4), which is similar to those reported in other studies for healthy people from developed countries (34,111,115,119,120,121), though more prolonged transit times have also been reported (111,116). The CTT will definitely vary with the population being investigated, the dietary and fluid intake, physical activity and study methodology. The control group in our studies was comprised of equal numbers of women and men to reflect a normal CTT and estimate a normal faecal load simultaneously. Yet, great variations were observed, indicating broad biological variability. Analyses within the control group found that CTT significantly and negatively correlates with age ($r = -0.340$, p

$= 0.024$, ad hoc data), and a significant decrease in distal faecal load was found across the age groups as well ($p = 0.016$, Jonckheere-Terpstra test, ad hoc data). The mean CTT was 36.4 h for persons 20–29 yr, compared to 13.5 h for persons 50–66 yr ($p = 0.013$, Mann-Whitney test). Although the mean CTT of control persons, who were without symptoms was 24.75 h, the CTT was found to be as high as 71 h, but no significant differences were found between the CTTs of the individual colon segments ($p > 0.05$, Wilcoxon signed ranks test, ad hoc data). Notably, the CTT measured by sitz or plastic marker studies in normal or control subjects has decreased gradually over the last three decades from 59 h to 25 h (111), which is also the niveau for the present studies (2). With regard to adults and children, the overall mean transit time did not differ significantly in the large bowel (111,122).

A special phenomenon was detected when analysing a subgroup of patients ($n = 90$) with a normal mean CTT of 24.75 h or less. These patients had significantly increased faecal loading scores (total: mean 4.9) compared to the controls (total: mean 4.4), which then seems to be the level of loadings to cause symptoms. The colon was equally loaded with faeces with a normal or prolonged transit time (Fig. 2A, B (2)), Obviously, a mismatch exists between the transport of markers and the propulsion of faeces at this lower level of CTT, indicating that the markers and faeces do not always travel at the same rate, which was not assumed previously (29). The condition may be due to the mechanism behind paradoxical diarrhoea. This type of faecal retention with a normal CTT and heavy faecal load of the colon is called *hidden constipation*. The patients had higher mean faecal loading scores than the controls in all colonic segments at 48 h and 96 h. Separate analyses showed that the right mean faecal loading of all patients (2) was significantly higher compared to the left and distal colonic segments (right: 2.3 vs left: 2.1 and distal: 1.8, $p < 0.001$, Wilcoxon signed ranks test, ad hoc data) and this was

similar for the right CTT. Notably, within the control group of healthy persons, the right-sided mean faecal loading was significantly greater than the left and distal loading (right: 1.8 vs left: 1.3 and distal: 1.3, $p < 0.001$, Wilcoxon signed ranks test, ad hoc data). It is concluded that the faecal reservoirs are frequently normal in Western countries, predominantly in the right colon, but far from biologically ideal.

The value of a plain abdominal radiograph has been evaluated in childhood constipation. As described earlier, the Barr (37), the Blethyn (38), and the Leech (39) scoring systems for the amount and localisation of faeces have been found to be reliable. The Leech score was chosen here and shown again to have the highest reproducibility with high intra- and inter-observer agreement (40, 118). However, others have found the Leech score to be of limited value in the diagnosis of constipation in children because of intra- and inter-observer variability and low diagnostic accuracy (123,124). A new study, which was far from being clear in design, concluded that the use of the Barr and Blethyn radiological scoring systems did not accurately discriminate between children with constipation and those without (113). This same study revealed that both scores expressing faecal load were significantly higher for constipated radiographs and correlated with CTT, which is in line with the present studies (2,3), with the exception of the subgroup of 90 patients with a CTT equal to or lower than the CTT of the control group. The objective assessment of faecal load using an abdominal radiograph has only scarcely been reported in adults. Various scoring procedures were recently compared (125). A five point scale similar to the present four-point scale was shown to correlate with the Barr scale for intra- and inter-rater variability and to provide a valid diagnosis of faecal loading. In addition, most authors stress the importance of experience in the radiologist's interpretation of a radiograph, as was the case in the present studies in which they were also unaware of the patients' clinical course.

Other researchers previously found that paediatric faecal loading scores correlate only with a total CTT exceeding 100 h (126), but if normal or moderately delayed the CTT poorly correlates with the faecal score, which they interpreted as an overestimation of faecal retention. It was found in a review of chronic constipation that a plain abdominal X-ray was a poor predictor of colonic transit time (24). In the present studies, we observed high faecal load with a low CTT, which was interpreted as being a new phenomenon, not disqualifying the estimation of faecal load, but proving faecal retention as *hidden constipation*. This mismatch between CTT and faecal load could not be explained easily. The explanation may be found in a difference in the density of accumulated faeces, which may not be observed on the radiograph. Scintigraphic measurements may help explain the retention of faeces and faster marker transit. This transit seems to reflect intermittent propulsive and retropropulsive activities in the colon and mass movement by a wave of contractions. Although there is a good correlation between colonic transit measured using plastic markers or a scintigraphic method (127), plastic markers have a faster transit time than by scintigraphy (111). Because the radioisotope technique is more reliable, it has been suggested as the gold

standard, instead of using radio-opaque markers (111). Very recently, a new wireless pH and pressure recording capsule (SmartPill) was used to measure colonic transit without radiation; it correlated well with the radio-opaque marker technique (128).

COLON ELONGATUM OR DOLICHOCOLON

In three studies (1,2,3), the patients were examined by a barium enema to see the anatomic outline of the colon, especially with regard to the number of redundancies, but also to identify eventual pathology. A redundant sigmoid was present in 72.5 % of all patients (2), to the splenic flexure in 26.6 %, to the transverse colon in 33.9 %, and to the right hepatic flexure in 18.6 %. In an old review of the dolichocolon, redundancies were overwhelmingly located to the left side (14). In addition, a lengthened colon was observed in infants. The prevalence of dolichocolon in the population is not known, because healthy people have not been investigated for that purpose, not even in the present setting. Earlier it was assumed that 3.5 % to 8 % of people would have a redundant colon (17). In another study, 16 % of 1,614 roentgenography patients had a redundant colon (54 % females) and the majority had constipation, which was usually dated from birth (41). Accordingly, the incidence of a redundant colon was 30 % in patients with constipation compared to 2 % in controls, suggesting a causal connection between this anomaly and constipation (16). One study has shown that differences in colon length are population based. Thus, the entire colon is longer among Africans compared to Whites and Indians and with the sigmoid colon being significant more redundant (129). In a comparative study of colonoscopic and barium enema examinations of polypi, the proportional distribution of redundancies was the same as found in the present studies (51 % sigmoid, 14 % splenic flexure, 4 % transverse colon, and 19 % hepatic flexure) (130). In the present studies, the mean CTT was 36.26 h in patients without redundancies, 43.80 h in patients with one redundancy, 41.65 h in patients with two redundancies, and 52.27 h in patients with three to four redundancies, with a significant difference between the four levels of redundancies. These findings are in line with an earlier study suggesting that the transit is largely proportional to the length and volume of a colon segment (119). The presence of a redundant sigmoid positively correlated with CTT and right sided faecal loading ($r = 0.131$, $p = 0.047$). Similarly, faecal loading at 96 h correlated with a redundant splenic flexure ($r = 0.145$, $p = 0.048$), and the number of redundancies correlated with both distal faecal loading at 48 h ($r = 0.154$, $p = 0.019$) and total loading ($r = 0.138$, $p = 0.035$ - all ad hoc data). An increased number of redundancies resulted in significantly more bloating and abdominal pain. These kinds of studies have been lacking (24,131) and are, to the best of my knowledge, the first to demonstrate that anatomical variations in colon length are of great importance in constipation, because CTT and faecal load increase with increasing colon length. After completion of the present studies, an experimental study in mice (132) and a clinical study in children (133) have shown the importance of colon elongation in slow transit constipation (STC). Older studies have identified a specific triade of constipation, bloating and painful abdominal crises to be attributed

to a redundant colon together with a variety of general symptoms as headache, fatigue, halitosis and feeling sick (14,17,42). This importance is highlighted by studies showing that the majority of colons in patients who undergo subtotal colectomy for slow transit constipation are significantly redundant (3,43,44,134).

SYMPTOMS, PHYSICAL SIGNS, COLON TRANSIT TIME, AND FAECAL LOAD

To the best of my knowledge, these clinical studies appear to be the first to simultaneously correlate bowel symptoms with CTT and faecal load (2,3). The studies demonstrated that abdominal symptoms and defaecatory disorders in patients significantly correlate with CTT and faecal loading. Abdominal pain was significantly positively correlated with distal faecal loading, and bloating significantly correlated with faecal loading in the right colon, total faecal load, and delayed CTT. New analyses showed that no significant changes occurred in CTT across the age groups ($p = 0.538$, Jonckheere-Terpstra test, ad hoc data). Also, no significant differences were found in faecal loadings across the age groups with the exception of right-sided load at 96 h, which demonstrates a significant decrease with increasing age ($p = 0.042$, Jonckheere-Terpstra test, ad hoc data). Consequently, abdominal pain negatively correlated (less pain) with increased age ($r = 0.221$, $p = 0.000$). Other studies found a delay in CTT in the right colon in IBS patients and controls with a CTT less than 70 h, whereas other patients had a delay in the left colon or rectosigmoid, or some patients were characterized by the absence of markers on the plain film (115). When comparing symptoms and colorectal transit, these researchers found no significance in the symptomatology between these groups. Other studies relating gastrointestinal symptoms to colon transit have found transit anomalies in patients with predominant nausea, vomiting, constipation, diarrhoea, and abdominal pain (135).

Patients with functional constipation had a significantly slower rectosigmoid transit time compared to IBS-C patients (78). Abdominal bloating has been found to be the overall most common symptom in constipation (82 %) irrespective of normal or prolonged transit time (136), as well as in IBS and being associated with a decreased energy level (137). Bloating has been associated with both accelerated and delayed colonic transit, but this was not easily explained (138). In the study looking at abdominal bloating and constipation, 35 % of the patients had no detectable disturbance of their anorectal or colonic function but complained of constipation (136). Instead of implying that no abnormality existed in colonic or anorectal function, the researchers found it more likely that the methods were too crude to detect clinically relevant disturbances. Several authors have stated that the investigation of patients with normal transit is inappropriate (115,135,136). As demonstrated in the present study (2), additional information may be provided by assessing a faecal score in combination with CTT. Thus, a stratified subgroup of 90 patients with a CTT ≤ 24.75 h (mean of control subjects) had a significant increase in faecal loading scores, with the exception of the distal colon segment, compared to the controls, which explains why patients with a normal CTT may have abdominal symptoms, such as

bloating, and defaecatory disorders. Apart from these findings, a recent study showed that symptom severity does not correlate with faecal loading, though there was a significant correlation with CTT (124).

In the present studies, factor analysis was used to indicate whether certain symptoms and clinical signs correlate in a way that shows that they belong to the same underlying disease dimension. Bloating occurred predominantly in three symptom factors, and CTT and faecal load had separate positive correlations with some of these symptom factors (2). Pain was the second dominant abdominal symptom and was significantly associated with bloating (1,2). Previous studies showed that balloon distension of different parts of the colon causes abdominal pain (139) and that the onset of pain in the right iliac fossa is associated with the arrival of residues from a test meal in the caecum (140). Follow-up studies in healthy persons revealed that the intensity of abdominal symptoms, such as pressure, bloating, and colicky and stinging sensations, linearly increase with gas infusion. The symptoms were referred higher over the abdomen during jejunal infusion of gas than during rectal infusion. Abdominal distension paralleled gas retention, irrespective of jejunal or rectal infusion (141). More recent work using plethysmography has suggested that, although an overall correlation exists between bloating and changes in girth (distension) in IBS, IBS-C patients are more likely to exhibit this correlation than IBS-D patients (142). IBS patients have been shown to have more distension and gas retention than excessive gas production (142), though some studies using plain radiography have suggested higher gas concentrations in IBS patients (143,144). IBS-C patients with delayed colonic transit exhibit greater abdominal distension than those with normal transit, and colonic transit correlates with abdominal distension (145). Intestinal gas comes from air (nitrogen, oxygen, and carbon dioxide) swallowed through the mouth and nose when eating and drinking. The endogenous source of intestinal gas is fermentation by yeast or bacteria, which produces hydrogen, carbon dioxide, methane, butyric acid, and odoriferous sulphur compounds (146). In particular, colonic gas production of hydrogen is greater in patients with IBS than in controls (147).

Abdominal bloating and distension have rather characteristic clinical features. The symptoms worsen over the course of the day with eating and some patients look pregnant, with an inability to bend or tolerate a security belt in a car. The abdomen is flat in the morning, suggesting that the gas is delivered as flatus or exhaled during sleep.

A significant increase in the occurrence of bloating and abdominal pain was seen with an increased number of colonic redundancies (colon length) and increased CTT (2,3). To date, colonic length has not been considered as a significant factor in constipation (133). However, the present findings are in line with older studies in which a redundant colon was associated with marked constipation, pain, and gas (16,17,41). Patients with an elongated colon often experience constipation disorders from childhood, indicating a congenital anomaly (variation).

With regard to the abdominal physical signs, CTT and faecal

load significantly positively correlated with a palpable mass in the left fossa and meteorism, whereas correlation with a right-sided mass was insignificant.

The transit of radio-opaque markers was shown to highly correlate with stool form in young and healthy volunteers kept on a standardized diet and physical activity. Women have been shown to have significantly harder stools, which significantly correlate with slow transit through the colon (loose stools correlate with fast transit). Stool frequency was not significantly correlated with stool form (148). Very recently, moderate correlations were found between stool form and CTT in constipated adults, but no correlation was found between stool frequency and the measured transit time. In healthy controls, no correlation was found between stool form and frequency and measured transit (149). Analysis of the defaecatory disorders in the present studies showed that CTT positively correlates with infrequent defecation and negatively with defecation ease, repetitiveness, and liquid faeces, which has been indicated also by others (135, 150). Similarly, segmental and total faecal loading were significantly correlated with these defaecatory parameters (2). These variables were also significantly loaded in separate symptom factors (factor I, Table 2 (2)). Thus, CTT and faecal load positively correlated with a factor consisting of bloating, proctalgia, and infrequent defecations of solid faeces for years, with soiling and bleeding, equivalent to a "constipation factor". On the other hand, CTT and faecal load negatively correlated with a symptom factor comprising frequent defecations with ease, repetitiveness, incompleteness with solid or liquid faeces and with soiling, equivalent to an "IBS factor" (factor II, Table 2 (2)). These patterns of CTT and symptoms, in many ways similar to the present results, were described recently but without an assessment of faecal load (115,138). The subgroup of patients with a heavy faecal load and a normal CTT showed remarkable great variations in defecation patterns. The majority had daily repetitive defecation with altering consistency, mostly with ease but with a feeling of incomplete emptying (2). In clinical practice this pattern is expressed as the so-called morning rush syndrome. It also shows that the large bowel may be overloaded with faeces in spite of daily evacuation.

INTERVENTION (AND THERAPY) FOR FAECAL RETENTION

Intervention was an essential part of the studies to prove that abdominal symptoms, physical signs, and defecation disorders are caused by faecal retention with or without prolonged colonic transit. Thus, the present studies aimed more to study the pathogenic mechanisms than to be a therapeutic trial and the patients received an established bowel stimulation treatment. First, instructions were given to adhere to a low-fat, high fibre diet (30–40 grams per day), consisting of three meals and three between-meal supplements (Danish Nutritional Council), together with an adequate intake of fluids (water, tea, coffee, etc. ca. 1.8 litres per day). Initiating the gastro-colonic response by frequent meals and drinking seems to be important, probably because of the sedentary lifestyle in Western society (151). The diet was supplemented with soluble fibre in the form of 5-10 g of psyllium (ispagula HUSK, Ratje Frøskaller, Kastrop,

Denmark), taken twice per day. The dietician pointed out how badly planned and fibreless the diet was for many of the patients. The intake of dietary fibre has been shown to shorten CTT (46,152, 153,154) and improve abdominal and defaecatory symptoms (9,46,76,152,155,156,157,158,159). The beneficial effects of soluble fibre are ascribed to their gel-forming capacity, contributing to colonic bulking with increased peristaltic activity. The underlying mechanisms have recently been demonstrated in animal in-vivo and in-vitro studies. The results suggested that psyllium husk has gut stimulatory components mediated through muscarinic or 5-HT₄ receptor activation, and that an antispasmodic effect of ispagula is mediated through blockade of Ca²⁺ channels and nitric oxide/cyclic guanosine monophosphate pathways, which may explain its dual efficiency in constipation and diarrhoea (160). Lately, rye bread significantly reduced total intestinal transit time compared with laxatives (161). Additionally, rye bread shortened transit time significantly compared to wheat bread, and increased the number and ease of defecations (161). Psyllium fibre has been shown to reduce serum cholesterol levels in hypercholesterolemia (162). In the present study (2), no significant correlations were found between CTT or faecal loading and serum cholesterol levels.

Secondly, as part of the stimulatory treatment regime, the patient was to perform physical activity relative to the individual's capabilities, leading to a long-term effect. Studies of the effect of physical activity have mostly been conducted in healthy subjects and shown an accelerated CTT for faecal residues (163,164) and intestinal gas (165). The same inverse relationship has been shown between constipation and physical activity, just as the defecation patterns of runners were more optimal (less firm stool, higher frequency, higher stool weight) than those of inactive controls (164). In a recent study, increased physical activity improved gastrointestinal symptoms in IBS (166). These beneficial reactions are in contrast to reactions to more extreme exercise conditions, under which intestinal ischemic damage may occur with a number of metabolic disturbances, increased gastrointestinal permeability, and endotoxaemia (164). The mechanical vibration of the body is more than doubled in running compared to cycling. However, the way in which the bouncing of the gut affects gastrointestinal function is unknown; it may have an initiating peristaltic effect like abdominal colonic massage. Some of our patients reported that they had to return to visit a toilet a short time after jogging had begun, indicating peristaltic movements in a colon overloaded with faeces. In addition, physical activity has a two-fold impact on the energy balance equation not only increasing energy expenditure but also modulating energy intake by increasing postprandial levels of satiety hormones (165).

Thirdly, a pharmacological adjuvant was used in the stimulatory treatment. Cisapride was available and acts throughout the length of the gastrointestinal tract. The drug stimulates gastrointestinal motor activity through an indirect mechanism involving the release of acetylcholine, mediated by postganglionic nerve endings in the myenteric plexus of the gut. This effect is most likely to result from the activation of 5-HT₄ receptors (167). Cisapride increases bowel transit in normal volunteers and constipated patients (168,169), and im-

proves symptoms significantly in patients with constipation and IBS-C (47,48). The initial dose of cisapride in the present studies was 5 mg taken 20 minutes before a main meal, with necessary adjustment according to the clinical course. The side effects of the drug are mainly headache and dizziness, which was observed in 7 % of the patients (1). However, the drug was discontinued in the United States in 2001, because of a risk of cardiac arrhythmia and fatal cases (170). The drug may potentially prolong the QT interval, but at that time only one patient had been registered for that reason in Denmark, and cisapride had been marketed since 1988. A recent review concludes that cisapride can not be justifiably used for chronic constipation or irritable bowel disease given its side effect, though it is widely available in third world countries (171).

Mid-way through the study (2) the patients were shifted to domperidone, a dopamine receptor antagonist and the only available promotility agent. The initial dose of domperidone was 10 mg 20 min before a main meal, with necessary adjustment according to the clinical course. Domperidone increases stomach and duodenal contractions and emptying and motor activity of the small intestine (172,173,174,175). Domperidone exerted a significant effect on bloating and belching in patients with non-ulcer dyspepsia (176). The effect exerted on the colon seems to be more diverse. Domperidone has been shown to have no effect on sigmoid motor activity (177), but as an antagonist it blocks the inhibitory effects of dopamine on the proximal colon in dogs (178) and may thereby facilitate movements. The suggested mechanism of increased acetylcholine release and acetylcholinesterase inhibition points in the same direction (174). In contrast to cisapride, the effect of domperidone has only been sporadically investigated in patients with colonic motility disorders. Small, controlled clinical trials of patients with IBS have demonstrated no symptom improvement, change in intestinal transit, or frequency of evacuation (172,179), except for a double-blind placebo controlled study in which 10 mg domperidone four times a day resulted in significantly reduced abdominal pain, flatulence, and abnormal bowel habits (49). Recently, it has been shown that domperidone had no additional effect on constipation in children treated with polyethylene glycol (180). Domperidone has poor penetration of the blood-brain barrier and minimal effects on the central nervous system. By inhibiting dopamine, administration may increase prolactin levels and induce gynecomastia or galactorrhea in up to 10 % of treated patients irrespective of the dose used (174). Other side effects include headache, muscle cramps, itching and skin rash, reported after rather high doses. Long-term treatment has been maintained for up to 12 years (174). However, very recently the current use of domperidone especially in high doses has been shown to be associated with sudden cardiac death (181,182). The cardiotoxicity of domperidone therapy seems related to prolongation of the QT-interval (182) (as for cisapride), occurring in older patients, just as polypharmacy seems to be involved (183).

The basic idea of the present studies (1,2) included a reinvestigation of the patients when they experienced a relief of their abdominal and defaecatory symptoms. The cumulative effect of the different parts of the prokinetic regimen can then be measured to

track the cause of symptoms, not to evaluate, for example, the specific effect of cisapride or domperidone. A symptom could have disappeared, still be present, still be absent, or have appeared. Bloating and abdominal pain were reduced significantly (1,2). Overall, the defecation process was improved with solid faeces evacuated at ease approximately once per day, with significant reductions in incompleteness and repetitiveness. As mentioned earlier, proctalgia and flue-like episodes were heavily reduced (1,2).

After a mean intervention period of 21.6 months, the mean CTT was significantly reduced from 40.71 h to 32.77 h ($p < 0.001$), which did not differ significantly from the CTT of the controls ($p = 0.075$) (2). Similarly, the faecal loading scores were reduced significantly in all segments of the colon, but they were still higher in the patients compared to the controls ($p < 0.001$). After intervention, no significant changes in CTT or faecal loading were measured in the subgroup ($n = 90$) with a CTT ≤ 24.75 h (equal to controls). Nevertheless, bloating and abdominal pain was significantly reduced in more than 50% of these patients, just as defecation was significantly easier with reduced incompleteness, repetitiveness, and liquid faeces (2). Overall, patients with faster marker elimination rates (greater slope) were significantly more likely to benefit from the intervention with cessation of bloating and pain; the elimination rate did not influence any of the defaecatory symptoms. Accordingly, the intervention significantly reduced the presence and tenderness of a palpable mass (faeces) in the right iliac fossa and the rectal constipation (1). Previously, CTT was significantly reduced after giving a laxative to constipated patients with simultaneous allivation of bloating and improved defecation. Opposite, when constipation was induced in normal subjects with loperamide there was a significant increase in CTT, bloating and rectal dissatisfaction (and pain) (184).

Quality of life was measured on a VAS as an index for the burden of symptoms on daily life. Such scales have been used by others (185,186), though more composite and detailed scores have been recommended (187,188). In concordance with the relief of symptoms, the patients' quality of life score increased significantly ($n = 272$) (2).

To summarize the effect of intervention with a combined prokinetic regimen, it verified the presence of an overload of faeces in the colon (functional faecal retention), giving rise to abdominal pain and bloating, a palpable mass in the right iliac fossa, and a variety of defaecatory symptoms. The present intervention demonstrated that the colon could be re-educated (48).

COLORECTAL MOTILITY AND DYSMOTILITY

The proof of functional faecal retention leads to the question of why faecal arrest occurs more or less in the colon and rectum. Four major types of neurons innervate the distal bowel: enteric, sympathetic, parasympathetic and extrinsic spinal sensory (189). The enteric nervous system controls most aspects of colorectal motility and consist of ganglionated plexuses lying between the longitudinal and circular muscle layers (the myenteric plexus). Different enteric neurons can be distinguished based on chemical coding such as neurotransmitters and neuropeptides. The muscular apparatus

X-rays after the ingestion of 24 markers by a 9-year-old boy (outside the present studies): Twenty-three markers are located distally at 48 h (left) and expelled at 96 h (right), demonstrating evacuatory dysfunction. CTT = 46 h.



consists of muscle cells and interstitial cells of Cajal, with the latter generally suggested as having three major functions: acting as a pacemaker cell, conducting the active propagations of electrical events, and mediating enteric neurotransmission (190). Recognized colonic motor patterns consist of non-propagating pressure waves and high-amplitude propagating sequences (189). These motor patterns are not distributed evenly throughout the colon, and the majority originate in the ascending colon and proximal transverse colon (191). In the healthy colon, antegrade propagating sequences are recorded with a three-fold higher frequency than retrograde sequences. The contractile activity has a phasic component that both moves and mixes luminal content. If the luminal content within the bowel meets no resistance downstream the smooth muscle shortens and the contents are propelled with a minimal increase in luminal pressure. Conversely, if resistance to flow is met during a phasic contraction, the smooth muscle will not shorten, but the tension of the smooth muscle will significantly increase and the intraluminal pressure will increase but not result in propulsion (189). Within the human, a mixture of smooth muscle shortening and increases in tension and pressure is usually present with resulting luminal propulsion (192). Recently, 24 h pan-colonic manometric recordings permitted the display of important colonic motor responses to physiological stimuli, such as food, defecation, sleep, and waking (193). In patients with slow transit constipation (STC) and IBS-C, the recordings showed that high-amplitude propagated contractions were significantly decreased in number and amplitude compared to normal controls. Fewer low-amplitude propagated contractions were seen in STC compared to IBS patients (194).

High-amplitude propagated contractions, responsible for colonic mass migration, have also been found to be decreased in number and duration. It has also been observed that patients with STC have often motility/transit disorders of the oesophagus, stomach, small bowel, gallbladder, and anorectum, thus lending more support to the involvement of a dysfunctional enteric nervous system (195,196). Recent evidence points to the interstitial cells of Cajal being crucial in motility disorders. Thus, the numbers were significantly decreased or absent in patients with STC, including children (197,198,199,200). In the present study (3), the removed colon was examined only by conventional microscopic examination (32 patients). Reactive changes, such as submucous fibrosis and hyperplasia of the tunica muscularis and nerves were seen in more than half of the patients, which is in agreement with a previous study (43). No absence of ganglia cells were found in the specimens. These changes seem to be a result of faecal stasis with increased intraluminal pressure. Enteric neurodegeneration also seems to occur with ageing (201).

The defaecatory mechanism involves a sequence of events that integrate smooth and striated muscle and the central, somatic, autonomic and enteric nervous systems. Faecal content is driven into the rectum by caudally migrating contractions until a threshold is reached, whereby conscious awareness of rectal filling results in an urge to defecate. Distension of the rectum results in contraction of the rectum, relaxation of the puborectalis and straightening of the anorectal angle. Relaxation of the internal anal sphincter (the recto-anal inhibitory reflex) and a combination of reflex and voluntary relaxation of the external sphincter and flattening of the anal cushions

cause faeces to be expelled. Contractions of the abdominal muscles and the diaphragm (Valsalva) assist with defecation to a variable extent. Upon the completion of defecation, the puborectalis and external sphincter temporarily contract and restore the anorectal angle, and the internal sphincter recovers its tone, which along with passive distension of the anal cushions closes the anal canal (189). In patients with constipation, the propulsive motor sequences are absent during attempted stool expulsion (189), and in constipated patients with normal colonic transit, and then presumably an evacuatory disorder, a reduction in the number and amplitude of rectal motor complexes has been found (202). Patients with an evacuatory disorder also have a significant reduction in the amplitude of propagating pressure waves throughout the entire colon (203). Additionally, specimen analysis has shown that enteric neurons are significantly decreased in patients with intractable constipation due to obstructed defecation (204).

To mimic rectal sensorimotor function, anorectal manometric measurements are used in clinical practice. In the present studies, correlation analyses between strain and squeeze pressure, volume, and CTT showed that a higher CTT, significantly correlated with greater volume at first sensation, which has also been shown by others (205). The recto-anal inhibitory reflex (RAIR) was elicited in 89.4 % of the patients (n = 142), whereas balloon expulsion was possible for 63.0 % of the patients (n = 211, ad hoc data). Rectal hyposensitivity appears to be demonstrated on the basis of elevated sensory threshold volumes, and this is, in many cases the only demonstrable abnormality in the physiological testing of patients with constipation or evacuatory disorders (203). Using a barostat, the perception of urge was found to be significantly reduced in patients with slow transit compared to IBS patients and controls (206).

However, whether sensory and motor dysfunction are primary abnormalities or acquired due to abnormal toilet behaviours and habits is not clear. Childhood constipation is a common problem worldwide with a prevalence of 0.7 % - 29.6 % (207). Transit studies with radio-opaque markers show that approximately 50 % of constipated children have delayed colonic transit (150) and the delay in transit is found distally in the majority of these children, suggesting that it may be secondary to an evacuation disorder (208). The triggering event is thought to be painful defecation and a subconscious decision to avoid repeating the act of defecation at all costs, creating a vicious cycle of withholding behaviour. Three vulnerable periods are known during which a child may develop constipation: (i) the change from breast to cow's milk or solid food may alter stool characteristics and become frightening for the infant; (ii) the time of toilet training; (iii) the start of school, when a resistance to using a toilet other than their own and not taking time to stop activities when it is time to have a bowel movement probably result in constipation (151).

Although the majority of children that exhibit stool withholding recover by the time they are adolescents, some continue this behaviour throughout adulthood. Furthermore, the call to defecate will disappear over time if it is suppressed regularly with the consequence of having a rectum permanently filled with faeces. The voluntary suppression of defecation results in the prolongation of total



Evacuatory dysfunction in a 68-year-old male patient (outside the present studies). Twenty-four markers are located distally at 96 h after the ingestion of 24 markers. CTT => 96 h.

and regional transit times, as shown by radio-opaque markers, indicating that a functional evacuatory disorder has an effect on the right colon (209). In adolescents with refractory constipation, pelvic floor dysfunction and delayed colonic transit may occur separately or in combination (210). A job situation may have marked influence on defaecatory patterns i.e. not having a toilet close when the call comes to defecate, such as being a busdriver or checkout assistant in a supermarket. The result may then be more frequent defecations during work-free weekends, or having voluminous and explosive bowel movements after days with a resting bowel; they have termed themselves collectors.

In Western society, most people take advantage of the gastro-colonic response by sitting on a toilet after a morning meal, and sometimes after a night meal, too. The sitting position for the evacuation of faeces may be a co-factor in building faecal retention reservoirs. Squatting, compared to sitting, relaxes the puborectalis muscle and straightens the anorectal angle, as shown in a defaecographic study (211).

Some characteristics of the personality profile of patients with constipation are evident. A significant correlation was found between the mean transit time in the ascending colon and levels of anxiety. However, interpreting these results is difficult: the more anxious, the more constipated, or is it the reverse? Constipation probably protects from free-floating anxiety (212). Moreover, depression leads to constipation, which is further aggravated by the use of antidepressant drugs. A recent psychological characterisation of patients with IBS revealed equal and higher anxiety and depression scores for IBS-C, IBS-D, and IBS-M, compared to healthy controls beside transit and sensory anomalies (213). Patients with chronic anal pain also have abnormally high anxiety and depression levels (214). In addition, sexual abuse is more frequently reported by IBS patients than by patients with organic digestive diseases (215), and abused patients are more likely to complain of constipation

(216,217). Disturbed anorectal motility or coordination (anismus) also occurs after sexual abuse (216).

In recent years, specific attention has been paid to the brain-gut axis i.e. the communication between the central nervous system and the enteric nervous system involving neural pathways and immune mechanisms (90,218). The numerous neurotransmitters found in the brain and gut are the messengers that regulate these activities. The enkephalins, substance P, nitric oxide, 5-hydroxytryptamine (5-HT), cholecystokinin, and others have varied and integrated effects on pain control, gastrointestinal motility, emotional behaviour and immunity (219). Thus, patients with IBS may have visceral hypersensitivity, which could be related to increased afferent processing in pathways ascending to the brain or an enhanced pattern of central nervous system activation, as shown in neuroimaging studies. Heightened activity has been demonstrated in regions in the brain involved with visceral or somatic pain, and the pain behaviour may be attentional (anticipated) rather than a transmission abnormality. Treatment interventions have resulted in decreased activity in certain brain regions (218).

Sensory and motor dysfunction in the rectum may occur in conjunction with structural pathologies in the anorectal area. Grade II or higher haemorrhoids were seen in 50.2 % (1) and 21.4 % (2) of patients in the present studies (1), including an internal rectal intussusception in which the distal rectal lumen could be seen to be occluded during straining in some cases. A rectocele, in which the stool may be trapped within the anterior wall protrusion into the vagina, was present in 28.2 % of female patients (n = 60/213), and a pelvic floor push-down phenomenon was seen in 9.8 % of these patients (ad hoc data (2)). Obstructed and ineffective evacuation may also be ascribed to rectal intussusception or to an overt rectal prolapse. These data are almost equal to the results of defecographic investigations of patients with constipation and emptying difficulties (220). The aetiology of these conditions is unclear, but they presumably arise through a weakness of the supporting structures of the distal rectum, either due to causes such as ageing, pregnancy, delivery, or connective tissue disorders, or secondary to years of straining to evacuate (203). A recent study showed significantly higher prevalence of pelvic floor damage among patients with constipation compared to those who were not constipated (221).

Faecal retention with or without delay in the colon and rectum is then supposed to be caused by inhibited colorectal motility patterns. In addition, the present studies (2,3) showed for the first time that a structural abnormality, such as the length of the colon (colon elongatum) is crucial to faecal arrest with prolonged CTT and overload of faeces in the colon and rectum, aggravating symptoms.

OTHER THERAPIES

Activation of neuronal 5-HT₄ receptors results in prokinetic activity throughout the gastrointestinal tract and triggers the release of neurotransmitters from the enteric nerves, resulting in increased contractility and stimulation of the peristaltic reflex (159). Cisapride belongs to this group of agonists, but was withdrawn from the market because of cardiac side effects. Its successor, tegaserod, is an

aminoguanidine indole compound, and 5-HT₄ /5-HT₁ partial agonist and a 5-HT₂ agonist, which also inhibit dopamine. The drug acts as a motility-enhancing agent, exerting activity throughout the gastrointestinal tract with inhibition of visceral sensitivity and pain (222). Tegaserod has been shown to significantly accelerate colonic transit in healthy volunteers of both sexes (223) and male patients with IBS-C (224). Large, randomized, placebo-controlled trials of oral tegaserod given to patients with IBS-C have shown superiority of the drug over placebo in regards to the subjects' global assessment of overall relief (76) and secondary end points (i.e. abdominal pain, bloating, bowel frequency, and stool consistency) (225,226,227, 228,229,230). In chronically constipated patients, significant improvements of these symptoms were also observed (231,232). The safety, tolerability, and efficacy of tegaserod are favourable during continuous long-term treatment (233). However, because of ischemic vascular events (234), the use of tegaserod is now restricted and only recommended for use in women under the age of 55, with no risk factors for ischemic disease and without hepatic or renal impairment. Since completion of the present studies, some patients who did not respond to domperidone have been treated instead with tegaserod, which has been available on an individual licence from the Danish Health Authorities.

Prucalopride, a dihydrobenzofuran carboxamide, is another selective 5-HT₄ receptor agonist with enterokinetic properties. In major multicentre trials, prucalopride significantly improved bowel function in chronically constipated patients, including frequency, straining, stool consistency, laxative use, and satisfaction (159, 235). The drug is now marketed in Denmark.

Renzapride is a mixed 5-HT₄ agonist and a 5-HT₃ receptor antagonist that has a stimulatory effect on gastrointestinal motility and transit and has been reported to induce a clinically significant dose-related acceleration of colonic transit associated with improved bowel function in female IBS-C patients (236). This drug is not marketed in Denmark.

Lubiprostone was recently approved in the U.S., but is currently not available in Europe. The drug is a fatty acid that acts as a chloride channel activator, stimulating intestinal fluid secretion and acting on the enterocytes from the luminal side. Lubiprostone is not systemically absorbed. Treatment is associated with faster colonic transit and softer stool consistency, improving the frequency of bowel movements and straining in patients with chronic constipation. In IBS-C patients, lubiprostone improved global and individual symptoms (237).

Other IBS initiatives have examined the efficacy of an herbal preparation. A combination of peppermint and caraway oil was comparable to cisapride for the treatment of functional dyspepsia (238), and in randomized trials, peppermint oil was more effective than placebo in the treatment of IBS (157).

Over time, laxatives have been the most frequent drugs used for constipation disorders, whether they belong to the bulking, stimulant or osmotic group (159,239). When patients in the present studies were using laxatives, they were told to finish the course gradually and let the stimulant prokinetic regimen take over.

Medical treatments have evolved by introducing probiotics and prebiotics: the former of which are living organisms that exert a health benefit on the host (159). The most commonly used probiotics are lactic acid bacteria and non-pathogenic yeasts. Meta-analysis and reviews of randomized, controlled trials with probiotics in IBS have documented that probiotics are significantly better than placebo (240) and improved the symptoms of all IBS subtypes (241). Data to support the use of probiotics in chronic constipation is lacking, though for example, *Bifidobacterium lactis* has demonstrated the ability to shorten colonic transit in healthy women, the elderly, and subjects with IBS (159). Several mechanisms have been suggested for the efficacy of probiotics in IBS, such as qualitative changes in the colonic flora, suppression of bacterial overgrowth in the small intestine (SIBO), antibacterial and antiviral activity, immuno-modulatory and anti-inflammatory properties, improved dysmotility, visceral hypersensitivity, and the brain-gut axis (241).

In contrast, prebiotics are non-digestible, fermentable foods that beneficially affect the host by selectively stimulating the growth and activity of one species or a limited number of species of bacteria in the colon (159). The data are currently insufficient to permit conclusions to be drawn.

Antibiotics have been used in the treatment of bacterial overgrowth in the small intestine and IBS. Thus, rifaximin, a non-absorbable antibiotic, showed a significant higher decontamination rate (63.4 %) than metronidazole (43.7 %) in patients with SIBO (242). Rifaximin improved global IBS-symptoms in 33–92 % of patients and eradicated SIBO in up to 84 % of patients with IBS (243). Although rifaximin demonstrated improvement in global IBS-symptoms, the findings suggest that relief of symptoms may not be durable after completion of the antibiotics (76). This shows indirectly that small intestinal bacterial overgrowth may be a result of faecal retention in the colon.

The most elaborate mix of human-derived probiotic bacteria is the entire bacterial faecal flora. Encouraging results have been observed following infusion of human faecal flora in patients with IBS and chronic constipation (244). The alteration of the colonic microbiota by the donor faecal flora seems to be durable and represents a promising field of new therapeutic strategies (245).

Intestinal lavage has a mythical origin from ancient times, where Egyptians learnt to wash out their bowels from observing the habit of the ibis: “He washes the inside of his body by introducing water with his beak into the channel, by which our health demands that the residue of our food should leave (246). In the 17th century, the enema reached the height of its popularity. A revival was seen in the beginning of the 20th century, when the theory of intestinal stasis and auto-intoxication dominated. It is well recognized that bowel cleansing often leads to a temporary relief of constipation symptoms, such as before a colonoscopy or a barium enema. Thus, transanal colonic irrigation is another supplementary tool in the treatment of constipation disorders. However, different studies have shown different rates of success, from 19 % to 79 % (247,248). In the present study (2), a few patients refractory to conservative treatment were temporarily offered transanal irrigation.

Another therapeutic option to relieve patients of constipation is biofeedback for pelvic floor dyssynergia, the paradoxical contraction or failure to relax the pelvic floor and anal canal muscles during defecation, and inadequate defaecatory propulsion, i.e. the inability to evacuate a 50 ml water-filled balloon (249). The biofeedback is instrument-guided behavioural training in which patients are taught to voluntarily control physiological responses. The training is based on trial-and-error learning, similar to acquiring a motor skill (sports), and often consists of six sessions (151). Whole gut transit normalized following biofeedback in most patients with dyssynergia but was unchanged in patients with slow transit constipation, suggesting that transit delays in dyssynergia are secondary to the evacuation disorder (250). In a few randomized trials, biofeedback-treated patients reported significantly more adequate relief compared to placebo, polyethylene glycol, standard care, or diazepam (151). Biofeedback was also recommended for patients with coexistent rectocele, intussusception, and abnormal perineal descent (251).

Patients with IBS are more likely to suffer from mood disorders, anxiety, and depression. Antidepressant drugs are often used in the treatment of chronic neuropathic pain and some effects on abdominal pain were recently reported in IBS patients (252). Psychotherapy has not been evaluated for an effect on chronic constipation or dyssynergic defecation. Different forms of psychotherapy have been reported to be more effective than standard medical care for improving the overall symptoms of IBS, but no studies have documented specific changes in transit time, outlet dysfunction, or the frequency of spontaneous bowel movements.

A new stimulatory treatment for patients with constipation and IBS developed over the last few years is sacral nerve stimulation (SNS). The technique requires two needle electrodes to be positioned trans-cutaneously into the S2 to S4 sacral foramina, initially connected to a portable stimulator. SNS significantly increases the frequency of high-amplitude propagating sequences and the frequency of propagating pressure waves, as shown by manometric recordings (253). Electrical stimulation of the sacral nerves has also been shown to result in high-amplitude pressure sequences originating in the caecum and extending the full length of the colon. Stimulation also leads to an improvement in rectal sensation, and patients report that the first urge for defecation occurs much earlier than without stimulation (254). Only a few reports have dealt with the effect of SNS on patients with chronic constipation. In patients, responding to SNS, a marked decrease in the Wexner constipation score, more defecation episodes, and a significant improvement in quality of life was observed. In patients with outlet obstruction, successful SNS led to improved defecation, and digital manipulation was no longer needed in all patients (255). In a multicentre study, 39 of 62 patients with intractable constipation achieved treatment success with SNS. Defecation frequency increased, and straining, incomplete evacuation, and abdominal bloating and pain all decreased significantly. The improvements in symptoms were associated with improved (reduced) CTT (256). In children with slow transit constipation, transcutaneous interferential electrical stimulation can significantly speed up colonic transit (257). Temporary SNS was very

recently evaluated in a pilot study (8 patients) of the treatment of IBS (258). Symptom clusters depicting pain, bloating and diarrhoea were reduced significantly, as well as the impact of IBS on quality of life. After ceasing stimulation, the patients' symptoms recurred.

FAECAL RETENTION, CONSTIPATION, AND IRRITABLE BOWEL SYNDROME

Systematic reviews have concluded that no one definition of constipation can be considered a gold standard (12,73). Experts in the field have developed the Rome criteria in recent years by establishing a consensus on which symptoms are required to establish the diagnosis of functional gastrointestinal disorders (67,259), but the accuracy of the criteria has not been evaluated (76). These criteria do not aid in the differentiating the three major types of constipation: normal transit (NTC), slow transit (STC) and obstructed defecation (194). The differentiation will demand a colonic transit study, supplemented by anorectal physiological testing. A substantial self-reporting of constipation without meeting the Rome criteria exists (12). The diagnosis of IBS is also symptom-based (67) and subtyped as IBS-C, IBS-D and IBS-M (mixed) or IBS-A (alternating), according to stool appearance, which may change from time to time in the individual patient. As described earlier, a frequency factor exists for symptoms incorporated in the diagnostic criteria for IBS and constipation. Other studies suggest a frequent symptom overlap between functional constipation and functional gastrointestinal disorders, such as IBS (260). Moreover, patients with functional gastrointestinal disorders have changing symptoms over time (261) and transition between different functional gastrointestinal disorders suggests a common cause behind bowel disorders.

Abdominal symptoms are included in the Rome criteria for IBS, but this is not the case for functional constipation (67), which is in contrast to the earlier reports from surgeons with interest in slow transit constipation. Including patients with a broad spectrum of bowel symptoms in the present studies without grouping allowed further analysis of the coherence between abdominal and defaecatory symptoms in constipation disorders. Thus, a new stratum was formed of patients who had one defecation per second or third day with difficulty (no ease) and solid faeces (Fig.1 (2,3), and ad hoc data). Out of 251 patients (1), 35 patients were within this stratum and had abdominal pain, and 8 patients were without pain. The rest of the patients with no difficulty defecating had significantly less abdominal pain compared to the patients within the stratum ($n = 35/43$ vs $124/206$, $p = 0.009$, ad hoc data). No significant differences in age or gender were found between the new stratum of patients with defecation difficulties and abdominal pain and the rest of the patients ($p > 0.05$). Among the physical signs, tenderness in the right iliac fossa occurred significantly more often in this stratum of patients ($p = 0.034$), as well as meteorism ($p = 0.036$).

Similar supplemental analyses of the second series of patients with bowel disorders (2) identified 115 patients (out of 261 patients) in the stratum with defecation difficulties and abdominal pain, and only 9 patients without pain. In this study, the patients without defecation difficulties had an equally high occurrence of abdominal pain.

No significant differences in age or gender were found between these strata and the rest of the patients ($p > 0.05$). The dominant physical signs occurred significantly more often in the new stratum of patients with severe defecation difficulties and abdominal pain compared to the rest of the patients (abdominal mass right fossa $p = 0.023$, abdominal tenderness right fossa $p = 0.001$, meteorism $p = 0.001$, all Pearson chi-square test, ad hoc data). Cluster analyses also documented the intimate coherence between abdominal symptoms and defaecatory difficulties due to solid faeces and infrequent defecation being significantly loaded in the same factor as abdominal bloating (2).

The CTT for the new stratum was 57.8 h ($n = 105$), which was significantly prolonged compared to the controls (24.75 h, $n = 44$, $p < 0.001$). Similarly, faecal loading was significantly greater in all colonic segments at 48 h (total: 6.7 vs 4.3, $p < 0.001$) and 96 h (total: 7.0 vs 4.3, $p < 0.000$) for this stratum of patients compared to controls; the results were equally significant for both genders. The presence of colonic redundancies in these patients with defaecatory difficulties and abdominal pain was similar to the presence in the remaining patients. From the new data, I reasonably conclude that pain is significantly linked with defaecatory difficulties and is an essential symptom in constipation, as also stated by others (65,82,262), but not included in the Rome criteria.

However, a symptom-based diagnosis does not seem to be sufficient, as CTT and faecal loading have to be determined to fully characterize the condition for a functional diagnosis. The intervention was an important part of this recognition in the present studies by decreasing the CTT and faecal load relieving of abdominal and defaecatory symptoms.

The data from the present studies suggest that an increased faecal load in the colon, even with a normal CTT ($n = 90$), can cause bloating and pain and induce different modes of defecation (2). New analyses (ad hoc data) showed that 80 patients had abdominal pain with a mean total CTT of 8.1 h (range 0–24 h), significantly faster than the 24.75 h for the controls ($p < 0.000$, Mann-Whitney U-test). Right colonic faecal loading correlated positively with bloating at 48 h ($r = 0.256$, $p = 0.022$) and 96 h ($r = 0.354$, $p = 0.07$), and total loading with bloating at 48 h ($r = 0.227$, $p = 0.043$) and 96 h ($r = 0.307$, $p = 0.022$). The patients without pain had a total mean CTT of 6.2 h (range 0–16 h), significantly faster than that of the controls (24.75 h, $p < 0.001$, Mann Whitney U-test). Even in these patients, faecal loading was significantly greater compared to the controls at 48 h (5.3 vs 4.3, $p = 0.032$) and 96 h (6.6 vs 4.3, $p = 0.004$, Mann Whitney U-test). However, no significant correlations were found between CTT and faecal loading with bloating in the subgroup of patients without abdominal pain or defaecatory difficulties. The influence of colonic redundancies on these two subgroups was minor. The distal CTT in the subgroup with abdominal pain positively correlated with the number of redundancies ($r = 0.262$, $p = 0.032$), and in the subgroup without pain, right faecal loading at 96 h correlated significantly with the number of redundancies ($r = -0.849$, $p = 0.08$). No correlations were found between CTT or faecal loading and the number of redundancies in the stratum of patients with difficult defecation.

From the studies and the new data presented here, one may frame a picture of the mechanisms underlying functional faecal retention. In normal subjects, meaning those without any abdominal or defaecatory symptoms, the faecal load and CTT is normal. However, some normal persons may have a right-sided faecal reservoir, as demonstrated here in the controls. The next step seems to be an accumulation of faeces in the colon with abdominal symptoms such as bloating and pain, but still with a normal CTT and with or without defaecatory disturbances. This context is called "hidden constipation". Stool consistency that is solid, liquid, or mixed (or alternating patterns) does not itself reflect the amount of faeces in the colon. Furthermore, with continuing accumulation of faeces in the colon, the CTT becomes prolonged with abdominal symptoms and increasing difficulty defecating, including infrequency. An elongated colon will prolong CTT and aggravate symptoms.

Classification of constipation may be symptom-based and measurements-based, or both. IBS is defined solely on symptom criteria and often after excluding other bowel diseases. The questionnaire used in the present studies encompassed the majority of symptoms for extant IBS questionnaires (263). Very recently, a conceptual framework proposed that IBS symptom experience might be determined by 35-item categories within five domains; pain; gas/bloat; diarrhoea; constipation; and extraintestinal symptoms (263) i.e. the same dominant symptoms focussed in the present studies. However, it may be inferred from the present results that a constipated or irritable bowel may belong to the same underlying disease dimension, where faecal retention is a common factor. This is in line with a new study, where patients with functional constipation and IBS-C appear to lie in the same spectrum of visceral sensitivity (264). The difficulty with symptom-based criteria was demonstrated recently where Rome III criteria did not pick up a substantial proportion of people who were severely troubled by constipation (265). The novel information on faecal retention gained here by measuring CTT and faecal load does not explain why faecal retention occurs, though it seems to be a guide to a positive functional diagnosis of bowel disorders, and thereby therapeutic intervention, compared to a constellation of symptoms alone.

COLECTOMY FOR REFRACTORY CONSTIPATION

RESULTS OF SURGERY

The patients were derived from a population of 281 patients (2) to a total of 35 patients (30 women and 5 men), including 7 additional patients, who also failed the conservative treatment of constipation described here. The main objective of the surgical treatment was the improvement of defecation and resolution of abdominal symptoms, thereby improving their quality of life (2,3). Anorectal physiological testing was also used to identify and exclude patients, who had concomitantly insufficient sphincter function; three patients received a primary ileostomy. A subtotal colectomy was chosen for elderly patients (mean age 55.8 yr), whereas segmental resections were performed in younger patients (mean age 47.1 yr) (56,134). This approach seems to be justified by the initial CTT adjusted for the removed part of the colon. Thus, the mean CTT was 23.36 h, which was not significantly different from that of the controls (24.75

h, $p > 0.05$), but less than the mean CTT of non-operated patients after conservative treatment (32.80 h, $p = 0.044$) (3). The similarly adjusted faecal loading scores were significantly less than those of non-operated patients after treatment, and even less than those of the controls. A segmental resection has the advantage of no risk of subsequent uncontrolled diarrhoea, in contrast to a subtotal colectomy, and the limited dissection is supposed to imply less post-operative risk of bowel obstruction.

The patients were followed post-operatively for a mean 42.06 months and up to 114.89 months. After hemicolectomy (20 patients), 71.4 % of the patients had daily defecation and 75.0 % had formed stools. After a subtotal colectomy (15 patients) with an ileosigmoid anastomosis (ISA), no patients experienced uncontrolled diarrhoea (3), which may be expected to occur in up to 52 % of the cases after IRA (ileorectal anastomosis) (70,266,267,268). The number of defecations per day was two to four, which is in line with other studies (36,50,53,268,269,270) and with consistency of faeces in 64.3 % of these patients (3). Other functional results were relief from bloating in 85.7 % of the patients after subtotal colectomy, similar to the results of another study (271), and this symptom disappeared in 93.3 % of patients after left-sided hemicolectomy. Abdominal pain disappeared in all patients after hemicolectomy and 85.7 % of patients after subtotal colectomy, whereas most other studies have reported the persistence of abdominal symptoms despite operation (50,53,70,134,195,267,268,269,270,).

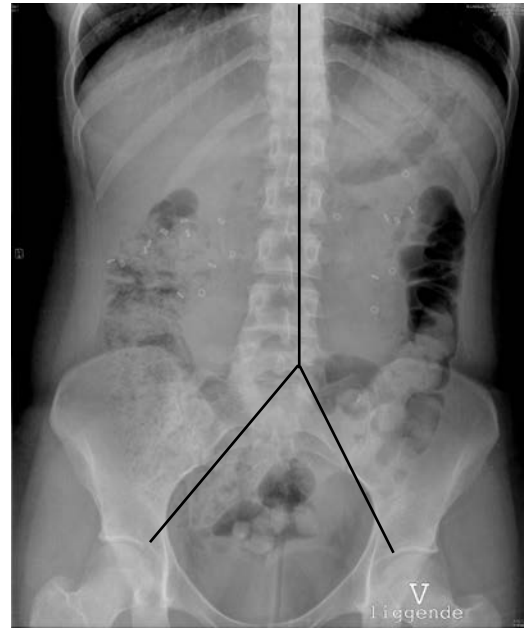
The same two senior surgeons performed the different colectomies. These operations are an invasive approach with potential serious complications, including mortality (51,64,268,270,272). In the present series, one patient died from an anastomotic leak after left-sided hemicolectomy, and one other patient had leakage after subtotal colectomy. An additional six subtotal colectomies with ISA were performed after the conclusion of the study (3), with one complication (post-operative ileus), resulting in an overall leakage rate of 4.9 % (2/41, ad hoc data). Most series of colectomies for constipation are relatively small and report anastomotic leak rates from zero up to 10 % (51,269,272); in contrast to studies of colectomy for reasons other than constipation, which report anastomotic leak rates of 1.9 % after segmental resection, 3.3 % after subtotal colectomy with ISA and 0.9 % after IRA (64). One patient was re-operated because of a bleeding ulcer, and another was re-operated because of a small stomach necrosis on the major curvature with perforation. Two other patients developed a minor wound infection. The abdominal rectopexy necessary in six of the patients undergoing a colectomy did not give rise to any specific complication (3,70,134), and no recurrent rectal prolapse was observed (3). Patients undergoing colectomy for constipation seem to have a more prolonged post-operative course than patients having the same operation for other reasons (64,72). Small bowel obstruction is considered a major risk after subtotal colectomy (36,51,72,194,268). Two patients experienced this complication while they were still in the hospital (3) and one patient has had repeated admissions for ileus, including operative intervention.

The concept of using colectomy for constipation is not new, and was introduced by Arbutnot Lane in 1905 (80). Initially, he performed

Colon transit study after the ingestion of 24 markers by a 19-year-old female patient, who later received a subtotal colectomy.

Left X-ray: $21 + 3 + 0 = 24$ markers, faecal load $3 + 3 + 3 = 9$.

Right X-ray: $13 + 9 + 0 = 22$ markers, faecal load $3 + 3 + 3 = 9$. CTT = 92 h.



a colonic by-pass by an ileo-colostomy to the sigmoid or rectum in patients with abdominal pain and chronic constipation, where all other treatment had hopeless failed. Calculation from the original data shows that in 25 out of 39 patients (33 females, mean age 35.0 yr, range 20–53 yr) the colon was subsequently removed up to the splenic flexure. The results were fairly good in 69.2 % of the cases; however, eight patients died from post-operative complications (20.5 %) (273). A second series of 50 patients (44 females, mean age 35.4 yr, range 18–55 yr) with the same characteristics of chronic intestinal stasis and additional generalized symptoms, showed a better outcome (85). Twenty-seven patients ended up with a colectomy, the vast majority with a good result and there was no mortality. Colectomy or complete colon by-pass (short-circuiting) spread in popularity and was done throughout Europe and North America (274,275). However, the surgical treatment of intestinal stasis fell into disfavour (246) and partial or complete colectomy were reserved for the most refractory cases of constipation, or for cases of auto-intoxication so severe as to demand drastic measures (275). Very recently, a few operations by-passing the whole colon by an end-to-side colorectal anastomosis have been re-introduced (276).

Surgery for constipation is a difficult area that could lead to successive operations when constipation returns after a period of relief (134,266,268). Four patients who had an initial segmental colectomy converted to a final subtotal colectomy, and two other patients ended up with an ileostomy after successive removals of the left and right side of the colon.

Quality of life was assessed on an arbitrary scale as a patient's satisfaction index from 0 to 10, which increased significantly from an initial mean of 3.08 to 7.25 after operation, and some even reported a score as high as 10. These figures can be explained by the relief of severe defecation difficulties for years, and relief from abdominal symptoms in most cases.

PATHOPHYSIOLOGY AND ANATOMY OF THE COLON

The main variables recorded at entrance into the study were compared between patients who were operated and those who were non-operated patients to explore eventual significant differences (3). The later operated patients experienced abdominal pain significantly more often than the non-operated patients, but with no difference in bloating or epigastric discomfort. The operated patients experienced significantly less frequent defecation with greater difficulty compared to more frequent and repetitive defecation by the non-operated patients. A push down phenomenon was observed significantly more often among operated patients, whereas the occurrence of anal mucosal prolapse, cystocele, or a rectal reservoir of solid faeces was equal within the two groups of patients. Tenderness in the right iliac fossa and a palpable mass were frequent in operated and non-operated patients, whereas tenderness and a left sided palpable mass were significantly more frequent in the operated patients.

The mean CTT for operated patients (66.0 h) was significantly longer compared to that of non-operated patients (37.6 h). The faecal loading scores were greater in operated than non-operated patients, except for the right colon segment. In operated patients, bloating correlated significantly positively with left and total CTT. A correlation was also found between CTT and the presence of a left-sided faecal mass (3).

The CTT is meant to be a measure of the speed of faecal propulsion through the colon, though it has limitations as demonstrated by heavy faecal loading (faecal retention) occurring with both a prolonged and normal transit time (2). Possible reasons for dysmotility of the colon may be disorders of the enteric nervous system, neuroendocrine system, or brain-gut axis as explained in a previous chapter, including the lack of interstitial cells of Cajal, the colonic pacemaker cell. Slow transit constipation has also been proposed as

a cause of pelvic surgery (277,278). In the present series, hysterectomy was previously performed in 37.9 % of the operated patients, which is not significantly different from 25.8% in the non-operated patients (ad hoc data) (2). A recent study showed that hysterectomy does not seem to cause constipation (279).

The operated patients had significantly more redundancies in the colon (length) than the non-operated patients, and a higher frequency of two redundancies occurring together. The mean CTT increased significantly with the number of redundancies, from 36.26 h without a redundancy to 52.27 for three to four redundancies. Faecal loading increased similarly. A separate analysis showed a significant positive correlation between CTT and faecal load and a redundant sigmoid colon. An increased number of redundancies resulted in significantly more bloating and pain and a reduced frequency of defecation, but did not influence ease of defecation, incompleteness, repetitiveness, or faecal consistency (solid or liquid). No correlations were found between colonic redundancies and the physical signs. The present studies (2,3) seem to be the first to demonstrate that CTT and faecal load significantly increase with the number of colonic redundancies, which is in line with an earlier study, suggesting that transit is largely proportional to the length of the colon (41,119). The dividing line between normal anatomical variations in colon length and congenital malformations is not clear. An elongated colon is often associated with agglutination failure in the mesentery with the parietal peritoneum and seems to be congenital. A dolichocolon is not fixed to the dorsal abdominal wall and may swing free on a long mesentery. However, very recently another mechanism has been shown in mice that may explain the association of an elongated colon and poor motility (132,280). The large bowel undergoes substantial changes in length, as it fills with faecal matter and stretching of longitudinal muscles result in slow colonic transit. It was shown that nitric oxide was released and activated inhibitory neurons reducing pellet propulsion and amplitude of colonic migrating motor complexes.

Earlier, segmentary resections were performed in patients with severe constipation after a barium enema had demonstrated a dolichocolon, and the results were described as good (17), including small children as well (15). In other studies of patients who underwent subtotal colectomy for STC, the majority of colon specimens were significantly redundant (43,44,134, S. Wexner personal communication). Also, free redundant loops represent a risk of volvulus.

Half a century ago, a triad of constipation, bloating, and abdominal pain was attributed to a redundant colon (16,17,42). However, an elongated colon seems to be perceived as not giving rise to specific symptoms (133). Actually, though, as demonstrated by the present analyses, increasing colon length aggravates symptoms, CTT, and faecal load (2,3).

EVALUATION OF PATIENTS FOR SURGERY

The goals of improved defecation and the relief of abdominal symptoms after colectomy were not achieved in a few of the present patients. Multiple studies have reported significantly poorer outcomes after subtotal colectomy in patients with concomitant



Dolichocolon with loose redundant loops.

small bowel dysmotility. The most common issues were continued abdominal pain, bloating, constipation, recurrent small bowel obstruction, and post-operative diarrhoea (268,281,282). A recent study reported that all patients with STC and 94 % of patients with NTC had this underlying small bowel neuropathy (196).

A high incidence of comorbid psychiatric conditions with a negative impact on outcomes has also been reported (283,284). A history of sexual abuse is strongly associated with an increased prevalence of functional disorders of the lower gastrointestinal tract, as high as 40 % (216). A relatively small new study (13 patients) showed sexual abuse to be a strong predictor of outcome after colectomy for STC (285). Eight patients who were sexually abused had a total of 32 operations before colectomy, compared to three operations for non-abused patients. Notably, the number of patients that acknowledged a history of sexual abuse doubled after the post-operative follow-up visits. Seven abused patients sought additional medical care for abdominal complaints, whereas none of the non-abused patients sought additional care. All patients said that surgery improved their quality of life and that they would have surgery again if given the choice, which is in agreement with previous colectomy series (50, 70,267). Psychiatric evaluation (and treatment) was not routinely conducted in the present series of operated patients, and the impact of sexual abuse on outcome of colectomy remains unknown.

All the affected patients in the present study (3) reported intense suffering from the abdominal pain, bloating, and defecation disorders and had failed medication trials. From an exploratory analysis of their data, they obviously differed from patients treated conservatively in regards to a prolonged CTT, heavier faecal load, and a redundant colon in the majority of cases. Anorectal physiological testing was conducted in the patients with constipation disorders (2) and, when considering colectomy, the results were used to ascertain that the patients were capable of controlling a more liquid stool post-operatively. Three patients received an ileostomy because of low squeeze pressures. No significant differences were found between the mean strain and squeeze pressures for operated and non-operated patients (3). The volume for first sensation, modest urge, and the maximum tolerable volume were significantly higher in operated patients compared to non-operated patients. None of the operated patients experienced uncontrolled diarrhoea.

The laboratory studies did not reveal any endocrine or metabolic abnormalities that contributed to STC.

Various surgical methods have been used to treat STC. In addition to segmental or subtotal colectomy with IRA or ISA, the outcome after a caecorectal anastomosis (CRA) with regard to post-operative success, complications, and quality of life has been shown to be comparable to IRA (286) but inferior to ISA (72). Subtotal colectomy with CRA has been done laparoscopically for less pain and better cosmesis (287), and this approach is recommended for IRA (195, 270). Another approach in an effort to reduce constipation is the use of antegrade colonic enema (288), which has had mixed results in small series of patients. Bowel movements changed from one per week to one per day in 12 women, but four of these women needed a later subtotal colectomy, two of whom ended up with permanent ileostomies (289). In addition, the percentage of patients needing a surgical revision (88 %) or reversal (59 %) was high after antegrade stoma (290). A recent retrospective study reviewed the long-term results of antegrade colonic enema in a heterogeneous group of adult patients, including idiopathic constipation (291). Different types of stomas were created in a combination with colostomy and considerable immediate and late post-operative complications and side effects were observed. However, when treatment was successful, significant improvements in bowel function, social function, and quality of life were observed. Some patients in the present series of colectomies (3) were offered these procedures or an end ileostomy, but denied. After many troublesome years, the patients wanted a more definitive solution, such as colectomy.

Based on the results presented here, we performed six more subtotal colectomies, all with good functional results and only one postoperative complication (ileus). Thus, an update of the symptoms a mean 60.76 months after subtotal colectomy (all patients) shows that 79.2 % of the patients are without abdominal pain and bloating, and 95.5 % has two to four defecations daily, as liquid stool in 54.5 % of the cases and with control. The mean QoL for these patients is now 7.5 (ad hoc data). Consequently, we have abandoned segmental resections of the colon because of a high risk of subsequent conversion to a final subtotal colectomy. Furthermore, before considering an invasive surgical procedure, patients with intractable constipation now to go through an SNS test (292). Four patients recently underwent the test prior to surgery, but without a significant response.

At pre-operative counselling the patients, they are told that the procedure is not perfect as there are potential risks for immediate per-operative and post-operative complications. Despite a comprehensive pre-operative evaluation, functional results may be difficult to foresee in individual patients. A realistic approach would be to expect considerable improvement in defecation, whereas abdominal bloating and pain may still occur (293). Eventual medical co-morbidities contribute to the overall operative risk of subtotal colectomy and have to be taken into account.

ACUTE APPENDICITIS: ORIGIN FROM FAECAL RETENTION FAECALITHS IN THE APPENDIX

During the night on my first 24-hour shift as a surgical resident, I operated on three patients with perforated appendicitis. I have since

observed that an obstructing faecalith (faecal concretion) is often present in the inflamed appendix. In the present study (4), a faecalith occurred in 49 % of the cases and was most often associated with a gangrenous or perforated appendix. The number may have been even higher because faecaliths can escape into the peritoneal cavity through a perforation. These figures are in line with an old Canadian study in which faecaliths were found during laparotomy for acute appendicitis in 52 % of the cases (294). The authors also determined the prevalence of incidental faecaliths to be 32 % (during cholecystectomy or bowel resection), compared to 4 % in South African patients (most were laparotomies for trauma). The incidence of faecaliths observed with acute appendicitis was 23 %.

The current incidence of appendicitis is roughly about 100 per 100,000 person years in Europe and the U.S., with one-fifth being perforated appendicitis (295). Thus, acute appendicitis is still the most common surgical emergency procedure with more than 300,000 patients operated annually in the U.S. and ca. 7,000 in Denmark. Prevalences of inter-ethnic South African school pupils of 16-18 yr were: rural blacks, 0.5 %; Indians, 2.6 %; Africans whites, 13.4 %; English whites, 9.9 % (296). A recent study showed that obstructive appendicitis is more common than non-obstructive appendicitis, with the obstructive lesions being faecaliths (52.8 %), lymphoid hyperplasia (22.2 %), foreign bodies (8.3 %), worms (5.6%), and tuberculous stricture (2.8 %), among others (8.3 %) (297).

In 1886, Reginald Heber Fitz presented a paper entitled "Perforating inflammation of the vermiform appendix" at the meeting of the Association of American Physicians, in which he stated that the term appendicitis is preferable for expressing the primary condition (298). Fitz also noted that in his experience it was rather the rule than the exception for the appendix to contain moulded, more or less inspissated faeces. Based on old experimental evidence, acute appendicitis seems to be the result of a primary obstruction of the appendix lumen (299,300). After obstruction, the appendix subsequently fills with mucus and distends with increasing intraluminal and intramural pressures, resulting in thrombosis and occlusion of the small vessels and stasis of lymphatic flow. The appendix then becomes ischemic and necrotic, and pus forms within and around the appendix when bacteria leak out through the dying walls. The result of this cascade is appendiceal rupture. The presentation of a faecalith is also associated with higher rates of perforation and, therefore, with more serious disease (298,301,302). A study in children found that the appendix was perforated in 57 % of cases if a faecalith was present, compared to 36 % of cases without a faecalith (303).

APPENDICITIS, FAECAL RETENTION, AND COLON TRANSIT TIME
Despite the rather convincing evidence from animal experiments (299,300), the present study (4) was the first with an effort to trace the origin of the faecalith in a day-to-day surgical setting using transit studies. The hypothesis tested was that adult patients with acute appendicitis have a longer CTT and larger faecal retention reservoirs than healthy controls, and that these observations are associated with the presence of a faecalith in the appendix (appendicolith). Faecal arrest and stasis were previously shown to potentially



Faecaliths from the appendix (right) and caecum (left).

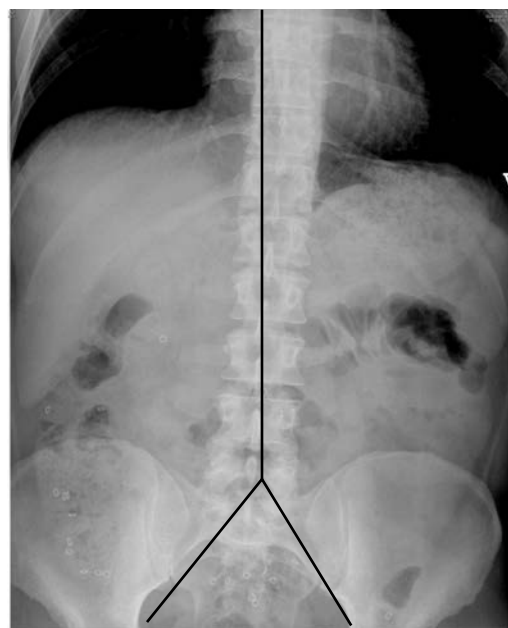
play an aetiological role because patients with acute appendicitis have significantly fewer bowel movements per week compared to healthy controls (304).

The evaluation began with a plain abdominal radiograph on suspicion of acute appendicitis before surgery to estimate the colonic faecal load (4). The diagnosis was confirmed at open surgery, when the appendix was removed and the surgeon recorded the degree of inflammation of the appendix, which was histiopathologically verified later. The surgeon also determined the presence or absence of a faecalith. One patient developed a surgical site infection and another developed an intra-abdominal abscess. Six weeks after the appendectomy, the patients underwent a colon transit study. At this time, the general condition and lifestyle of the patients, including bowel function, was assumed the same as before the appendicitis began. Sixty-eight patients were enrolled in the study, before the diagnosis was finally established at operation: five patients were excluded after the operation due to not having appendicitis, as were four patients who did not complete the post-operative transit study. Data were missing for three patients. Therefore, a total 56 patients were eligible for the analysis. The mean CTT was longer in patients with appendicitis than in controls, though not significantly different (28.4

h (range 1-107 h) vs 24.7 h (range 0-71 h), $p > 0.05$). No significant differences in age or gender were identified between the two groups.

However, this case-control study had a risk of type II error, because of the limited number of participants. New analyses with power calculations relying on the actual data showed that in the case of a new study, 106 persons are needed in each group to obtain a significant difference between faecal scores and 250 in each group to demonstrate a significant difference between their CTTs. This agrees with the findings in the study of patients with functional bowel disorders (2); patients who have previously had an appendectomy exhibited a significantly higher mean CTT (45.4 h) compared to those who did not (36.3 h). In addition, the patients with bowel disorders had an appendectomy rate of 29.9 %, which increased with the number of colonic redundancies, up to 31.6 % for fully developed dolichocolon (ad hoc data). The appendectomy rate increased to 60.0 % in patients operated for constipation and having a full redundant colon (ad hoc data). A lifetable model in the U.S. has suggested that the lifetime risk of appendicitis is 8.6 % for males and 6.7 % for females; the lifetime risk of appendectomy was 12.0 % for males and 23.1 % for females (305). The patients with colonic redundancies were the patients with the greatest faecal load and most prolonged CTT (2, 3). A higher frequency of appendectomy with in the presence of a redundant colon (22%) was observed as far back as 1934 (42), but has not been quoted since. However, it is not possible to determine the exact reason for removing the appendix because some patients may have had it removed when they were explored surgically for right fossa abdominal pain (from a dilated caecum).

A faecalith occurred in 49 % of the present cases, most often, though not significantly, associated with a gangrenous or perforated appendix. Some other faecaliths may have escaped into the abdominal cavity and may not have been detected through the small inci-



34-year-old male patient with acute appendicitis.
 Left X-ray: Preoperative faecal load: $2 + 1 + 2 = 5$
 Right X-ray: Colon transit study 6 week postoperatively CTT = 29 h, faecal load: $2 + 1 + 2 = 5$.

sion with limited exposure. No significant correlations were found between the presence or absence of a faecalith and CTT or faecal loadings ($p > 0.05$, Spearman's rho, ad hoc data). Similarly, no significant differences were found between CTT and the faecal load of patients with or lacking a faecalith ($p > 0.05$, Mann-Whitney test, ad hoc data).

No significant differences were demonstrated in faecal loading between pre-operative and post-operative (six week) radiographs, indicating equal bowel function and that the CTT measured post-operatively fairly reflected the patient's general transit time. Significant correlations existed between post-operative faecal loading scores and the number of markers (transit time), both totally and within the left and distal colonic segments. Fewer correlations were found in the control group. Because the study discovered greater amounts of faeces in the colon than expected physiologically, further analyses were carried out to understand the role of these faecal reservoirs. Analyses within the patient group showed that neither CTT nor faecal load changed across the age groups ($p > 0.05$, Jonckheere-Terpstra test, ad hoc data). However, the right-sided postoperative mean faecal load was significantly higher than the left and distal load (right: 1.80 vs left: 1.36 and distal: 1.42, both $p < 0.000$, Wilcoxon signed ranks test, ad hoc data). Similarly, the new analyses of the patients with functional bowel disorders found the greatest faecal load in the right side of the colon within all age groups and a significant decrease with increasing age (ad hoc data). Thus, patients with bowel disorders and appendicitis demonstrate similar patterns with regard to CTT and faecal load. Others have previously observed on abdominal radiographs that the ascending colon was containing more faeces compared to the rest of the colon (306). Although CTT and faecal load were higher in patients with appendicitis than controls, both segmental and totally, the rather high values in the normal controls were remarkable. Analyses within the control group found that CTT significantly and negatively correlates with age and a significant decrease in distal faecal load was found across the age groups as well.

Another research group recently focussed on faecal loading in the caecum as a radiological sign of acute appendicitis (307). The association of acute appendicitis with the images of faecal loading in the caecum had a sensitivity of 97 % and specificity of 85.3 % compared to other common causes of acute right-sided abdominal pain. These authors also showed that faecal loading had disappeared in the most cases on the second postoperative day. The pathophysiological explanation was that the phenomenon is related to the presence of an acute inflammatory condition. However, as demonstrated in the present studies (2,3,4), a right-sided faecal reservoir seems to occur often among people in Western countries. This finding does not disqualify the primary hypothesis that the origin of a faecalith in the appendix is related to colonic faecal reservoirs, but is more difficult to prove, as seen from the actual power calculations. Thus far, none of the control persons has been operated on for acute appendicitis, though they may be at some risk.

Acute appendicitis is generally considered a disease of youth. In the present study (4), the distribution of patients was 32.7 % 19-29 yr, 21.8 % 30-39 yr, 18.2 % 40-49 yr, and 27.3 % 50+ yr (ad hoc data).

This distribution is similar to the results of a recent study showing that middle-aged and older patients now represent a substantial portion of acute appendicitis cases (308).

Dimishing trends in the incidence of acute appendicitis have been observed since 1930 and reported in studies from the U.S., Great Britain and Scandinavia (309). Dietary fibre intake has attracted attention as an explanation. However, the data are conflicting, with some studies supporting a protective effect of fibre (310,311, 312), and others being unable to demonstrate this effect (313). Burkitt suggested a fibre-depleted diet to result in faecal stasis and a blocking faecalith (314). In a large study from England and Wales, the rates of acute appendicitis correlated with the consumption of different foods per caput (315): a significant and positive correlation with potato consumption and a negative correlation with mainly green vegetables and tomatoes was reported. No consistently significant correlation was found with any other main food group. The researchers stated that green vegetables and tomatoes might protect against appendicitis, possibly by affecting on the bacterial flora and altering the transit time.

STAPLED HAEMORRHOIDOPEXY

RESULTS OF SURGERY

Haemorrhoids were proven in half of the patients (1,2). Further, 76 out of 251 patients in the first study had performed banding or excisions of haemorrhoids and 34 out of 281 patients had anamnestic data of a haemorrhoidal operation before entering the second study. During the study period, 24 patients were operated for haemorrhoids. Subsequently, we participated in a multicentre randomized trial, comparing excisional haemorrhoidectomy and a novel surgical technique, the stapled haemorrhoidopexy (22). Following this, we continued with the present observational study, primarily to test the durability of the new operation (6).

The main objective of the present surgical treatment of 258 patients (143 women and 115 men) with stapled haemorrhoidopexy (PPH) was to eliminate the haemorrhoidal prolapse by restoring the ano-rectal anatomy, thereby relieving the patients from pain, bleeding, pruritus, and severe hygienic difficulties. Consequently, a specific measure, the so-called surgical anatomy score, was used. Using a VAS from 1 (normal anus without visible or sliding mucosa or external dermal elements) to 7 (worst prolapse, eventually also with skin tags), this grading system comprised the usual symptomatic degrees of haemorrhoids: prolapsing haemorrhoids with spontaneous reduction (grade II), haemorrhoids requiring manual reduction (grade III), and irreducible haemorrhoids (grade IV). The majority of patients entered the study with a high pre-operative anatomy score, meaning a severe grade of haemorrhoids (Fig. 4 (5), Fig. 3 (6)). In most other series of PPH, patients with grade IV haemorrhoids constituted a minority (316). Seven surgeons performed PPH in the present study (5, 6). Thus, the VAS score for the anus was the key instrument for monitoring how well PPH performed and how long the result of the PPH lasted. A five-year follow-up period was chosen as recommended recently (316). The median follow-up time from the first observation until present was 34 months for 240 patients who had at least one



Grade IV prolapsed haemorrhoids treated by stapled haemorrhoidopexy.



follow-up (6). Eighteen patients chose to have no post-operative follow-up, and attendance decreased at follow-up appointments for various reasons. The patients' VAS scores decreased significantly from a pre-operative median score of 6 to a post-operative score of 1 for males and 2 for females after 5 years, but this difference was not significant (Fig. 3A, (6)). The elimination of the mucosal prolapse seems to be far better than shown in a multicentre trial in which prolapse remained in 9.1 % of the stapled patients after 1 year (22). Patient satisfaction was high and correlated significantly with the anatomy score. In a recent observational study with long-term results after PPH, 86.0 % of patients were very satisfied or satisfied with the procedure (317).

The major reservation after the introduction of PPH has been and still is the recurrence rate. A recent meta-analysis reported rates ranging from 0.3 % to 50 % and that PPH has a significantly higher incidence of recurrence and additional operations compared to conventional excisional haemorrhoidectomy (316,318,319,320,321,322). Longo (61) reported that after 6 months, and photodocumentation a few cases were poor, as the stapling instrument can only resect a certain amount of tissue. Especially, a high rate has occurred in patients having a PPH for grade IV haemorrhoids (323). This explanation certainly applies to the present studies (5,6), in which the patients presented almost only with grade IV haemorrhoids.

Out of 258 patients, 31 patients (12.0 %) had the PPH repeated, including significantly more females than males (Table 1 (6)), and one patient later underwent a third PPH. These patients had a higher initial anatomy score (more severe haemorrhoidal disease) com-

pared to patients with only one PPH. In the 31 patients who had the PPH repeated after an average of 16.2 months, the median VAS anatomy score changed from 7 pre-operatively to 2 immediately after the first PPH, 4 before the second PPH, and finally to 1 at the last follow-up, meaning a normal appearance of the anus. A second PPH as used to treat a residual prolapse in the present studies has been suggested for repetition at periodic intervals (324). However, reports of a second PPH are scarce, and 12 patients is the highest number to compare having no complaints after 12 months (325).

A statistical model was used in the present studies to explore the predictability of the final outcome of PPH. Gender, the pre-operative anatomy score, the position of the staple line, and the immediate post-operative anatomy score all had significant bivariate correlations with the final anatomy score (Kendall's tau, $p < 0.05$). After controlling for the model fit, linear regression analysis showed that only the pre-operative anatomy score (severity of haemorrhoidal disease) and the immediate post-operative anatomy score (result judged in the operation room) contributed significantly to predicting the final anatomy score at the last follow-up (that is, to the durability of the operation). Other variables such as age, operation time, concomitant external procedures, appearance of the doughnut, and post-operative bleeding were not exploratory variables for the final outcome in this model (6).

Twenty-five female patients and 13 male patients had subsequent surgical excisions to treat persisting skin tags or mucosal prolapse. Specific technical difficulties occurred in 18 patients (9 males) in whom the inspection of the staple line revealed a lack of stapling

over some distance (partial stapling), resulting in a corresponding partial persistence of the initial mucosal prolapse: 13 patients had the prolapse excised, two were re-stapled immediately, and three were managed conservatively. The immediate pre-operative intervention of conversion from the stapled to a conventional anorectal procedure shows that the surgeon must be familiar with these procedures (326). These patients ended up with a median anatomy score of 1 at their last follow-up; however, five of the 18 patients dropped out of the study (6). Recently, it has been proposed that to achieve a high level of patient satisfaction and symptom control, stapled hemorrhoidopexy should be accompanied by resection of insufficient lifted tissue and removal of tags during the operation (317).

An unusual complication occurred when one patient had to have a captured stapler head excised, and acute rectal obstruction had occurred from a purse-string suture entrapped by the staplers (327).

Because stapled haemorrhoidopexy is a new procedure, one may expect complications in the beginning of the learning curve, which is seen in the present studies (5,6) and demonstrated by others (328,329). The learning curve may vary from 5 to 30 procedures (318).

Bleeding, most often requiring surgical haemostasis, occurred in 15 patients (5.8 %) (6), which is the same or less than other series reporting a rate of immediate post-operative haemorrhage as high as 9.6 % (318,319,328,329,330,331). However, this complication did not interfere with the results, which were as good as those in patients with no complications (6). When comparing stapled haemorrhoidopexy with any conventional technique using scalpel, scissors, or diathermy for excision in clinical trials, no significant difference was found in the incidence of bleeding (22,316). In addition, no significant difference in the incidence of anastomotic stricture was found between conventional haemorrhoidectomy and stapled haemorrhoidopexy, or for anal fissure, anal, or recto-vaginal fistula complications (22,316), which occurred only rarely in the present series of PPH (6).

PPH has a significantly shorter operation time, hospital stay, and faster return to normal activities compared to conventional haemorrhoidectomy (316,318). In addition, conventional haemorrhoidectomy such as Millighan-Morgan's technique (60), has been feared because of excessive pain and wounds that take many weeks to heal. Therefore, the significantly reduced pain in PPH, shown in many clinical trials is a real gain (22,316,318). The present studies also showed rather low and declining pain scores in the immediate post-operative period, with no differences between genders. Significantly, more females than males had external procedures performed in addition to PPH, and these procedures resulted in significantly greater pain (Fig. 2 (6)). In a much smaller study, the excision of residual skin tags during stapled haemorrhoidopexy did not increase post-operative pain (332). Surgical analgesia was achieved mostly by a spinal block, though some patients preferred general anaesthesia, but sacral or anal blocks were also used (5,6). Remarkably, patients have also been treated with PPH on an ambulatory basis in private colorectal practice and given monitored sedation with local anaesthesia (333).

Prophylactic antibiotics were given in most of included trials for meta-analysis of PPH compared with conventional haemorrhoidectomy (318). Positive blood cultures, predominantly by anaerobic colonic bacterial flora, have been demonstrated in 11 % of patients with stapled haemorrhoidopexy and 5 % with diathermy haemorrhoidectomy (334). Life-threatening pelvic sepsis requiring a diverting stoma after PPH was reported the same time as the first results of randomized clinical trials appeared (335). Thirteen patients across three continents have required emergency abdominal exploration and faecal diversion related directly to stapled haemorrhoidopexy, resulting in two mortalities (336). At our institution, after 10 years of experience with the stapling technique, we have had one serious septic complication (7). A few hours after the PPH was completed in a 38-year-old male, the patient had lower abdominal and right scrotal pain, as well as inguinal subcutaneous emphysema. An abdominal roentgenograph and CT-scan later showed retro-rectal, retro- and intra-peritoneal, and mediastinal gas. No clinical signs of sepsis were present except intestinal arrest, but biochemical infection parameters were elevated. The patient recovered after treatment with oxygen, i.v. antibiotics, i.v. fluids, and restricted enteral intake; the accumulation of gas disappeared from the cavities over time. Another case with rectal perforation recently occurred in this country, and an 84-year-old female ended up with a permanent colostomy after PPH (337).

By 2002, an estimated 350.000 procedures had been performed worldwide (338). With our own practice as a mirror, this amount has to be multiplied several times to provide an updated count of PPH. With this comparison in mind, the risk of a life-threatening complication is very low. Serious infectious complications, including six deaths, also occur after conventional procedures to treat haemorrhoids, such as injection sclerotherapy, rubber band ligation, and excision (339,340,341).

The key avoiding infectious complications after PPH is to concentrate on the proper placement of the purse-string suture. The suture should be placed 3-4 cm above the dentate line, as proposed by an international consensus (342). In the present complicated case (7), the staple line was placed 6-7 cm proximal to the dentate line and obviously had a leak. Serious complications seem to be linked to a surgeon with limited experience (336), as was the case in the present study (7). With correct lower placement of the staple line, a leak will do no harm in most instances, but with higher placement, the rectal luminal content may spread into the peritoneal cavity. Impaired wound healing at the staple line may be a result of nutritional status, smoking, alcoholic abuse, or steroid medication, but also immuno-compromised patients and patients with Crohn's disease may be at greater risk (339). Thus, training and supervising surgeons to perform PPH correctly is mandatory.

No incontinence or sphincter lesions were observed based on clinical measures (5,6). No significant differences were found in the resting and squeeze pressures or incontinence scores before and after haemorrhoidopexy or conventional haemorrhoidectomy (318,343,344). However, internal anal sphincter fragmentation has been shown to occur after using the PPH set and could be problematic as the patient ages (344). Long-term results after haemorrhoid-



The anoscope was pulled back (to produce a bigger doughnut) before the stapling instrument was fully closed and fired. A solid doughnut was then obtained.

ectomy have shown that impaired anal incontinence is common after the Milligan-Morgan procedure (345). After PPH, the patients may complain of faecal urgency during the first post-operative months.

RECURRENCE AFTER STAPLED HAEMORRHOIDOPEXY AND RE-STAPLING

The incidence of a recurrent prolapse following PPH has potentially prevented its full acceptance as a worthy alternative to excisional procedures. However, in a new randomized controlled study, the cumulative recurrence rates after 5 years were 18 % in the stapled hemorrhoidectomy group and 23 % in the Milligan-Morgan group ($p = 0.65$)(346). In the present study (6), the cumulative risk of re-operation was greatest in the first two years after the initial PPH (Fig. 4 (6)). Females were more prone to requiring re-intervention compared to males. To counteract an eventual residual prolapse, a minor change in the usual recommended technique for PPH was made from the beginning. After the stapler was introduced through the anoscope protecting the sphincter, the anoscope was released and pulled back over the stapling instrument to enable loose anorectal mucosa distal to the knotted purse-string suture to be pushed into the stapler housing without interference from the edge of the anoscope. The stapler was then fired after a controlling digit in the vagina to ensure the posterior wall was not entrapped in the stapler. This technique results in a more solid doughnut (344) and ensures better lift and anchoring of the anorectal wall. Thus, smooth muscle fibre was present in 95.7 % of the excised tissue rings (6), as desired (339), and similar to what other investigators found (347). Histological studies of doughnuts have confirmed that circular smooth muscle is found in 25-100 % of specimens (339). With this approach, the staple line was placed 2 cm above the dentate line (6). Using a purse-string suture line height at 4–5 cm and comparing patients by pre-operative and post-operative photography, Longo reported 91 % to be very good or good and 9 % to be sufficient or poor at 6 months. Despite these findings, no relapse was recorded (61).

Thirty-one patients were identified with prolapse after their initial PPH and re-stapled (6). A symmetric prolapse is most suitable for a second PPH. The initial surgical steps are the same except for placing the purse-string suture distal to the previous staple line, which is

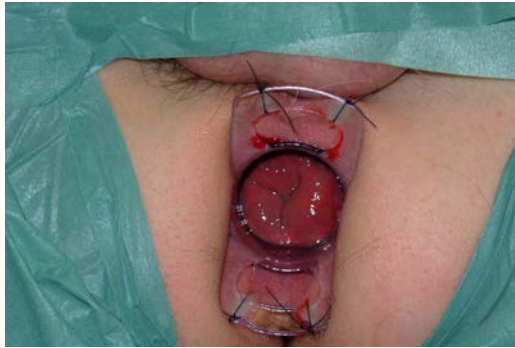
visible as a white circular fibrous line and now to be included in the resected tissue. The mean position of the new staple line was 1.5 cm proximal to the dentate line, significantly lower than the position of the first staple line (2.25 cm). As for the first PPH, the purse-string suture was placed deeply in the submucosa for a better fibrous healing and anchoring, but this obviously resulted in more pain. The re-stapled patients showed as good a surgical anatomical result (normal anus) as the patients who underwent only one PPH (6). Two patients had a bleeding episode, but no other complication, such as stenosis, infection, or incontinence, has been observed in the re-stapled patients. To date, we have performed more than 2,000 PPHs with a low rate of re-operations in line with others (329). This could be due to the patients having a lower grade of haemorrhoids, or to an improved surgical technique and skill, but it may also be related to the equipment.

The patients were recommended to permanently follow a high fibre, low fat diet, pursue physical activity to improve colonic and rectal function, and to avoid straining post-operatively. Patient satisfaction was high at all follow-up visits, irrespective of the number of operations performed, which is in accordance with other studies (331,348,349). Patient satisfaction significantly correlated with the appearance of a normal anus and no prolapse (6).

INNOVATIVE INITIATIVES

In 1990, Allegra developed a method in which a circular stapler was used to perform a haemorrhoidectomy and simultaneous vascular transection of the haemorrhoidal cushions. The method involved the placement of a rectal purse-string suture and the insertion and actuation of a stapler (350). In addition, the stapled transanal excision of an internal mucosal prolapse was reported in 1997 (351,352) and adopted shortly thereafter for treating haemorrhoids (61). In this very beginning of the PPH era, I also used anal specula to retract the anal sphincter. Later, a special PPH kit (Ethicon Endo-Surgery, Inc., Cincinnati, OH, U.S.) was introduced, facilitating the placement of the purse-string suture using a suture anoscope and providing safer insertion of the stapler through an anoscope protecting the sphincter. The majority of PPH performed in the present studies used the PPH33-01 stapler. A recent trial has shown that intraoperative bleeding from the staple line and post-operative

A longitudinal anoscope now used in patients with a deeply located anus and/or a short distance between the ischial tuberosities (designed by the author).



pain at defecation can be significantly reduced by using the new PPH33-03 stapler compared to the PPH33-01 (353). Others have manufactured and used a four component advanced anoscope (354). The innovation here was a butterfly-shaped anoscope, which could be placed correctly through the sphincter better than a circular anoscope in patients with a deeply located anus or a small distance between the ischial tuberosities. At the same time, and without knowing this, I converted the original anoscope into the butterfly shape by local handicraft for vertical placement.

The placement of the purse-string suture seems to be crucial to the results of PPH. Longo (1998) started the suture at 4–5 cm from the dentate line and reported the average minimum distance between the suture and the dentate line after the completion of the PPH to be 22 mm. The staple line in the present study was located at 2 cm in both sexes, except for the patients with a second PPH, who had a mean position 1.5 cm proximal to the dentate line. This lower staple line correlates with higher average daily or peak pain (6) and an inverse relationship has been shown between post-operative pain and the distance of the anastomosis from the dentate line (355). This relationship was highlighted in a recent study, in which patients with a staple line higher than 22 mm above the dentate line required a significantly shorter duration of pain management (356). In addition, the height of the staple line was inversely related to a return to work, but otherwise the staple line position was not a significant predictor of post-operative complications. Recurrent prolapse occurred in 10 % of the cases. Five patients in the present study experienced prolonged pain and urgency (6) and may have had staples retained in the sphincter or puborectalis muscles for a long period of time (357). Longo recorded complete expulsion of the staples in 88.8 % of cases within 30 days (61). This may be because of a rather superficial placing of the purse string suture, with 38.9 % smooth muscle present in the specimens (61). Others have modified the original stapling kit to facilitate the correct placement of the purse-string suture, which has been tried in nine patients (358).

The amount of tissue removed at the correct height clearly seems to be of ultimate importance to the outcome of the operation. Even Longo carried out two parallel purse-string sutures if the prolapse was more than 3 cm (in 59 of 144 cases) (61), a technique that revealed greater doughnuts (355). Double-purse string stapled haemorrhoidopexy was followed by a 7 % recurrence after long-term follow-up (359). Others have recommended a belt-loop stitch

placed diagonally opposite the purse-string knot to encompass as much tissue as possible in the stapler house (360) or to supply additional traction sutures 1 cm distal to the purse-string suture (361). Two successive PPH in the same patient during the same operative session, aimed at excising a wider segment of prolapsed mucosa, have been rare (352), though it has been demonstrated being feasible in a porcine model (362). By leaving an approximately 1 cm ring of mucosa between the two staple lines, no significant changes in blood flow, collagen levels, or the histopathological picture of the mucosal ring between the staple lines and specimens from areas external to the staple lines were observed after one month; no anal stenosis was seen in any of the pigs. A large haemorrhoidal prolapse was recently overcome by using a quite different technique with two staplers in accordance with the STARR (Stapled TransAnal Rectal Resection) technical criteria. The overall failure rate of residual plus relapses in 83 patients was 9.6 % (363). In an effort to further control or adjust the volume of resected haemorrhoidal tissue, a new mucosal impalement device has been investigated in a porcine model (364). The technique does not use a purse-string suture. Instead, the stapler rod is filled with a washer that has spikes on the outer rim. After placing the opened stapler into the rectum, the washer is manually advanced towards the anvil, gripping the inward ballooned mucosa and stabilizing it against the anvil. The stapler is then fired, opened, and removed. The authors concluded that this new device might have a potential for use in the treatment of haemorrhoidal disease.

Until recently, the stapler commonly used for a PPH accommodated a set volume of tissue within its housing, which the variants of the original technique, including the present method (6), have tried to increase. A new stapler has been introduced (EEA, Covidien, U.S.), and I was involved in the design. The new stapler differs from the previous type of stapler in that the rod has three openings. After inserting the detachable anvil proximal to the purse-string suture, it is knotted loose around the centre rod, and the ends of the suture are passed through chosen openings and knotted tightly to secure the tissue to the centre rod. The anvil is then assembled with the stapling instrument, closed, and fired. After using the stapler in some cases, this new device seems to create a larger doughnut, but there is no other evidence to support this at this time.

Economic analysis of conventional haemorrhoidectomy and stapled haemorrhoidopexy showed that the cost of the staple gun is offset by the lower average length of stay and theatre time for conventional haemorrhoidectomy (365). Moreover, patients undergoing PPH will return to normal activities, including work, quicker.

Transanal haemorrhoidal dearterialisation (THD) also known as haemorrhoidal artery ligation (HAL) is another innovative technique to treat haemorrhoids using a specially designed proctoscope for Doppler-guided ligation of the haemorrhoidal arteries (366). The recurrence rate was considerable in the initial studies, especially when treating grade III and IV haemorrhoids. Subsequently, the operation has been modified to achieve a combination of haemorrhoidal artery ligation and proctoscopic assisted transanal rectal mucopexy of the prolapsing tissue (rectoanal repair: RAR) (367). As a result, initial

high recurrence rates were lowered to 10.5 % (368). The overall recurrence rate after THD at one year or more was for bleeding 9.7 %, and for pain at defecation 8.7 % (369).

In a recent randomized study, patient with third degree haemorrhoids were allocated to THD or PPH (370). There was no statistical significant difference in recurrence between the groups (14 % vs. 7 %). Likewise, there was no significant difference in postoperative pain.

Until now, life-threatening complications have not been reported after the HAL/RAR-operation. The reasons may be that HAL/RAR is a lesser invasive procedure than PPH, but also that many fewer operations have been performed.

Thus, the skill of the surgeon is to tailor the operation to the individual by their choice of technique as no case of haemorrhoids is the same.

Haemorrhoids (from Greek: haema = blood, rhoos = flowing) are mentioned in ancient medical writings from every culture, including Egyptian, Babylonian, Hindu, and Greek, the latter by Hippocrates (371). Many medical treatments and advice have been advocated, including prayer to the patron saint of haemorrhoidal sufferers, St. Fiacre, an Irish priest. Bothersome haemorrhoids may also have had a serious impact on history. Napoleon suffered from constipation and haemorrhoids throughout his life (372). Unfortunately, on the day of the battle at Waterloo, Napoleon seemed to have “une crise haemorroïdale”, that is thrombosed haemorrhoids, which may have affected his generalship that day (372).

Surgical treatment of haemorrhoids in ancient times was mostly by burning iron, and later by cautery and excision. The stapling technique now used has revolutionized the surgical treatment of haemorrhoids.

FUNCTIONAL FAECAL RETENTION: A COMMON CAUSATIVE FACTOR IN COLON, AND ANORECTAL DISEASES

COLONIC CO-MORBIDITIES

During surgical training and in textbooks, I was educated to look at appendicitis, constipation, IBS, and haemorrhoids as completely separate diseases. Therefore, I was surprised, when in my research, I came across the work of the surgeon and medical researcher Denis P. Burkitt (1911-1993). Burkitt served as an army doctor during the Second World War in Africa. He realized that colon cancer occurred at a much lower incidence in Africa than Europe and America (373), and that white Americans and African-Americans (immigrated) had equal rates of colon diseases and appendicitis (314). In addition, diverticular disease, adenomatous polyps, appendicitis, colitis, and haemorrhoids were all rare in these populations in which cancer of the bowel was rare and occurred with the highest incidence in areas in which bowel cancer was most prevalent (373,374). Historical evidence suggests that most of these diseases were rare, even in the Western world, before the 20th century, after which the prevalence of each has greatly increased. Worldwide, 945,000 new cases of colorectal cancer occur yearly, and it is the second most common tumour in developed countries (375). Denmark has reported a 42.0 % increase in colorectal malignancies since 1978, to 4,258 new cases

in 2009, 66.3 % of which have a colon tumour (National Board of Health in Denmark). In Africa and Asia, most of these diseases first appeared or became common in the upper socioeconomic groups and urbanized communities. Epidemiological studies have recognized that constipation increases the risk of colon cancer (376,377,378). Almost a hundred years ago, Lane was convinced that cancer was the last stage in a sequence with chronic intestinal stasis (379). Many of these diseases are characteristic of modern Western civilization and are not only associated geographically, but also are frequently associated with one another in individual patients (108,374,380,381). This association was also seen in the present studies: haemorrhoids occurred in every second patient with a bowel disorder, and significantly increased with age (1,2). Notably, in the first study, right-sided colon diverticula occurred in 16 % of the patients and left-sided in 42 % (1), whereas in the second study 20.5 % of the patients had left-sided diverticula and 7.6 % had right-sided diverticula (2). The occurrence of colon diverticula significantly correlated with increased age, but no significant correlations were found with prolonged CTT or faecal load (2). Epidemiologic studies have found that the risk of left-sided colorectal cancer seemed to be increased in patients with diverticulosis and it significantly rose according to the length of follow-up. The risk of left-sided colorectal cancer was even higher in those patients with a previous history of diverticulitis (382,383). However, other studies have failed to confirm these observations (384). A special observation was that the presence of sigmoid diverticula was associated with an increased risk of a right-sided colon cancer (383, 384).

One of the main concern of patients with IBS is could there be a risk of developing organic disease, especially cancer. In a follow-up of IBS patients from the United Kingdom General Practitioners Database, an increased risk of colorectal tumour (adenoma/cancer) was found during the first year after an IBS diagnosis; after the first year the risk of a colorectal tumour was closer to that in the general population (385). Very recently, a Danish nationwide cohort study has shown that the risk of colon and rectal cancer was increased in the first year after an IBS diagnosis (386). They explain their findings because of overlapping symptomatology between the two diseases. However, this does not agree with establishing an in hospital diagnosis of IBS by exclusion of other diseases, especially cancer, after investigative procedures.

Appendicitis is also a colonic co-morbidity that occurred at a high rate of 29.2 % in the present studies (ad hoc data (2)), and the disease was previously shown to occur antecedent to an increased incidence of cancer in the colon and rectum (387).

Taken together, the results strongly indicate that environmental factors must be primarily responsible for the diseases considered here. The main environment of the colonic mucosa is the faecal content of the bowel, and in the colon and rectum, this is largely determined by undigested fibre in the diet. As a common cause may be suspected for diseases constantly associated with one another, evaluating the amount and distribution of faeces in the colon seemed wise. Thus, the present studies were initiated to create a picture of the faecal content during its passage or arrest in the bowel by meas-

uring the CTT and faecal load, as well as making clinical observations in patients with bowel disorders, appendicitis, and haemorrhoids (1,2,3,4,6). The findings were remarkable in that much more faeces was found in the colon than expected. A significant factor may be that man adopted a vertical posture during evolution, facilitating the formation of, for example a faecal reservoir in the right colon. The ascending colon normally receives a mixed liquid chyme from the ileum. The watery waste material then moves forward, excess water is absorbed, and the stool becomes semi-solid as it moves through the descending colon. However, faecal reservoirs were palpated and radiologically shown in the right and left colon segment in both patients and controls (2,4), in the same areas bearing the highest incidences of adenomatous polyps and malignancies (388). With the size of the present patient series (1,2), only a few neoplastic lesions could be expected. In fact, a total of four malignancies and 25 polyps were identified in 532 patients, which is a much higher incidence than the 0.8 per 1,000 inhabitants for colon cancer in Denmark. In this context, the prominent symptoms of bowel cancer, such as abdominal pain and bloating, and defecation disorders (388) are the same as for functional bowel disease (1,2). These diseases and colon cancer have predominance among women, whereas rectal cancer occurs with a higher frequency in male patients. Even with the passage of faeces, the load seems to be rather consistent in an individual, as shown by the same observations at 48 h and 96 h (2), and before and after appendectomy (4). In control persons, a significant decrease in distal faecal load and CTT was seen with increasing age. In patients and controls, the right-sided faecal load was significantly greater than the left and distal faecal load (2,4).

This evidence from the present studies supports the concept that general factors act on the bowel mucosa to produce neoplasia, benign or malign, and they must be located within the faeces. As described earlier, constipation with delayed transit increased the concentrations of potentially pathogenic microorganisms, inducing stimulation and suppression of the immune system. Also, mildly increased bacterial counts were more common in patients with IBS with an increased number of inflammatory cells in the colonic mucosa. This condition could play a role in colorectal cancer development, since chronic inflammation of the colonic mucosa is being widely regarded a risk factor for cancer onset (389). Patients with a heavy faecal load and prolonged CTT may run a cumulative risk of developing neoplastic lesions, but patients with a normal CTT, or even asymptomatic persons with faecal retention, also bear a risk.

Although acute appendicitis has been and still is the most frequent surgical emergency disease in Western countries, no effort has been made to trace the origin of an obstructing faecalith before now in the present study (4). The study had relatively limited numbers of patients and controls but should have, as calculated, used greater numbers to extend the higher CTT and faecal loads observed in appendectomized patients to statistical significance. However, other observations point to colonic content as a decisive factor in the genesis of acute appendicitis. Thus, patients previously appendectomized who now present with a functional bowel disorder exhibit a significantly higher CTT compared to patients who did not

have this operation (2). These patients had a much higher appendectomy rate than the general population, and an even higher rate when having a redundant colon with prolonged CTT. A recent study showed that recurrent abdominal pain, chronic constipation, and a family history of appendectomy are significantly more frequent in appendectomized children (312). In addition, appendicitis has been shown to occur antecedent to an increased incidence of cancer of the colon and rectum (387). At this point, acute appendicitis seems to be the first sign in a series of colon events, when viewed from a life perspective. A functional bowel disorder is likely to occur with later manifestations of diverticular disease, benign and malign neoplasia, and anal diseases such as haemorrhoids and gradually transition from a primary functional disease into specific organic diseases.

INTERVENTION AND PREVENTIVE MEASURES

Burkitt recorded over a thousand transit times among various ethnic groups, showing that fibre-deficient diets are associated with prolonged transit times and small daily stool that is voided only with effort (390). Using Hinton's method (29), UK boarding school pupils living on an institutional diet along with cakes, sweets, etc. had a mean transit time of 76.1 h compared to a mean 33.5 h for rural school-children not yet supplementing their diet with Western-type processed foods. Whatever the diet, there was found an inverse relationship between daily stool weight and transit time. Astronauts make use of these observations when fed a diet almost free from fibre, resulting in constipation with five to six days elapsing between bowel actions (391). Dietary fibre intake has been advocated as far back as 1851 (392) and been shown to shorten CTT (46,121,154). The longer colon as demonstrated in Africans (131) is probably then without influence. Recently, a multicentre epidemiological and nutritional study investigated the associations between dietary fibre intake and cancer (393). Dietary fibre was inversely associated with colorectal cancer and did not differ by age and sex. Other large studies showed that the intake of vegetables and fruit is associated with a lower risk of colon cancer, more than for rectal cancer (394,395,396,397,398). The meat and potatoes factor was associated with an increased risk in both men and women (397,398). A risk of rectal cancer seems to differ within racially diverse populations. A high fat/meat/potatoes pattern was observed in both Whites and African-Americans, but was only positively associated with rectal cancer risk in Whites (399). The vegetables/fish/poultry and fruit/whole grain/dairy patterns in Whites had significant inverse associations with risk. In African-Americans, a positive dose-response was seen for the fruit/vegetable pattern and an inverse linear trend for the legumes/dairy pattern (399). Lately, the intake of dietary fibre, especially from cereal foods or whole grain has been shown to be associated with a lower incidence of colon and rectal cancer (400,401). One mechanism may be as demonstrated in the present studies that dietary fibre accelerates the passage of faeces (CTT) and reduces faecal load and thereby decreasing carcinogen exposure. This is in line with a recent meta-analysis that showed that a high fibre intake is inversely associated with the risk for colorectal adenoma, the precursor of colorectal cancer (402). The same mecha-

nism may be associated with acute appendicitis from a faecolith and a fibre-rich diet may be preventable, since meat eaters have a higher risk of an ensuing appendicitis (403).

Good evidence is available that physical activity reduces the risk of colon cancer (164). Physical exercise is considered a voluntary activation of the skeletal muscle leading to short-term effects (minutes or hours), whereas physical activity is considered as repetitive exercise periods leading to long-term effect (days, months, or years). Several studies have indicated an inverse relationship between physical activity and the risk of colon cancer (164). Some studies have found accelerated CTT after physical activity, whereas others have observed no overall effect (164). Running specifically has been shown to accelerate CTT in studies on the effect of exercise on gut motility (163,165), whereas other studies did not find that running alters small bowel or colon motility (165).

At the time the present studies were initiated, an effect of physical activity on constipation seemed likely (164). Also, regular exercise reduces faecal levels of calprotectin, indicating diminished gut inflammation (389). The defecation patterns of runners indicate less firm stools, with higher frequency and stool weight than inactive controls (164). Along the same line, an inverse relationship had been shown between physical activity and the occurrence or risk of diverticular disease (164). In addition to these reports, physical activity may inhibit muscle loss, improve appetite, and improve general well-being via positive mood changes (164). It may be inferred from the present studies that regular physical activity accelerates colon transit and reduces faecal retention.

In fact, the interrelationship between energy intake, energy expenditure and specific physical activity requirements for current humans remains very similar to that originally selected for Stone Age men and women who lived by gathering and hunting. However, technological achievement and social organization disrupted this basic relationship for contemporary humans. In today's affluent nations, there is no longer an obligatory link between the food we eat and the energy we expend. Mechanization has reduced work-related physical exertion and recreational pursuits have become more sedentary (404). However, comparisons of mitochondrial DNA from diverse ethnic groups indicate that the genetic constitution of contemporary men and women has changed relatively little over fifty millennia despite the enormous societal changes associated with agriculture and industrialization. Hence, the relationship between energy intake, energy expenditure, and specific motor activity is still that originally selected for Stone Agers living in a foraging environment (404). Thus, it seems desirable to return to physical activity patterns for which our genetically determined biology was originally selected.

Physical activity is also associated with reduced breast cancer risk (405). Dietary fibre from cereals is inversely associated with a risk of breast cancer, and epidemiological studies show that fibre from cereals and fruit may be protective (406,407). When viewed in the context of constipation measured by self-reported bowel movements frequency (no measure of CTT), constipation was not significantly associated with increased risk, and women with very frequent

bowel movements had a non-significant decrease in breast cancer risk (408). However, a significant positive association with dysplasia was found in nipple aspirates of breast fluid from women with severe constipation (409), and that women with abnormal cytology have an increased risk of breast cancer was later confirmed (410). We found no significant correlations between a prolonged CTT or faecal loading and the occurrence of breast cancer (2). Nevertheless, the above studies do support the hypothesis that a link exists between bowel motility (and faecal load) and breast cancer risk.

In the U.S. and most Western countries, diet-related chronic diseases represent the single largest cause of morbidity and mortality and are rare or nonexistent in hunter-gatherers and other less Westernized people. With the advent of agriculture, novel foods were introduced as staples for which the hominin genome had little evolutionary experience. More importantly, food processing procedures were developed, particularly following the Industrial Revolution, which allowed for quantitative and qualitative food and nutrient combinations that had not previously been encountered over the course of hominin evolution (411). Increasingly, clinical trials and interventions use dietary treatments with nutritional characteristics similar to those found in preindustrial and preagricultural diets.

The importance of combining physical activity (> 30 min per day) with other lifestyle factors, such as diet (> 600 g fruit and vegetables per day, >= 3 g dietary fibre per MJ dietary energy, <= 500 g red and processed meat per week, <= 30 % of total energy from fat), alcohol consumption (<= 7 and <= 14 drinks per week for women and men, respectively), and no smoking, considerably reduced colorectal cancer risk (412). The principle of a fibre-rich diet and physical activity were used here as an intervention in patients with functional bowel disorders (1,2). However, diet, meal planning, and physical activity were assumed too weak a combination to stimulate colonic motility in these patients. Thus, a prokinetic drug was added, resulting in a significant decrease in the CTT and faecal loading towards normal values. Consequently, major abdominal symptoms such as pain and bloating disappeared and the patients' defecation patterns improved significantly (2).

The spread of sitting toilets at the end of the 19th century gave ordinary people, now sitting on a porcelain throne, the same dignity previously reserved for kings and queens. However, this new posture may be a co-factor in building faecal retention reservoirs. For hundreds of thousands of years everyone used the squatting position for the evacuation of faeces (and childbirth). Squatting, compared to sitting, relaxes the puborectalis muscle and straightens the anorectal angle (211). Moreover, the weight of the torso presses against the thighs, possibly squeezing the caecum and the sigmoid colon. These events are opposed when sitting on a toilet and straining, which may result in faecal retention. Thus, in a volunteer-study both the time needed for sensation of satisfactory bowel emptying and the degree of subjectively assessed straining in the squatting position were reduced significantly in all persons compared to sitting positions (413).

Supporting evidence from different studies, including the present, makes it possible to form a picture of how unhealthy faecal re-

tention emerges. The lifestyle of Western civilization leads to the retention of faeces starting in childhood. Many of these individuals will develop abdominal and defaecatory symptoms and become patients with functional bowel disorders. Thus, a considerable proportion of the population with faecal retention, with or without significant symptoms, may have a higher risk of developing appendicitis, diverticular disease, benign or malign neoplasia, and haemorrhoids over time.

Burkitt proposed "a common cause" for constipation, colon diverticula, cancer, appendicitis, and haemorrhoids. The actual results of the present studies support this unifying theory for these colon diseases, in which the functional retention of faeces may be the common cause.

SUMMARY WITH CONCLUSIONS

The present studies explored whether faecal retention in the colon is a causative factor in functional bowel disease, appendicitis, and haemorrhoids. Faecal retention was characterized by colon transit time (CTT) after radio-opaque marker ingestion and estimation of faecal loading on abdominal radiographs at 48 h and 96 h.

Specific hypotheses were tested in patients (n = 251 plus 281) and in healthy random controls (n = 44). A questionnaire was completed for each patient, covering abdominal and anorectal symptoms and without a priori grouping. Patients with functional bowel disorders, predominantly women, had a significantly increased CTT and faecal load compared to controls. The CTT was significantly and positively correlated with segmental and total faecal loading. The faecal load was equal at 48 h and 96 h, mirroring the presence of permanent faecal reservoirs. In these first clinical studies to correlate bowel symptoms with CTT and colon faecal loading, abdominal bloating was significantly correlated with faecal loading in the right colon, total faecal load, and CTT. Abdominal pain was significantly and positively correlated to distal faecal loading and significantly associated with bloating. A new phenomenon with a high faecal load and a normal CTT was observed in a subset of patients (n = 90), proving faecal retention as hidden constipation.

The CTT and faecal load were significantly higher in the right-side compared to the left and distal segments. Within the control group of healthy persons, the right-sided faecal load was significantly greater than the left and distal load. The CTT and faecal load significantly positively correlated with a palpable mass in the left iliac fossa and meteorism.

Cluster analysis revealed that CTT and faecal load positively correlated with a symptom factor consisting of bloating, proctalgia and infrequent defecation of solid faeces. On the other hand, CTT and faecal load negatively correlated with a symptom factor comprising frequent easy defecations, repetitiveness, and incompleteness with solid or liquid faeces. The majority of patients with a heavy faecal load but normal CTT had repetitive daily defecation, mostly with ease and with altering faecal consistence. Flue-like episodes co-existed in symptom factors with abdominal pain and meteorism, and

these symptoms together with a palpable right iliac fossa mass and tenderness, and in other factors with seldom and difficult defecation, and with epigastric discomfort and halitosis.

Patients with seldom and difficult defecation of solid faeces experienced abdominal pain significantly more often and presented a palpable mass in the right iliac fossa with tenderness and meteorism. The CTT was significantly prolonged and faecal load significantly increased. In patients with a normal CTT and increased faecal load, only patients with abdominal pain had a significant correlation between faecal loading and bloating. CTT and faecal load were shown for the first time to increase significantly with the number of colonic redundancies (colon length), which also resulted in significantly increased bloating and pain.

Intervention with a bowel stimulation regimen combining a fibre-rich diet, fluid, physical activity, and a prokinetic drug was essential to proving that abdominal symptoms and defecation disorders are caused by faecal retention, with or without a prolonged CTT. The CTT was significantly reduced, as was faecal load. Bloating and pain were reduced significantly. The defecation became easy with solid faeces, towards one per day and with significant reductions in incompleteness and repetitiveness. Proctalgia and flue-like episodes were significantly reduced. The intervention significantly reduced the presence of a tender palpable mass in the right fossa and rectal constipation. In patients with a normal CTT but increased faecal load, the intervention did not significantly change the CTT or load, but bloating and pain were significantly reduced, just as defecation improved overall.

The novel knowledge of faecal retention in the patients does not explain why faecal retention occurs. However, it may be inferred from the present results that a constipated or irritable bowel may belong to the same underlying disease dimension, where faecal retention is a common factor. Thus, measuring CTT and faecal load is suggested as a guide to a positive functional diagnosis of bowel disorders compared to the constellation of symptoms alone.

Thirty-five patients underwent surgery after being refractory to the conservative treatment for constipation. They had a significantly prolonged CTT and heavy faecal loading, which was responsible for the aggravated abdominal and defaecatory symptoms. The operated patients presented with a redundant colon (dolichocolon) significantly more often. These patients also had an extremely high rate of previous appendectomy. Twenty-one patients underwent hemicolectomy, and 11 patients had a subtotal colectomy with an ileosigmoidal anastomosis; three patients received a stoma. However, some patients had to have the initial segmental colectomy converted to a final subtotal colectomy because of persisting symptoms. Six more subtotal colectomies have been performed and the leakage rate of all colectomies is then 4.9 % (one patient died). After a mean follow-up of 5 years, the vast majority of patients were without abdominal pain and bloating, having two to four defecations daily with control and their quality of life had increased considerably.

A faecalith is often located in the appendix, the occlusion of which is responsible for many cases of acute appendicitis, which is infrequent in all except white populations. An effort to trace the origin

of the faecalith to faecal retention in the colon was made in a case control study (56 patients and 44 random controls). The CTT was longer and faecal load greater in patients with appendicitis compared to controls, though the difference was not significant. Power calculations showed that more patients were needed to reach statistical significance for these parameters. The presence of a faecalith was most often associated with a gangrenous or perforated appendix. No significant differences were found between the CTT and faecal load of patients who had or did not have a faecalith. However, the right-sided faecal load was significantly higher than the left and distal load.

Haemorrhoids are often a consequence of constipation and defaecatory disorders and were found in every second patient with functional bowel disorders. The present studies are the first Danish reports of a novel operation to cure this disease, stapled haemorrhoidopexy (n = 40 and 258 patients). The majority of patients had prolapsed haemorrhoids, and the durability of procedure was confirmed with a follow-up of up to 5 years, meaning a normal anus. The operation time was short, post-operative pain was low, and recovery was rapid. No incontinence was observed, and patient satisfaction was high and significantly correlated with the appearance of a normal anus without prolapse. The cumulative risk of re-operation was greatest in the first 2 years after the stapled haemorrhoidopexy. Patients with persisting haemorrhoidal prolapse had the procedure repeated with results as good as those obtained in the rest of the patients. It was shown in a statistical model that the preoperative severity of haemorrhoidal disease and the immediate postoperative result contributed significantly to predicting the outcome that is the durability of the operation.

The most frequent post-operative complication was bleeding requiring surgical haemostasis. One serious complication occurred after an anastomotic leak from a highly placed anastomosis, resulting in retro rectal, retro- and intra-peritoneal, and mediastinal gas. The patient recovered after conservative treatment and without surgical intervention. The stapling technique now used has revolutionized the surgical treatment of prolapsing haemorrhoids.

Finally, a common cause may be suspected for diseases constantly associated with one another. Epidemiological evidence has recognized that constipation, diverticulosis and IBS increase the risk of colon cancer (and adenomas), diseases exceedingly rare in communities exempt from appendicitis. Haemorrhoids are a colonic comorbidity as well. Notably, the patients with a functional bowel disorder had a much higher rate of a previous appendectomy than the background population. In addition, the patients who had previously had an appendectomy had a significantly longer CTT compared to patients, who had not. The data points to the involvement of faecal retention in the origin of faecaliths and, thus, acute appendicitis. Faecal reservoirs were shown in the right and left colon segments in both patients and controls, which are the same areas bearing the highest incidences of adenomatous polyps and malignancies. Familial colorectal cancer occurred significantly more often in patients who had a higher faecal load than the controls. Four malignancies and 25 adenomas were identified. An increased faecal load in the colon with or without delayed transit will increase bacterial

counts and create a chronic inflammation of the colonic mucosa, which is a risk factor for cancer onset. A functional bowel disorder is then likely to occur with gradually transition from a primary functional disease into specific organic diseases. A diet rich in fibre and regular physical activity have a therapeutic and preventive effect on colorectal diseases associated with faecal retention.

A "common cause" was earlier proposed for constipation, colon diverticula, cancer, appendicitis, and haemorrhoids. The actual results of the present studies support this unifying theory for these diet-related diseases, in which the functional retention of faeces may be the common cause.

WHAT THESE STUDIES ADD

After cautious interpretation of the results, the following new knowledge is recognized:

- Faecal retention occurs in a vast majority of patients with functional bowel disorders and causes abdominal bloating and pain.
- Faecal retention occurs with prolonged or with normal colon transit time (*hidden constipation*).
- Defecation patterns imperfectly mirror faecal retention and transit time.
- Faecal retention occurs even with normal defecation patterns.
- Proctalgia may arise from faecal retention in the rectum.
- Haemorrhoids occurred in every second patient with functional bowel disorders.
- In the case of an elongated colon (dolichocolon), colon transit time and faecal retention increase and aggravate symptoms.
- Intervention with a fibre-rich diet, supplementary fluids, physical activity, and a prokinetic drug accelerates colon transit and reduces faecal load, thereby relieving abdominal symptoms and improving defecation.
- Measuring colon transit time and assessing faecal retention is a better guide for a positive functional diagnosis than symptom criteria in patients with functional bowel disorders.
- Familial colorectal cancer occurs significantly more often in patients with bowel disorders, who had greater faecal retention than the controls.
- A right-sided faecal reservoir in the colon occurs predominately in patients with functional bowel disorders, acute appendicitis, and in healthy people with a normal colon transit time.
- An obstructing faecalith seems to be derived from faecal retention in the colon.
- Patients with functional bowel disorders are more frequently appendectomized and have a prolonged colon transit time.
- Patients operated for refractory constipation often have a redundant colon with prolonged colon transit time and faecal retention. These patients have a high rate of a previous appendectomy.
- A subtotal colectomy with ileosigmoidal anastomosis usually

results in relief of the defecations difficulties, abdominal pain, and bloating.

- Stapled haemorrhoidopexy for prolapsing haemorrhoids is a durable operation. In the case of a residual or persisting prolapse, re-stapling can be performed with the same good results.
- The actual results further support an earlier unifying theory of “a common cause” of diet-related colon diseases, such as constipation, colon diverticula, cancer, acute appendicitis, and haemorrhoids.

Faecal retention in the colon may be the common cause involved in these diseases.

FUTURE DIRECTIONS

No study has yet assessed colonic faecal loading and transit time in bowel disorder patients or healthy persons from countries that have not adopted a Western lifestyle. Comparing such studies from rural districts (Africa) with the present ones would be valuable. Because acute appendicitis seldom occurs in these areas, demonstrating the presence or absence of a right-sided faecal reservoir would be of particular interest for exploring the genesis of obstructing faecaloliths that lead to acute appendicitis. Investigating why a large proportion of the Western population has faecal retention in the colon and rectum is of great interest. Studies of colorectal motility and dysmotility and the brain-gut axis, together with behavioural studies, will hopefully provide a better understanding of the underlying malfunction. In addition, studies have to continue to investigate the cellular structure of the colon and rectum in patients with functional disorders compared to healthy persons. Exposure of the colon mucosa to faeces is a threat, and studies have to continue to determine the carcinogens present.

An elongated colon aggravates bowel symptoms and seems to be congenital. Because the same history of early symptoms occurs in mother and daughter, analyzing heredity is essential.

Electromyographic and pressure studies may reveal if it is the colon length in itself or motor disturbances, which are responsible for the slow transit with increased faecal load.

A cohort study will be needed to finally substantiate a causal relationship between faecal retention and colonic diseases, such as irritable bowel syndrome, constipation, appendicitis, colon diverticula, cancer, and haemorrhoids. Diet and physical activity have to be recorded specifically, and the colon transit time and faecal load of the cohort should be measured with intervals. Such studies would be ideal to prevent faecal retention.

The present studies were prospectively observational with intervention, including a prokinetic drug, domperidone, the effect of which has to be demonstrated further in a controlled clinical trial. Emerging therapies will include novel drugs with prokinetic properties.

Colon transit time and faecal loading are key investigations in

our daily practice, along with a thorough clinical history, for establishing a functional diagnosis in patients with a variety of abdominal and defaecatory symptoms. A need exists to clarify the use of colon transit time and faecal loading for the diagnosis and treatment of patients with gastrointestinal symptoms compared to a diagnosis relying solely on symptom criteria. As seen in the present studies, some patients with epigastric discomfort have faecal retention. These patients were formerly classified as having functional dyspepsia if a gastroscopy was normal, and they lacked a specific diagnosis. This track should be followed to determine if faecal retention is a significant factor in these patients.

In patients with refractory constipation, subtotal colectomy seems to currently be the safest surgical option for relieving severe defecation difficulties and accompanying abdominal pain and bloating, and to improve quality of life. Thus, the laparoscopic approach may be implemented to reduce post-operative pain, accelerate recovery, and achieve better cosmesis.

Stapled haemorrhoidopexy was introduced for the treatment of prolapsing haemorrhoids, but the technique may still be improved to secure a durable result without recurrence. Different types of stapling instruments appear to remove different sizes of doughnuts, and comparative trials are necessary to identify which stapler is preferred.

Informing and advising the population along the way is important because so many people are affected by functional bowel disorders and its co-morbidities, which are mostly environmentally acquired.

ACKNOWLEDGEMENTS

This research was supported in part by grants from the Legacy of Ellen Margrethe Cramer, from the Olga Bryde Nielsens Fund, from the Hoerslev Fund, and from the Research Funds in the Department of Surgery and the former Frederiksborg County. I wish to thank them all.

ABBREVIATIONS

Ad hoc data: New analyses for this thesis from the databases.

CTT: Colon Transit Time

HAL: Haemorrhoidal Artery Ligation

IBS: Irritable Bowel Syndrome

IBS-C: - /Constipation dominant

IBS-D: - /Diarrhoea dominant

IBS-A: - /Alternating

IBS-M: - /Mixed

IRA: Ileorectal anastomosis

ISA: Ileosigmoidal anastomosis

PFD: Pelvic Floor Dysfunction

PPH: Procedure for Prolapse and Haemorrhoids

QoL: Quality of Life

RAIR: Recto-Anal Inhibitory Reflex

RAR: Recto Anal Repair

SIBO: Small Intestinal Bacterial Overgrowth
 SNS: Sacral Nerve Stimulation
 STARR: Stapled Transanal Rectal Resection
 STC: Slow Transit Constipation
 THD: Transanal Haemorrhoidal Dearterialisation
 VAS: Visual Analogue Scale

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