Transanal endorectal pull-through for Hirschsprung Disease
– Outcome in relation to surgical approach, age and anal canal morphology

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Kjetil Juul Stensrud, Oslo, August 2016
LIST OF PAPERS

I. Stensrud KJ, Emblem R, Bjørnland K.  

II. Stensrud KJ, Emblem R, Bjørnland K.  

III. Rehman Y, Stensrud KJ, Mørkrid L, Bjørnland K, Emblem R.  

IV. Stensrud KJ, Emblem R, Bjørnland K.  
**ABBREVIATIONS**

ACL – anococcygeal ligament

AES – anal endosonography (ultrasound)

EAS – external anal sphincter

HEC – Hirschsprung associated enterocolitis

HD – Hirschsprung disease

IAS – internal anal sphincter

ICC – intraclass correlation coefficient

LEPT – laparotomy or laparoscopy assisted transanal endorectal pull-through

LM – longitudinal muscle layer

PACCT – the Paris Consensus on Childhood Constipation Terminology group

TEPT – completely transanal endorectal pull-through

TAA – transabdominal approach (Paper IV)

(laparotomy or laparoscopy assisted transanal endorectal pull-through)
**DEFINITIONS**

**Anal incontinence:** Involuntary leaking of stool or flatus.

**Anastomosis stricture:** A narrowing of the anastomosis requiring anal dilatations more than eight weeks postoperatively.

**Anococcygeal ligament (by endosonography):** A hyporeflective sector in the posterior midline of the EAS.

**EAS thickness (by endosonography, technical definition for this study):** The width of the moderately reflective zone surrounding the IAS, or when applicable, the distance between the interface reflection between the IAS and the longitudinal muscle and the interface reflection at the outer margin of the EAS (Fig. 2.1.1).

**Fecal continence:** The ability of being clean between bowel movements.

**Fecal incontinence:** Involuntary leaking of stool, requiring change of underwear or diapers.

**Fecal soiling:** Involuntary leaking of small amounts of stool, requiring change of underwear or diapers (Papers I and II).

**Hirschsprung associated enterocolitis (HEC):** Episodes of acute abdominal distension, fever and diarrhea.

**IAS thickness (by endosonography):** The width of the hyporeflective band surrounding the subepithelium (Fig. 2.3).

**Long segment HD:** Aganglionosis extending oral to the sigmoid colon.

**Mid anal canal (by endosonography):** The most cranial level at which the EAS forms a complete ring anteriorly.

**Resting pressure:** The lowest point of the slow wave fluctuation curve at rest.

**Sphincter defect (by endosonography):** Lack of normal sphincter reflectivity in a sector representing 15 degrees or more of the circumference.

**Squeeze pressure:** The maximum peak pressure of three voluntary squeeze events.
1. SUMMARY

Background:
Hirschsprung disease (HD) is a rare, congenital condition in which the ganglion cells of the enteric nervous system are absent in rectum and lower part of colon. HD usually manifests with obstructive bowel symptoms in the neonatal period, and these children are usually operated on within the first months of life. However, HD can also be diagnosed in older children with massive constipation. The treatment for HD is surgical removal of the aganglionic bowel segment. There are several different operative techniques.

Fecal incontinence and constipation are common problems after surgery for HD. The anal sphincters are important for fecal continence and may, theoretically, be impaired by surgery for HD. Anal endosonography (AES) and anal manometry are tools that may be used to examine the anal sphincters.

The aims of these studies were to evaluate the outcome after transanal endorectal pull-through for HD with special focus on bowel function, and to identify risk factors for sphincter defects and poor bowel function. Furthermore, we aimed to describe and discuss characteristics and postoperative results in the patient group with late diagnosed HD.

Patients and methods
All HD patients treated with transanal endorectal pull-through from 1998 to 2011 were invited to participate in these studies. Endorectal dissection was performed from below in all, contrary to the classic Soave technique. Colon and rectum was mobilized either via transanal dissection (TEPT) or through laparotomy or laparoscopy (LEPT). The aganglionic bowel segment was removed, and colon with ganglion cells anastomosed to the anal canal.

After surgery, complications and long term bowel function, especially fecal incontinence and constipation, were recorded. The anal sphincters were examined by AES to identify sphincter defects, and sphincter function was estimated by anal manometry measuring the pressure in the anal canal.

We also included children without HD to establish a reference for the endosonographic examinations.

Main results
Paper I: More than half of the patients (29/52) reported some form of fecal incontinence at least once a week, and one in five (11/52) was constipated. There was no significant difference in the rate of fecal incontinence or constipation after the
different operative approaches. However, the TEPT procedure seemed to be associated with an elevated risk of daily incidents of fecal incontinence. This possible association was further explored in paper IV.

**Paper II:** Eleven children had their HD diagnosis and surgery after the age of three years (late diagnosis). While severe early postoperative complications were rare in younger children (Paper I), major complications were reported in 5/11 patients with late diagnosis. Two patients had complications related to anastomotic leakage. The long term bowel function was similar after early and late diagnosis.

**Papers III & IV:** The anal sphincters could be visualized by AES in all healthy children and patients. In half of the patients (26/54), defects in the internal anal sphincter (IAS) were detected, more frequently after TEPT procedure. IAS defects were not seen in healthy children. We believe the IAS defects found in the patients represent scarring after surgery. Patients with IAS defects had higher risk of daily fecal incontinence. The manometry results were not correlated to the AES findings or long term bowel function.

**Conclusions**

Our results reveal that fecal incontinence is a frequent and severe problem after transanal endorectal pull-through for HD. Close long term follow-up of these patients is crucial. AES without anesthesia proved to be a useful supplement to clinical assessment. IAS defects were frequently detected and associated with daily fecal incontinence. The TEPT procedure seems to give more anal sphincter defects and thereby possibly more fecal incontinence than LEPT. Therefore, the preferred surgical techniques for HD in our department are now laparoscopy assisted procedures.

Patients with late diagnosis were more likely to have serious early postoperative complications. Based on these results, we now consider a perioperative diverting stoma in older HD patients with dilated colon.
2. INTRODUCTION

2.1. Anatomy of the anal canal and sphincters

Fig. 2.1.1 Anatomy of the anal canal
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2.1.1. Anal canal
The surgical anal canal extends from the proximal level of the levator ani muscle complex to the anal verge and is approximately 4 cm long in adults and shorter in children (Fig 2.1.1) [1,2]. In the lateral view, there is an angle between the rectum and the anal canal. This anorectal angle is maintained by a sling of the levator ani muscle complex, the puborectalis sling, running behind the high anal canal. The anatomic structures surrounding the anal canal vary throughout the canal. Therefore the canal is usually described at three levels, the high (proximal), mid and low (distal) anal canal. The high anal canal is lined with rectal mucosa (columnar epithelium) organized in longitudinal folds (anal columns), which terminate in the dentate line in the mid anal canal. The subepithelium is highly vascular proximal to the dentate line (submucosa) and
contains multiple sensory nerve endings. The low anal canal is lined by anoderm (modified squamous epithelium) and sparse subepithelium. The subepithelium is surrounded by a circular ring of smooth muscle fibers, the internal anal sphincter (IAS) and the voluntary controlled external anal sphincter (EAS). Between the IAS and EAS lays the continuation of the longitudinal smooth muscle layer (LM) of the rectum.

2.1.2. Internal anal sphincter (IAS)
The IAS is located within the bowel wall in the upper two thirds of the anal canal as a thickened continuation of the circular smooth muscle layer of the rectum and is absent in low anal canal (Fig 2.1.1). The IAS is innervated by the autonomic nervous system and the enteric nervous system. The normal IAS has a muscle tone at rest, and relaxes temporarily when the rectum is dilated (rectoanal inhibitory reflex) and during defecation [1]. Relaxation of the IAS is dependant of an intact enteric nervous system.

Fig. 2.1.2 Transverse Female pelvic floor and external sphincter (EAS), inferior view.
The EAS is adjacent to the perineal body, the transverse perineal muscles, the puborectalis sling of the levator ani muscle complex and to the anococcygeal ligament. (Reproduced from “Anal sphincter trauma”, 2007, Ch 1: “Anatomy of the perineum and the anal sphincter” by R.Thakar, fig 1.2a with kind permission from Springer Science and Business Media").
(© Springer-Verlag London Limited 2009.)
2.1.3. Longitudinal muscle layer (LM)
In the anal continuation of the LM of the rectum, the smooth muscle fibers are intermixed with striated muscle fibers from the puborectalis and with collagenous tissue. Fibers from the LM pass through the EAS to the perianal skin in the low anal canal (Fig 2.1.1) [2]. The function of the LM is unknown. Probably this muscle layer does not contribute to the anal canal pressure, but the LM might be involved in the defecation process.

2.1.4. External anal sphincter (EAS)
The EAS consists of circular striated muscle fibers. In the high anal canal, the EAS is intimately related to the puborectalis sling of the levator ani muscle (Fig 2.1.1). In the mid and low anal canal, the EAS is attached posteriorly to the coccyx through the anococcygeal ligament (ACL) and anteriorly to the perineal body. The transverse perineal muscles, the posterior part of the urogenital diaphragm, are adjacent to the anterolateral EAS in the low anal canal (Fig. 2.1.2) [2]. Even though the EAS consists of skeletal muscle cells, it maintains a constant tone and contributes to the anal resting pressure. The EAS contracts to maintain continence as a reflex response to rectal filling sensation or sudden increase in intraabdominal pressure (i.e. coughing) and relaxes during defecation. The EAS can also be voluntarily contracted for a limited period (squeeze) [1]. The EAS is innervated by somatic sacral nerves and functions independently from the enteral nervous system.

2.2. Bowel function

2.2.1 Normal bowel function
The intestines constitute a complex organ system with various functions including absorption of nutrients in the small intestine and water in the large bowel, propelling of the intestinal contents from the stomach to the rectum, storing of feces in the rectum, withholding of stools, and, when appropriate, defecation. The bowel also attends immune functions.

The term “bowel function” generally refers to the ability of feeling the urge to defecate, withholding stools, and having voluntary bowel movements without anal incontinence or constipation. Coordinated high-amplitude propagated contractions of the bowel’s circular muscle layer propel stool from the right colon towards the sigmoid colon. This antegrade peristalsis does not traverse through the rectum, which therefore serves as a “break” and a reservoir for the fecal content. Healthy adults have 6 to 12 peristaltic movements a day through the colon, while children have more [3]. The lower part of the rectum in a healthy human is inactive and empty most of the time [1,4]. The rectum reservoir fills slowly with feces delivered through the peristaltic movements. The anal sphincters remains automatically contracted as the rectum fills, constricting the anal
opening [1,4]. The highly vascular submucosa of the high anal canal may act as a cushion securing the anal canal closure [1,5]. The anorectal angle also contributes to stool withholding in the rectum [1]. When the degree of rectal filling is sufficient, the IAS relaxes temporarily as a result of the rectoanal inhibitory reflex. The stool may still be withheld in the rectum by reflexive and voluntary contraction of the EAS and the puborectalis sling, constricting the anal canal and reducing the anorectal angle. These mechanisms are depending on intact anal sensation and innervations, which also enable differentiation between solid and liquid stools and gas [6]. Rectal filling sensation and the urge to defecate are mainly initiated by sensory nerve endings in the anal canal submucosa when the rectal contents is pushed downwards dilating the high and mid anal canal. When in an appropriate place for defecation, the EAS and the puborectalis muscle may be voluntarily relaxed, and the rectum is evacuated by peristaltic contractions of the rectum [4].

2.2.2. Constipation

Constipation is a frequent problem in children. There is no simple and straightforward definition of constipation. Most definitions or diagnostic criteria involve hard stools and infrequent bowel movements. Many authors refer to the Rome II or Rome III criteria for functional constipation, defined by international pediatric working teams in 1999 and 2006 respectively (Table 2.2.1) [7,8]. In 2005 The international Paris Consensus on Childhood Constipation Terminology (PACCT) group defined chronic constipation in children, with similar criteria [9]. Constipation may be the result of either insufficient peristaltic movements through the colon (slow transit constipation) or a distal functional or anatomical obstruction (bowel outlet obstruction) or a combination of both [10]. In children, most cases of constipation are functional in nature [11], although cow’s milk allergy or intolerance, metabolic disorders or drug induced constipation should be ruled out. Rare congenital conditions, including spinal anomalies, sacrococcygeal terratoma, anorectal malformation or Hirschspunng disease (HD) are differential diagnoses in children with severe constipation. In patients with prolonged duration of constipation, liquid stool may perlocate around hard retained stool and pass involuntarily per anum. Furthermore, the fecal impaction in the rectum in untreated constipation may lead to dilatation and impaired sensation of the anal canal and thereby cause fecal incontinence. This paradox fecal incontinence in constipated patients has traditionally been called soiling or pseudoincontinence and may also be the presenting symptom of constipation [7,11].

Most constipated children can be successfully treated by dietary adjustments, including increased intake of water and foods rich in fiber, or by laxatives [10]. Some children need regularly enemas or surgery for constipation.
Table 2.2.1 Rome III Diagnostic Criteriaa for Functional Constipation in children

<table>
<thead>
<tr>
<th>Must include 2 or more of the following in a child with a developmental age of at least 4 years with insufficient criteria for irritable bowel syndrome:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Two or fewer defecations in the toilet per week</td>
</tr>
<tr>
<td>2. At least 1 episode of fecal incontinence per week</td>
</tr>
<tr>
<td>3. History of retentive posturing or excessive volitional stool retention</td>
</tr>
<tr>
<td>4. History of painful or hard bowel movements</td>
</tr>
<tr>
<td>5. Presence of a large fecal mass in the rectum</td>
</tr>
<tr>
<td>6. History of large diameter stools that may obstruct the toilet</td>
</tr>
</tbody>
</table>

a Criteria fulfilled at least once per week for at least 2 months before diagnosis

2.2.3. Fecal continence and incontinence

Fecal continence, the ability of being clean between bowel movements [12,13], is the result of a complex interaction of several anatomical and physiological mechanisms mentioned above. When one or more of these mechanisms are disturbed, true fecal incontinence may be the result.

The term fecal incontinence generally means “any involuntary loss of fecal material”, while anal incontinence also includes involuntary flatus [14]. Fecal incontinence may vary from total incapacity to withhold stools to occasional leakage of small amounts of stool or staining of underwear. That the term fecal incontinence implies such a wide variety of symptoms complicates and impedes systematic fecal incontinence reporting and comparison between studies. The term soiling has often been used to describe episodes of small leakage of liquid stools in patients with constipation [15]. However, soiling is an imprecise term with different interpretations, including staining of underwear, pseudoincontinence due to constipation and non specific fecal incontinence [16–18]. The PACCT group have recommended the term soiling to be discontinued and replaced with fecal incontinence [9].

True idiopathic fecal incontinence is rarely seen in children. When a child presents with fecal incontinence, pseudoincontinence due to constipation should be suspected [6]. True fecal incontinence and pseudoincontinence associated with constipation are well known problems in children with spinal anomalies or injuries. When performing surgery for anorectal malformations or HD, both the anal sphincters, the anal sensation, the rectum reservoir and the anorectal angle may be impaired [19]. Thus, true fecal incontinence, as well as pseudoincontinence, is a well known problem after surgery for these conditions.

In patients with pseudoincontinence due to constipation, the incontinence will resolve when the constipation is properly treated. Some children with true fecal incontinence after surgery or spinal anomalies or injuries can achieve continence by dietary
adjustments (constipating diet) or motility regulating drugs (e.g. loperamide), or by introducing regular bowel movements. However, a bowel management program with rectal enemas or antegrade colonic enemas is often warranted in patients with true fecal incontinence. A sigmoid colostomy is considered the last resort for patients with severe fecal incontinence not manageable by a bowel management program.

2.2.3. Scoring and classification of bowel function

In order to quantify fecal incontinence for clinical use and research, various scoring systems have been developed. In adults, St. Mark’s score and Wexner’s score are the most widely used [20–22]. These validated scores are based on 5-7 item questionnaires regarding anal incontinence symptoms and are usually used in a structured interview in a hospital setting.

Several pediatric surgeons have developed scoring systems to assess postoperative bowel function, including fecal incontinence, after anorectal surgery [15,17,19,23] (Table 2.2.2). Some of these scoring systems have also been adopted by others [15,24]. These include the Kelly clinical continence score [25], the Holschner clinical and manometric score [15] and the Rintala bowel function score (BFS) [26]. The Wingspread score was established by an international consensus group in 1984. In recent years, several authors have used the Krickenbeck score from the Krickenbeck consensus conference in 2005 [27]. The Wingspread and Krickenbeck scores are descriptive and do not provide a numerical continence score or bowel function score for each patient. While most scoring systems were established for scoring results after surgery for anorectal malformations, El Sawaf et al. have described a scoring system particularly for HD patients [19]. Furthermore, there are specific scoring systems for measuring disease specific quality of life in children with fecal incontinence [28,29]. In a review of different scoring systems for postoperative results after surgery for anorectal malformations in 2006, the authors concluded that none of the scoring systems were properly validated, and a specific instrument for measuring postoperative result could not be recommended [15].
<table>
<thead>
<tr>
<th>Year</th>
<th>Scoring system</th>
<th>Data collection</th>
<th>Assessed outcomes</th>
<th>Numerical score</th>
<th>Populated</th>
<th>Score</th>
<th>Population</th>
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</thead>
<tbody>
<tr>
<td>1972</td>
<td>Kelly</td>
<td>History, rectal exam</td>
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<td>No</td>
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<td>1983</td>
<td>Holschneider, modified</td>
<td>History, anal manometry</td>
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<td>Numerical score</td>
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<tr>
<td>1988</td>
<td>Wingspread</td>
<td>History</td>
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<td>Yes</td>
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<tr>
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<td>St. Mark's</td>
<td>Structured interview (7 items)</td>
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<td>Numerical score</td>
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<tr>
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<td>Questionnaire (7 items)</td>
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<td>Partially</td>
<td>ARM patients</td>
</tr>
<tr>
<td>1995</td>
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<td>Structured interview (6 items)</td>
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<td>Each item graded separately</td>
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<td>No</td>
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<td>Adults</td>
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<tr>
<td>2003</td>
<td>PICS</td>
<td>Questionnaire (39-42 items)</td>
<td>Bowel function and QOL</td>
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<td>Yes</td>
<td>HD &amp; ARM patients</td>
</tr>
<tr>
<td>2007</td>
<td>El Sawar</td>
<td>Structured interview (15 items)</td>
<td>Bowel function</td>
<td>Numerical score</td>
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<td>No</td>
<td>ARM patients</td>
</tr>
<tr>
<td>2007</td>
<td>Krickenbeck</td>
<td>Structured interview (3 items)</td>
<td>Bowel function</td>
<td>Each item graded separately</td>
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<tr>
<td>2008</td>
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<td>Questionnaire (7 items)</td>
<td>Fecal incontinence</td>
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<td>ARM patients</td>
</tr>
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<td>Questionnaire (5 items)</td>
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<td>Adults</td>
</tr>
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<td>Numerical score</td>
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<td>Yes</td>
<td>HD patients</td>
</tr>
<tr>
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<td>History, rectal exam</td>
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<td>Numerical score</td>
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<td>No</td>
<td>ARM patients</td>
</tr>
</tbody>
</table>

**Table 2.2.2** Scoring systems for bowel function and QOL. **HEC** - Hirschsprung associated enterocolitis, **QOL** - Quality of life.
2.3. Anal endosonography

Anal endosonography (AES) allows good anatomical evaluation of the anorectal region and adjacent structures and is currently the preferred method for assessing the structural integrity of the anal sphincters in adults. Identification of the anal canal layers and measurements of sphincter thickness by AES have been validated in adults by magnetic resonance imaging and anatomical dissection, and good inter-rater agreement has been demonstrated [30–33]. The endosonographic appearance of sphincter defects in women after childbirth has been thoroughly described [34,35].

The endosonographic appearance of the normal anal sphincters and the reference ranges of sphincter thickness in children are sparsely documented and with inconsistent results [36–39]. Anal sphincter defects have been described after surgery for anorectal malformations, and the extent of the muscle defects correlated with fecal incontinence [40]. AES might be useful in understanding and predicting fecal incontinence also after HD-surgery. Defects in both the IAS and EAS have been visualized by AES after the Duhamel procedure, and sphincter defects were associated with fecal incontinence [41,42]. The endosonographic appearance of the anal sphincters after a transanal endorectal pull-through procedure has not been described so far.

![Endosonographic image from mid anal canal in a boy.](image)

**Fig. 2.3 Endosonographic image from mid anal canal in a boy.**

The internal anal sphincter (IAS) can be seen as a hyporeflective (black) ring (arrow-heads). The zone with mixed reflectivity (arrows) surrounding the IAS represents the longitudinal smooth muscle layer and the external anal sphincter (EAS). The perineal body (PB) is seen anteriorly to the EAS.

2.3.1. Endosonographic appearance of the anal canal

In the anal canal, several more or less circular layers can be identified. The layers may be separated by the different reflectivity. In adults, hyperreflective (white) lines appear in the interface between structures of different texture. These interface reflections may be useful in distinguishing the different layers. The epithelium is not visible by AES. Thus the innermost layer of moderate reflectivity (grey) represents the subepithelium. The next layer, the IAS, consists of homogenous smooth muscle tissue and is visualized as a hyporeflective (black) circular band (Fig. 2.3). The IAS is surrounded by a broader zone of
moderate reflectivity, which previously was denoted the EAS. However, cadaver dissection and endosonographic studies have revealed that a considerable part of this zone represents the LM [30,33,43]. The interface reflections may be used to distinguish the EAS from the LM in adults.

AES has been performed considerably less in children than in adults. The appearance of the different layers has been assumed to be the same in the pediatric population. The IAS has been described as hyporeflective and the EAS as hyperreflective or of mixed reflectivity [36–38]. In one study, the structures of the anal canal were sometimes difficult to differentiate in children younger than 5 years [36]. The LM has been briefly mentioned in one study in children [37]. So far, the interface reflections have not been discussed in pediatric AES studies.

2.3.2. Anal sphincter defects and artifacts
Sphincter defects can be seen as a relatively hyperreflective sector in the IAS and a hypo- or hyperreflective sector of the EAS [42]. Scoring systems have been established for endosonographic sphincter defects in adult females after childbirth [44]. Similar scoring systems for sphincter defects in children after surgery are nonexistent. Artifacts i.e. areas of relatively hyporeflectivity within the EAS and even apparent sphincter defects may be seen in an intact EAS, and should not be misinterpreted as sphincter defects: In the high anal canal the EAS merges with the puborectalis muscle laterally and posteriorly, but not anteriorly (Fig 2.1.1). Furthermore, the EAS is shorter anteriorly in females [2]. Thus, there will be an apparent anterior EAS defect in the high anal canal in healthy individuals, and this may also be seen in the mid anal canal, especially in women and girls [37,45,46]. The ACL has been described in children as well as in adults as a hyporeflective sector in the posterior midline of the EAS in the mid and low anal canal [36,37]. The perineal body may be seen as a hyporeflective area anterior to the EAS in the midline in the mid and low anal canal (Fig. 2.3).

2.4. Anorectal manometry
Anorectal manometry has been widely used in the diagnostics of defecation disorders in adults and has also been performed in children for several years. Some pediatric centers use anal manometry as a supplement to rectal biopsies to diagnose HD [47–49] (Fig. 2.4). An anorectal manometry examination may give the following measurements: Anal resting pressure, anal squeeze pressure, length of the anal high pressure zone, rectoanal inhibitory reflex, and rectoanal pressure changes during attempted defecation. A full anorectal manometry examination is a time consuming procedure and depends on full cooperation from the patient and may, therefore, be difficult in children. Anal resting pressure, length of the anal high pressure zone and rectoanal inhibitory reflex can be measured while under general anesthesia without muscle relaxants. While some
anesthetic drugs lower the anal resting pressure [50], ketamine seems not to affect the resting pressure [51].

Some authors have used anal manometry and anal sphincter pressures as an early postoperative indicator for sphincter function when evaluating operative techniques [52,53]. However, there is little evidence concerning the association between anal sphincter pressures and long term continence in children [54,55].

2.4.1. Manometry equipment
The manometry equipment consists of an anorectal probe with one or more pressure transducers connected to an external unit which displays the pressure measures. Many systems also include a rectal balloon for dilating the rectum. Most probes have one rectal transducer near the tip and one or more transducers for measurements in the anal canal. Some recommend using a probe with at least six transducers in adults to assess the entire length and circumference of the anal canal simultaneously [56,57]. There are several different principles for measuring the pressure:

*Micro balloons:* In a micro balloon system, the probe consists of water or air filled micro balloons connected by tubes to an external unit. The pressure in the micro balloons located in the anal canal is transferred through the tubes to the external unit where the analogue pressure signal is converted to a digital signal and displayed.

*Water perfusion system:* In a water perfused system, the probe has channels continuously perfused with water. Like in the micro balloon system, the analogue pressure signal is converted to a digital signal in the external unit.

*Sleeve manometry:* In a sleeve manometry sensor, the water perfused side holes are incorporated in a silicone sleeve. A sleeve sensor measures the highest pressure within the sleeve.

*Micro tip catheter:* A micro tip manometry catheter is a probe with micro transducers converting the pressures to digital signals directly in the rectum and anal canal. This system has the advantage of smaller probe diameter and no moisture of the anal canal.

*High resolution manometry:* High resolution manometry is a novel technique that allows simultaneously retrieval of pressures from more than hundred sensor points distributed circumferentially along the anorectal probe. The output data are presented as a color map with different colors representing different pressures.

2.4.2. Anal resting pressure
Anal canal pressure is usually measured in mmHg. In older reports, cm H₂O was the most used unit. The anal resting pressure is the maximum pressure within the anal canal during rest (Fig. 2.4). The resting pressure usually shows cyclic variations with amplitude
of 1-25 mmHg in adults (slow waves). Sometimes, spontaneous variations in the resting pressure with amplitude of 30-100 mmHg in adults can be observed (ultra slow waves) [56]. The IAS accounts for most of the anal resting pressure, but the EAS also contributes. There are two different ways of measuring the resting pressure throughout the anal canal:

**Stationary pull-through:** The anal resting pressure is measured either simultaneously at different levels using a probe with multiple transducers or side holes or by repeated measurements at different levels of the anal canal. The anal canal pressure rises above the resting pressure if the examined person is unable to relax and when the probe is inserted or moved within the anal canal. Therefore, the probe should be in the same position for at least 10 seconds before the anal resting pressure is recorded [56].

**Rapid pull-through:** The probe is inserted through the anus to a level above the anal canal. The pressure is then continuously recorded while the probe is slowly withdrawn through the anal canal. By this technique, also the pressure profile and length of the high pressure zone can be measured. However, the resting pressure tends to be higher than measured by stationary pull-through due to movement artifacts.

**Fig. 2.4 Anal manometry with a two channel microtip catheter in a 9 year old girl with constipation.** One sensor (Pana) is placed in the anal high pressure zone and a reference sensor (Prec) is located in the rectum. The anal resting pressure is 45 mmHg and the squeeze pressure is 78 mmHg. After distention of a rectal balloon with 20 ml of air, there is a temporarily decrease of the resting pressure, representing relaxation of the internal sphincter due to the rectoanal inhibitory reflex, ruling out Hirschsprung disease.
2.4.3. Anal squeeze pressure
When resting pressure has been measured without anesthesia, and the probe is still located in the high pressure zone, the examiner can tell the patient to squeeze, as if holding back stool. The maximum anal canal pressure in this situation is denoted the anal squeeze pressure (Fig. 2.4).

2.4.4. Rectoanal inhibitory reflex
Still with one sensor in the anal high pressure zone and, preferably, a reference sensor in the rectum, the rectoanal inhibitory reflex may be provoked in healthy individuals. A rectal balloon is rapidly distended with 10-50 ml of air in adults and older children or 5-20 ml in neonates [47,48,56,57]. In prematures, 1-5 ml of air may be insufflated directly into the rectum without a balloon [58]. A normal rectoanal inhibitory reflex will cause a temporary decrease in the anal canal pressure (Fig. 2.4). A positive rectoanal inhibitory reflex may be defined as a drop of at least 5 mm Hg or 25% of the anal resting pressure. The rectoanal inhibitory reflex will not be present in patients with HD.
3. HIRSCHSPRUNG DISEASE

3.1. Epidemiology
Hirschsprung disease (HD) is a congenital bowel motility disorder with an incidence of 1:7000 to 1:4000 live born in the western world, affecting boys four times more often than girls [59,60]. Most HD patients are otherwise healthy, but HD is associated with other congenital anomalies and with chromosomal abnormalities such as Down syndrome and some more rare syndromes [61]. The genetics of HD is complex and multifactorial, and the genetic penetrance is low. The RET gene is the major gene responsible for HD, but also mutations in other genes are associated with HD. In 50% of familial and 15% of sporadic HD cases, coding sequence mutations can be identified in the RET gene [61].

3.2. Pathophysiology
In healthy fetuses, the neurons of the enteric nerve system, known as ganglion cells, migrate from the neural crest via the foregut (fetal esophagus) to colonize the entire enteric system within the first 18 weeks of gestation. The gene product of the RET gene, a tyrosine kinase receptor protein, is involved in this process. In HD patients, this migration is disturbed. Thus, the ganglion cells are absent in the distal intestines, always including the rectum. In most HD patients (80%) the aganglionosis is restricted to the rectum and sigmoid colon. In the remaining cases the aganglionosis is more extensive.

The ganglion cells are mandatory for bowel peristalsis and relaxation. There are also other histological abnormalities in the aganglionic bowel wall. The most striking finding is the hypertrophy and hyperplasia of the extrinsic nerve fibers in the submucosa. Some studies have also revealed reduced numbers of interstitial cells of Cajal, the bowel wall pacemaker cells, in the aganglionic segment [62]. The aganglionosis and associated histological abnormalities cause constant constriction and loss of peristalsis in the affected bowel segment leading to intestinal obstruction. The IAS is always aganglionic in HD patients. Thus, the relaxation of the IAS, seen in healthy individuals during defecation (rectoanal inhibitory reflex), is impaired in HD patients. This internal sphincter achalasia also contributes to the bowel outlet obstruction. Some studies also indicate altered histological appearance and motility in the ganglionic bowel in HD patients [3,16,54,63,64], and this may also contribute to the intestinal obstruction.

As a result of the distal bowel obstruction, the ganglionic bowel oral to the aganglionic segment becomes dilated. In untreated HD the dilated bowel oral to the aganglionosis may also be hypertrophic.
3.3. Symptoms and diagnosis
HD patients usually present with intestinal obstruction in the early neonatal period. Hirschsprung associated enterocolitis (HEC) may also be the presenting symptom. HEC is a condition with abdominal distension, diarrhea and fever, and the pathogenesis is unknown [65,66]. HD can also be diagnosed in older children or adults with massive constipation [67,68]. The gold standard for definite HD diagnosis is rectal biopsy proving absence of ganglion cells and hypertrophy and hyperplasia of extrinsic nerve fibers [69]. Anal manometry may also be useful in the diagnostics; a normal rectoanal inhibitory reflex will exclude HD [47–49]. In most cases a contrast enema will show the transition zone between the dilated ganglionic colon and the constricted aganglionic segment. However, the contrast enema is not sufficient to confirm or exclude HD [70].

3.4. Surgery for Hirschsprung disease
With few exceptions, the treatment of HD is surgical resection of the affected bowel, including the rectum. Different surgical procedures are used for HD. The main principle of these operations is to remove the pathologic aganglionic bowel segment and re-establish bowel continuity. Furthermore, some techniques specifically aim to weaken the IAS to prevent anal sphincter achalasia due to aganglionosis of the IAS. Most techniques include anal approach with dissection and anastomosis. Even though most of the procedures described below were first introduced as one stage procedures without diverting stoma; traditionally, operation for HD used to be a three stage procedure: Stoma formation shortly after diagnosis, resection of aganglionic bowel at the age of 6-12 months if neonatal diagnosis, and stoma closure some weeks after bowel resection. Most surgical techniques are variants of the original Swenson, Duhamel, Rehbein or Soave procedures; by laparotomy, as in the original descriptions, or by minimally invasive techniques (laparoscopy or transanal procedures). Nowadays, most children are treated in one single surgical procedure without a stoma.

3.4.1. Swenson
The first curative treatment for HD was described by Swenson and Bill in 1948 [71]. In the Swenson procedure the colon and rectum are mobilized through a laparotomy. The rectal mobilization is extended below the peritoneal reflection down to the levator ani muscle. The mobilized rectum is intussuscepted through the anus and resected. The ganglionic colon is pulled through, and a circular colo-anal anastomosis is performed before the anastomosis and anal canal is retracted within the anus. Nowadays, many surgeons do a one stage transanal procedure with a modified Swenson anastomosis [72].
3.4.2. Rehbein - Deep anterior resection
Deep anterior resection is an entirely transabdominal technique with no transanal dissection and was first described by Rehbein in 1953 [73]. The aganglionic bowel is dissected down to the peritoneal reflection and transected. A circular anastomosis is performed between the ganglionic colon and the aganglionic rectal stump. The main objection to this technique has been related to the aganglionic rectum left in situ, which could cause obstruction. Still, some surgeons use a modified one or three stage Rehbein procedure. To prevent persisting bowel outlet obstruction, the anastomosis is now performed below the peritoneal reflection. Furthermore, the anal canal and sphincters are intentionally dilated intra-operatively and regularly the first weeks postoperatively.

3.4.3. Duhamel
In 1956, Duhamel described a combined transabdominal and transanal procedure that bypassed some of the challenges from the Swenson and Rehbein procedures [74]. Also in the Duhamel technique an aganglionic rectal stump is preserved after laparotomy and removal of the rest of the aganglionic segment. Thereby, dissection deep in the pelvis is avoided, and the risk of damaging the nerves to the bladder, genitalia and anal sphincters, known from the Swenson technique, is potentially diminished. Blunt dissection is carried out in the midline behind the rectum until the level of the pelvic diaphragm is reached. In the transanal part of the procedure an incision is made in the posterior anal canal. The ganglionic bowel is pulled down behind the rectum, through this incision, and an end-to-side anastomosis is performed. The septum between rectum and the ganglionic segment is then divided (nowadays by a linear stapling device) forming a side-to-side, or a functional end-to-end, anastomosis. In the original technique, to prevent postoperative internal sphincter achalasia, the anal canal was incised below the dentate line to ensure division of the anal sphincters when dividing the septum. In the modified Duhamel techniques, the anal incision is made at or above the dentate line, to preserve the anal sphincters [75]. The Duhamel procedure is still one of the most frequently used operations for HD. Most surgeons use laparotomy, but this procedure may also be performed laparoscopically [69,75].

3.4.4. Soave extramucosal endorectal pull-through procedure (Soave/Boley)
The principle of endorectal dissection, known from colorectal surgery for other conditions, was first described for HD by Soave in 1963 [76]. In the original endorectal pull-through operation, as described by Soave, the aganglionic bowel is dissected down to the peritoneal reflection via a laparotomy. Further dissection down to the anorectal line is performed endorectally, separating the seromuscular coat from the rectal mucosa. By this extramucosal endorectal dissection, pelvic innervations and the sacral nervous plexuses may be spared. In the transanal stage of the procedure, the anal canal is dilated; the mucosa is incised 10 mm above the dentate line, and the extramucosal dissection is completed from below. Originally, the ganglionic bowel was pulled through
without performing anastomosis. The protruding colon stump was resected after 15-20
days.

Boley presented a modified technique in 1964. He transected the pulled through colon
and performed a primary circular anastomosis between the pulled through ganglionic
colon and the rectal mucosa of the anal canal [77]. This modification was then adopted
by most surgeons. The original Soave or Soave/Boley technique is rarely used nowadays,
but the principles of endorectal dissection and a circular anastomosis between the
pulled through ganglionic colon and the mucosa of the anal canal are widely used by
many novel techniques, usually denoted modified Soave or transanal endorectal pull-
through.

3.5. Transanal endorectal pull-through – modified Soave
Over the past years, the popularity of minimal access surgical techniques has led to a
number of modifications of the standard HD operations, like the transanal endorectal
pull-through, a modified Soave procedure with the endorectal dissection performed
from below. There has also been a shift from three stage towards one stage surgery in
the neonatal period without a diverting stoma.

3.5.1. Laparotomy assisted transanal endorectal pull-through
Rintala and Lindahl modified the Soave Boley operation and performed the endorectal
dissection from the anal side [78]. First, they performed a long endorectal dissection like
the original Soave procedure, leaving a long rectal cuff. Later, they and others have
reduced the length of the rectal cuff [79]. From 1998 to 2001 one stage laparotomy
assisted transanal endorectal pull-through was the standard operative technique for HD
at our hospital. The technique is more thoroughly described in chapter 5.3.

3.5.2. Laparoscopy assisted endorectal pull-through
Laparoscopy assisted endorectal pull-through was described by Georgeson in 1995 [80].
Frozen sections and mobilization of colon and rectum are performed by laparoscopic
technique. The transanal part of the procedure is similar to the laparotomy assisted
technique as described by Rintala. This procedure was introduced in our department in
2008. In this thesis, the abbreviation LEPT refers to laparotomy or laparoscopy assisted
transanal endorectal pull-through.

3.5.3. Completely transanal endorectal pull-through (TEPT)
TEPT was independently described by De la Torre-Mondragón and Ortega-Salgado in
1998 and Langer et al. in 1999 [81,82]. The transanal mucosectomy is identical to the
LEPT technique. Originally, a long endorectal dissection was performed, leaving a long
muscle cuff. Nowadays, most surgeons leave a short muscle cuff of approximately 2 cm.
The transanal dissection is continued outside the bowel wall to mobilize the aganglionic
segment by division of the mesocolic blood vessels close to the bowel wall. In most patients, the sigmoid colon can easily be mobilized by this completely transanal technique. In some cases, the whole colon has been mobilized this way. Some surgeons split the muscle cuff before performing the coloanal anastomosis. TEPT was introduced in our department in 2001.

3.6. Postoperative results

3.6.1. Short term results

Major intraoperative complications are uncommon in HD surgery. After surgery for HD, most children start early enteral feeding and can be discharged within 2-7 postoperative days [83–85]. Frequent loose stools are common the first weeks after surgery, causing perianal excoriations in up to 42% of the patients [17,83,85,86]. Anastomosis stricture is reported with varying incidents up to 15% [17,83]. Several patients have episodes of HEC after surgery. Other major postoperative complications, including anastomosis dehiscence and pelvic abscess, adhesion ileus or persisting aganglionosis, do also occur after HD surgery [17,75,83–85,87–91] (Table 3.6.1).

Good short term results with complication rates comparable to or better than the traditional techniques have been reported for the novel operative techniques TEPT and LEPT [83,84,87,92,93]. However, there has been some concern about one stage TEPT in older children with delayed diagnosis. Technical difficulties have been reported, related to the hypertrophic, dilated colon being pulled through and anastomosed to the anal canal. Therefore, a theoretical risk of severe intraoperative and postoperative complications has been discussed when one stage endorectal pull-through, and TEPT in particular, is performed in older children [84,85,94].

Table 3.6.1 Complications after surgery for Hirschsprung disease

<table>
<thead>
<tr>
<th>Complication</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perianal excoriations</td>
<td>4-42%</td>
</tr>
<tr>
<td>Stricture</td>
<td>4-15%</td>
</tr>
<tr>
<td>Hirschsprung enterocolitis (HEC)</td>
<td>6-42%</td>
</tr>
<tr>
<td>Wound infections</td>
<td>4-9%</td>
</tr>
<tr>
<td>Anastomosis leakage</td>
<td>0-3%</td>
</tr>
<tr>
<td>Other infections</td>
<td>0-3%</td>
</tr>
<tr>
<td>Wound hernia</td>
<td>0-7%</td>
</tr>
<tr>
<td>Adhesion ileus</td>
<td>0-5%</td>
</tr>
<tr>
<td>Persistent aganglionosis</td>
<td>0-1%</td>
</tr>
</tbody>
</table>

Complications after various surgical procedures for Hirschsprung disease, including one stage transanal endorectal pull-through [17,75,83–90,92,93]
3.6.2. Long term bowel function
Many studies have reported good long term results after surgical treatment for HD with all the traditional surgical procedures. Persistent constipation has been regarded the most common long term problem, affecting 10 - 33% of the patients. Fecal incontinence has been reported in 4 – 27% [17,24,41,75,79,86]. However, some novel reports indicate higher fecal incontinence or soiling rates, up to 56% [16,18,89–91,95], and it has been discussed whether fecal incontinence has previously been under-reported, especially in retrospective chart reviews [6,18,96]. Bowel function tends to improve with increasing postoperative time and patient age in some studies [18,19,41,88,91].

Long term results after TEPT and LEPT are sparsely documented and with inconsistent results [19,85,90–92]. During the transanal dissection and fashioning of the anastomosis in neonates, there is a theoretical risk of anal sphincter damage which might disturb long-term anorectal function, particularly fecal continence. This has caused considerable concern about fecal incontinence after transanal endorectal pull-through, especially the TEPT procedure [52,92].
4. STUDY HYPOTHESES AND AIMS OF THE STUDY

4.1. Study hypotheses

- Transanal endorectal pull-through procedure for HD is associated with few postoperative complications and good long term bowel function.
- Children with late diagnosed HD have more short term complications than neonates and toddlers.
- Anal manometry and AES findings are correlated to long term bowel function.
- Bowel function after the TEPT procedure is similar to bowel function after LEPT.

4.2. Aims of the study

- Evaluate complications and long term bowel function in HD patients operated with transanal endorectal pull-through procedures (Paper I).
- Identify and discuss complications and particular challenges of the surgical treatment in children with late diagnosed HD (Paper II).
- Establish a normal reference for the endosonographic appearance of the anal sphincters in children (Paper III).
- Examine postoperative morphology and function of the anal sphincters by AES and anal manometry and correlate these findings to long term bowel function (Paper IV).
- Identify risk factors for sphincter defects and poor bowel function after endorectal pull-through procedures (Papers I & IV).
5. PATIENTS AND METHODS

5.1. Study design
This thesis is based on a prospective cohort study in which all eligible HD patients from 1998 to 2011 were invited to participate (Paper I, II and IV). Paper III reports the results from a cross sectional study to establish a normal material and to validate methods used in paper IV.

5.2. Patients and controls
All children treated for HD by a transanal endorectal pull-through procedure (modified Soave) in our department from 1998 to 2011 were eligible for this study. The diagnosis was based on rectal biopsies, and contrast enemas were used for preoperative identification of the transition zone. The study was approved by the regional ethics committee (IRB0006244, ref S-06103), and written informed consent was obtained. Background characteristics were recorded at the time of operation. The patients were prospectively followed. Early and late complications and long term bowel function were registered. Since 2008, anal manometry and AES without sedation have been offered as a supplement to clinical examination in the follow up of children older than three years. Children younger than three years of age at the time of the last follow up were excluded because continence could not be evaluated.

Paper I includes all eligible patients per 2010. In Paper II the patients with late diagnosis, after the age at three years, were presented. All patients with a rectosigmoid HD and valid results from anal manometry and/or AES were included in Paper IV.

For Paper III, 45 children aged 1 to 14 years, admitted for minor surgery, were recruited as a control group to describe the endosonographic appearance of normal anal sphincters in a pediatric population. These children had neither anorectal or defecation problems nor any history of previous anorectal surgery. AES was performed while under general anesthesia after written informed consent from the guardians. The study was approved by the regional ethics committee (IRB0006244, ref S-04061).

5.3. Surgical techniques
Since 1998, variants of one stage transanal endorectal pull-through with a short muscle cuff have been the standard operations for rectosigmoid HD. Contrary to the classic Soave procedure, the endorectal dissection was performed from below in all patients.

5.3.1. Completely transanal endorectal pull-through (TEPT)
TEPT was introduced in 2001 [81,82]. Four surgeons performed TEPT, and two of these had experience with LEPT. The Lone Star retractor or stay sutures were placed around
the anal verge to expose the anal canal and the distal rectal mucosa. A hand held nasal speculum or two Langenbeck’s retractors were used for further exposure when necessary. The anorectal mucosa was incised circumferentially, 5-10 mm oral to the dentate line. Endorectal dissection was performed transanally, leaving a 2-3 cm long muscle cuff which we did not split. The transanal dissection was continued outside the bowel wall to mobilize the aganglionic segment by division of the mesocolic blood vessels close to the bowel wall until the macroscopic transition zone was reached. Biopsies to verify ganglionic bowel were obtained through the anus after mobilization of the transition zone or through a small umbilical incision prior to the transanal dissection. The aganglionic colon was resected and a hand-sewn circular end-to-end anastomosis performed.

5.3.2. Laparotomy or laparoscopy assisted endorectal pull-through (LEPT)

The endorectal dissection of the lower rectum by laparotomy or laparoscopy assisted transanal endorectal pull-through (LEPT) procedures was similar to the TEPT technique. The main difference was that the mobilization of the upper rectum and colon was performed via the transabdominal route. In Paper IV the term “transabdominal approach” (TAA) was used to describe these procedures.

From 1998 to 2001, five surgeons performed Laparotomy assisted transanal pull-through for HD [79]. Mobilization of the aganglionic colon and rectum was performed through a laparotomy. Frozen sections were taken to verify ganglion cells. The anal canal was exposed using the Lone Star retractor or stay sutures around the anal verge, assisted by two handheld Langenbeck’s retractors when necessary. The transanal endorectal dissection and anastomosis and the length of the muscle cuff were identical to the TEPT procedure.

Laparoscopy assisted endorectal pull-through [80] was introduced in our department in 2008 as an alternative to TEPT for patients with expected difficult colonic mobilization or at the surgeon’s preference. Three surgeons familiar with TEPT performed laparoscopy assisted endorectal pull-through. Laparoscopic technique was used for biopsies to verify ganglionic bowel, mobilization of the colon and rectum and dissection close to the rectal wall below the peritoneal reflection as far as to the pelvic diaphragm. The transanal part of the procedure; exposure of the anal canal, endorectal dissection from below and anastomosis were performed as in the laparotomy assisted technique and TEPT.

5.4. Postoperative complications

Postoperative complications were registered consecutively during the postoperative hospital stay and outpatient visits. Anastomosis stricture was defined as a narrowing of the anastomosis requiring anal dilatations more than eight weeks postoperatively. HEC was defined as episodes of acute abdominal distension, fever and diarrhea.
5.5. Classification of bowel function

Long term bowel function was recorded in all patients by dedicated nurses in semi-structured interviews in all outpatient visits after the age of three years (Appendix). These nurses were blinded to the manometric and endosonographic findings. We used the descriptive Krickenbeck score [27] (table 5.5.1) to grade voluntary bowel movements, fecal incontinence and constipation. Constipation and fecal incontinence were given a score 0 (normal) to 3. The Krickenbeck score reflects bowel function in children who are not undergoing therapy. Thus, a child who used enemas to treat constipation or to maintain continence was scored as either constipation grade 3 (resistant to diet and laxatives) or fecal incontinence grade 3 (constant, social problem). We have defined fecal incontinence as involuntary leaking of stool, requiring change of underwear or diapers. In papers I and II, as in the original description of the Krickenbeck score, the term fecal soiling was used to describe fecal incontinence.

<table>
<thead>
<tr>
<th>Table 5.5.1 Krickenbeck score for postoperative results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Voluntary bowel movements  yes/no</td>
</tr>
<tr>
<td>Feeling of urge, capacity to verbalize, hold the bowel movement</td>
</tr>
<tr>
<td>2. Soiling / Fecal incontinence  yes/no</td>
</tr>
<tr>
<td>Grade 1: Occasionally (once or twice per week)</td>
</tr>
<tr>
<td>Grade 2: Every day, no social problem</td>
</tr>
<tr>
<td>Grade 3: Constant, social problem</td>
</tr>
<tr>
<td>3. Constipation  yes/no</td>
</tr>
<tr>
<td>Grade 1: Manageable with diet</td>
</tr>
<tr>
<td>Grade 2: Requires laxatives</td>
</tr>
<tr>
<td>Grade 3: Resistant to diet and laxatives</td>
</tr>
</tbody>
</table>

5.6. Anal endosonography (AES)

AES in HD patients (Paper IV) was performed without anesthesia in the left lateral position, using a Hitachi EUB 6500 HV system and a rectal probe (EUP-RS4AW-19) (diameter 12 mm) with a 10 MHz rotating transducer covered by a latex balloon filled with degassed water.

In controls without HD (Paper III), AES was performed using a Brüel and Kjaer Ultrasound System (Brüel & Kjaer, Oslo, Norway) with a 7 MHz or 10 MHz rotating transducer covered by a hard, sonolucent plastic cone (diameter 19 mm) filled with degassed water. These children were examined while under general anesthesia in the lithotomy position.

The ultrasound probe was covered by a latex condom, inserted into the rectum, and slowly withdrawn throughout the length of the anal canal. Serial axial images through
the anal canal were captured on a computer and de-identified. The images were assessed, first independently by two of the authors to evaluate inter rater reliability, and then by the three authors in common to achieve consensus.

The images were oriented with the anterior uppermost and described according to the clock-face method. The thickness of the anal sphincters was assessed in the mid anal canal at the 3 and 9 o’clock positions (left and right side, respectively), using the image-processing software, Image-Pro Express (Media Cybernetics, Inc, Bethesda, MD- USA). Mid anal canal was defined as the most cranial level at which the EAS formed a complete ring anteriorly. The IAS thickness was defined as the width of the hyporeflective band surrounding the subepithelium (Fig. 2.3). The EAS can be difficult to distinguish from the LM, and in this study, the LM was included in the EAS measure. Thus, the EAS thickness was defined as the width of the moderately reflective zone, or when applicable, the distance between the interface reflections at the inner margin of the LM and the outer margin of the EAS.

In the control group (Paper III), the endosonographic appearance of the sphincters was described in terms of circularity and reflectivity, and sphincter thicknesses were measured. Naturally occurring hyporeflective areas in the EAS (artifacts) were recorded. The images were also searched for sphincter defects.

In patients (Paper IV), areas of abnormal sphincter reflectivity, not resembling artifacts, were assessed. Sectors representing 15° or more of the circumference with relative hyperreflectivity in the IAS or relative hypo- or hyperreflectivity in the EAS were defined as sphincter defects. Both the localization and the angular distribution were recorded for each defect.

5.7. Anal manometry
Anal manometry was performed without anesthesia in the left lateral position with no routine bowel preparation before the examination. Anal resting and squeeze pressures were measured with a Ch 8 microtip catheter (Unitip, Switzerland) connected to a urodynamic system (Ellipse, Andromeda, Germany). Maximal anal resting and squeeze pressures were measured by stationary pull through technique with a reference transducer in the rectal cavity (Fig. 2.4). Anal resting pressure was defined as the lowest point of the slow wave fluctuation curve in rest [56]. Squeeze pressure was defined as the maximum peak pressure of three voluntary squeeze events. Rectal exploration was performed after the manometry. If palpable fecal masses were found, the manometry results were excluded.
5.8. Statistics
Statistical analyses were performed with SPSS® and Microsoft® Excel software packages. Continuous measures are expressed as mean (+/− SD) or, when appropriate, as median and range. Group differences were compared by non-parametric tests (Mann-Whitney U test and Wilcoxon signed ranks test) because the data sets were small. Differences in categorical variables were analyzed with Fisher’s Exact test. Significance level was set at 5%.

5.8.1. Regression analyses
Multiple binary logistic regression analyses were used in paper I & IV to control for confounders and to identify predictors for IAS sphincter defects and fecal incontinence. Two-tailed bivariate Spearman correlation analyses were used to identify variables to include in the final regression models.

Associations between sphincter thickness and age and gender were evaluated by multiple linear regression analyses (Paper III).

Deming regression was used to calculate the regression line for sphincter measures from the two observers. The Deming regression model aims to find the line of best fit for a two-dimensional dataset, the least squares line. It differs from the simple linear regression in that it accounts for errors in observations on both the x- and the y- axis.

5.8.2. Inter rater reliability
Inter rater reliability was evaluated by kappa statistic for categorical variables (sphincter defect detection, Paper IV), and by the intraclass correlation coefficient (ICC) for continuous variables (sphincter thickness, Paper III). There is no consensus in interpreting inter rater reliability analyses. For this study, the Cohen’s K or ICC analyses were interpreted as suggested by Altman as poor (< 0.4), fair (0.4 to 0.59), good (0.6 to 0.79) or very good (excellent) inter rater reliability (> 0.8) [97].
6. MAIN RESULTS OF THE STUDIES

6.1. Paper I
Functional outcome after operation for Hirschsprung disease – transanal vs transabdominal approach

Postoperative complications and long term bowel function were reported after either TEPT (n=28) or LEPT (n=24) in 52 HD patients. All patients in the LEPT group had a laparotomy. Median age at operation was 2 months for TEPT and 13 months for LEPT. Six children were older than 3 years at the time of surgery. The median age at follow up was 5.7 years for TEPT and 10.1 years for LEPT.

There were no intraoperative complications. Postoperative strictures occurred in 17 patients (33%), twice as often after TEPT than LEPT, although not significantly different. All strictures were managed by anal dilatations. Temporary perianal excoriations were seen in 25 children (48%) and HEC in 8 (15%). There were few other postoperative complications (table 6.1.1).

At long term follow-up, 29 patients reported fecal incontinence. There was no significant difference in the rate of fecal incontinence between children operated with TEPT or LEPT (54% vs. 58%) (Table 6.1.2). However, daily fecal incontinence (grade 2-3) seemed to occur more often after TEPT, although this difference did not reach statistical significance (50% vs. 29%). Constipation was reported in 11 children (TEPT 25%, LEPT 17%).

<table>
<thead>
<tr>
<th>Table 6.1.1 Postoperative complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Perianal excoriations</td>
</tr>
<tr>
<td>TEPT (n=28)</td>
</tr>
<tr>
<td>14 (50%)</td>
</tr>
<tr>
<td>LEPT (n=24)</td>
</tr>
<tr>
<td>11 (46%)</td>
</tr>
<tr>
<td>p value</td>
</tr>
<tr>
<td>1.00</td>
</tr>
<tr>
<td>Stricture a</td>
</tr>
<tr>
<td>TEPT (n=28)</td>
</tr>
<tr>
<td>12 (43%)</td>
</tr>
<tr>
<td>LEPT (n=24)</td>
</tr>
<tr>
<td>5 (21%)</td>
</tr>
<tr>
<td>p value</td>
</tr>
<tr>
<td>0.08</td>
</tr>
<tr>
<td>Enterocolitis (HEC) b</td>
</tr>
<tr>
<td>TEPT (n=28)</td>
</tr>
<tr>
<td>7 (25%)</td>
</tr>
<tr>
<td>LEPT (n=24)</td>
</tr>
<tr>
<td>1 (4%)</td>
</tr>
<tr>
<td>p value</td>
</tr>
<tr>
<td>0.056</td>
</tr>
<tr>
<td>Wound infections</td>
</tr>
<tr>
<td>TEPT (n=28)</td>
</tr>
<tr>
<td>2 (7%)</td>
</tr>
<tr>
<td>LEPT (n=24)</td>
</tr>
<tr>
<td>2 (8%)</td>
</tr>
<tr>
<td>Anastomosis leakage</td>
</tr>
<tr>
<td>TEPT (n=28)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>LEPT (n=24)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Wound hernia</td>
</tr>
<tr>
<td>TEPT (n=28)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>LEPT (n=24)</td>
</tr>
<tr>
<td>1 (4%)</td>
</tr>
<tr>
<td>Other infections</td>
</tr>
<tr>
<td>TEPT (n=28)</td>
</tr>
<tr>
<td>2 (7%)</td>
</tr>
<tr>
<td>LEPT (n=24)</td>
</tr>
<tr>
<td>2 (8%)</td>
</tr>
<tr>
<td>Persistent aganglionosis</td>
</tr>
<tr>
<td>TEPT (n=28)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>LEPT (n=24)</td>
</tr>
<tr>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

a Need for dilatation > 8 weeks postoperatively

b Episodes of acute abdominal distension, fever and diarrhea
Table 6.1.2 Long term bowel function (Krickenbeck score)

<table>
<thead>
<tr>
<th></th>
<th>TEPT (n=28)</th>
<th>LEPT (n=24)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at follow up, (range)</td>
<td>5.7 (3.1-13)</td>
<td>10.1 (7.7-16)</td>
<td></td>
</tr>
<tr>
<td>Voluntary bowel movements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18 (64%)</td>
<td>16 (67%)</td>
<td>0.9</td>
</tr>
<tr>
<td>No</td>
<td>10 (36%)</td>
<td>8 (33%)</td>
<td></td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (46%)</td>
<td>10 (42%)</td>
<td></td>
</tr>
<tr>
<td>Yes Grade 1</td>
<td>1 (54%)</td>
<td>14 (58%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Grade 2-3</td>
<td>14 (50%)</td>
<td>9 (29%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21 (75%)</td>
<td>20 (83%)</td>
<td></td>
</tr>
<tr>
<td>Yes Grade 1</td>
<td>7 (25%)</td>
<td>4 (17%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Grade 2-3</td>
<td>6 (21%)</td>
<td>2 (8%)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

6.2. Paper II
Late diagnosis of Hirschsprung disease – patient characteristics and results
Eleven children had their HD diagnosis after the age of three years (late diagnosis). All these children had experienced severe constipation from early infancy. Nine of the patients had been admitted to their local hospital for treatment of constipation at least once before the diagnosis of HD. After diagnosis, the dilated colon was decompressed for 2-19 months in 8 children before surgery. Decompression was achieved by reinforced laxative treatment (2), weekly enemas (3) or a diverting ileostomy (3). After decompression, any remaining dilated colonic segment was resected together with the aganglionic bowel. The surgical techniques were TEPT (4), LEPT (6) and laparoscopic Duhamel (1).

Table 6.2.1 Postoperative complications in 11 children with late diagnosis

<table>
<thead>
<tr>
<th>Complication</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perianal excoriations</td>
<td>3/11</td>
</tr>
<tr>
<td>Stricture</td>
<td>1/11</td>
</tr>
<tr>
<td>Fever, unknown origin</td>
<td>1/11</td>
</tr>
<tr>
<td>Anastomosis leakage a</td>
<td>2/11</td>
</tr>
<tr>
<td>Bowel obstruction due to twisted colon</td>
<td>1/11</td>
</tr>
<tr>
<td>Temporary depression</td>
<td>2/11</td>
</tr>
</tbody>
</table>

*a Treated with a diverting ileostomy and repeated irrigations of the abscess cavity*

While major intraoperative or early postoperative complications were rare in younger children, such complications were reported in 5/11 patients with late diagnosis (Table
6.2.1). Two patients had anastomotic leakage with abscess and needed a temporary diverting stoma. The long term functional results, however, were comparable with the results after surgery in neonates and toddlers. At last follow up, median 3 years postoperatively; seven had normal bowel function, one had frequent loose stools, and three had weekly incidents of fecal incontinence.

6.3. Paper III

Endosonographic evaluation of anal sphincters in healthy children
Forty-five children with median age 3.6 years (range 1.0-14.5) were studied to describe the endosonographic appearance of normal anal sphincters in a pediatric population. These children had neither anorectal or defecation problems nor any history of previous anorectal surgery.

IAS and EAS could be identified in all children (Fig. 2.3). The morphology of the sphincters in children differed somewhat from what has previously been described in adults. Identification of the inner and outer border of IAS was difficult, especially in children younger than 3 years. The thickness of EAS was easier to assess, and the results proved to be reproducible when measured independently by two investigators (ICC = 0.86 – very good reliability). EAS thickness increased with age. No sphincter defects were detected. However, the reflectivity varied within the EAS. Lower reflectivity was frequently seen in the anterior midline, adjacent to the perineal body, most so in girls. Lower reflectivity was also seen in the anterolateral EAS adjacent to the transverse perineal muscles, and in the posterior midline, representing the anococcygeal ligament. The mean thickness of IAS and EAS were 1.3 mm and 5.3 mm respectively.

6.4. Paper IV

Anal endosonography and bowel function in patients undergoing different types of endorectal pull-through procedures for Hirschsprung disease
Fifty-two HD patients had AES and/or anal manometry examinations as a supplement to clinical evaluation in the postoperative follow-up.

<table>
<thead>
<tr>
<th>Table 6.4.1 Predictors for IAS defect - logistic regression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR (95 % CI)</strong></td>
</tr>
<tr>
<td>Operative approach (TEPT)</td>
</tr>
<tr>
<td>Age at operation (m)</td>
</tr>
<tr>
<td>Age at follow-up (y)</td>
</tr>
</tbody>
</table>

Odds Ratio (OR) for IAS defects by binary logistic regression analyses. Adjusted OR was achieved by multiple logistic regression analysis.
IAS defects were found in 24/50 patients (Fig. 6.4), more frequently after transanal than transabdominal procedures (TEPT 69% vs LEPT 19%, p = 0.001). In a multiple variable logistic regression model, operative approach was the only significant predictor for IAS defects (Table 6.4.1). The inter rater reliability for detecting IAS defects was good (Cohen’s $K = 0.75$). An EAS defect was detected in one child, who also had an IAS defect.

Daily fecal incontinence occurred more often in patients with IAS defects (50% vs 23%, p=0.045) (Table 6.4.2). Anal resting pressure (median 40 mmHg, range 15 – 120) was not correlated to presence of IAS defects or to fecal incontinence.

Fig. 6.4 Internal anal sphincter (IAS) defects.

a) Axial image from the mid anal canal in a 7 year old boy (anterior is uppermost). The IAS can be seen as a hyporeflective band (arrowheads) surrounding the subepithelium. A small, relatively hyperreflective defect (17°) can be seen in the posterior part. The surrounding, broader zone of moderate reflectivity (arrows), representing the longitudinal smooth muscle layer and the external anal sphincter (EAS), is intact. The hyporeflective sector in the posterior midline of the EAS represents the anococygeal ligament.

b) In this 8 year old boy, nearly half of the IAS is absent while the EAS is intact.

### Table 6.4.2 Fecal incontinence related to IAS defects and anal pressures

<table>
<thead>
<tr>
<th>Endosonographic appearance</th>
<th>None or grade 1 (Occasionally)</th>
<th>Grade 2-3 (Daily)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact IAS (n=26)</td>
<td>20 (77 %)</td>
<td>6 (23 %)</td>
<td>0.045</td>
</tr>
<tr>
<td>IAS defects (n=24)</td>
<td>12 (50 %)</td>
<td>12 (50 %)</td>
<td></td>
</tr>
<tr>
<td>Resting pressure (mmHg) a</td>
<td>40 (25-60)</td>
<td>45 (15-120)</td>
<td>0.5</td>
</tr>
<tr>
<td>Squeeze pressure (mmHg) a</td>
<td>130 (60-230)</td>
<td>132 (90-250)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*a Anal pressures are expressed as median (range).*
7. DISCUSSION

7.1. Long term outcome after endorectal pull-through

7.1.1. Bowel function.
This thesis reveals frequent fecal incontinence after endorectal pull-through for HD. More than half of the patients in Study I reported fecal incontinence (soiling), and almost one third used rectal or antegrade colonic enemas or had a colostomy to stay clean and empty the bowel sufficiently. Lately, also others have reported fecal incontinence or soiling frequencies of 40%-65% after TEPT and LEPT [89,90,96], as well as after the traditional Swenson, Duhamel, Rehbein and Soave procedures [16,18,41,89].

Most older publications report lower incidence of fecal incontinence after the traditional HD procedures [13,24,75,86], and some studies have also reported better long term bowel function after TEPT and LEPT [79,85,88,92,98]. Two recent meta-analyses found better results regarding fecal incontinence and constipation after TEPT and LEPT when compared to the traditional Swenson, Duhamel, Rehbein and Soave procedures [99,100]. In contrast to our report, most previous studies were retrospective, and the functional results were not always assessed by independent personnel. There is a potential risk of underestimating complications and problems in retrospective studies and when patients or parents are asked to report problems to the surgeon who performed the operation. We used semi-structured interviews of the patients and their guardians rather than a questionnaire. Thereby, the risk of misinterpretation was reduced. Furthermore we scored all children according to how their bowel function would be with no treatment after surgery. This gives reliable frequencies of incontinence and constipation for the whole patient population. In several previous publications based on questionnaires, the reported bowel function might reflect function after treatment with laxatives or enemas [18]. In addition, patients with stomas were excluded from most analyses. Thus, it is not unlikely that the incidence of fecal incontinence has been underestimated in several previous reports [6,101].

Traditionally, persistent constipation has been regarded the most frequent bowel function problem after surgery for HD, and pseudoincontinence due to constipation should be ruled out before treating patients with postoperative fecal incontinence [17,24,75,102]. In the present studies, the frequency of constipation was comparable to previous studies. Most of our patients with both fecal incontinence and constipation still had incidents of incontinence after the constipation was treated with laxatives. Thus, these children were considered to have true incontinence in addition to constipation.

The high frequency of fecal incontinence presented in this thesis is worrying, and we believe it is possible to achieve better results. The studies included the learning curve for
both TEPT and LEPT. Furthermore, our hospital is a relatively small centre treating less than 80 new children with HD during a 10 year period. Seven different surgeons have performed these operations, and it could be argued that fewer surgeons should have operated the HD patients, as volume's effect on quality has been shown for several complicated procedures [103]. The details of the surgical technique are important contributors to the long term bowel function, as discussed below.

7.1.2. Anal endosonography and bowel function
Postoperative AES demonstrated IAS defects in half of the patients and a defect in the EAS in one patient. To the best of our knowledge, postoperative AES examination after TEPT or LEPT has not been published before. Three previous reports about postoperative AES results after other HD operations show contradictory results [41,42,54]. In a study of 40 adults operated with the Duhamel technique, IAS defects were found in 23 patients and EAS defects in 17 [41]. In another study of 19 patients (16 Duhamel, 2 Soave, 1 Rehbein procedure), Keshtgar et al. found intact IAS and EAS in all patients [54]. Kuhawara et al. performed AES after Duhamel and Rehbein procedures, and described IAS and EAS defects corresponding to the intended internal sphincterotomy or myectomy in all patients [42]. Since there are so few data from postoperative AES examinations in HD patients, and the results are conflicting, we cannot conclude that endorectal pull-through is inferior to other operations for HD with respect to avoiding anal sphincter damage.

Daily fecal incontinence occurred more frequently in children with IAS defects. This result corresponds with findings in HD patients operated with the Duhamel procedure, where all patients with fecal soiling had scars in both IAS and EAS [41]. We believe IAS defects contribute to fecal incontinence in many HD patients. On the other hand, some surgeons perform partial IAS myectomy as a part of the surgical procedure for HD and report excellent long term results without fecal incontinence [42,104]. Thus, the IAS may not be crucial for fecal continence. In study IV, fecal incontinence was also reported by one fourth of the patients with intact IAS. This is not surprising since other factors than the anal sphincters also contribute to fecal continence. These include the anal folds and the submucosa of the high and mid anal canal, anorectal sensation, the anorectal angle, altered colonic motility, and absence of the rectal reservoir [3,5,6,10,16,54]. All these factors can be affected during surgery for HD. Especially, focus has been drawn to the distance from the dentate line to the level of the coloanal anastomosis and the risk of disturbing the anal submucosa and the anorectal sensation if the dissection is started too low [6].

It is a disturbing finding that half of the patients in this series were found to have IAS defects. Since healthy children and adolescents do not have IAS defects (Study III), these defects must be iatrogenic. We hypothesize that anal dilatation during the endorectal pull-through is an important contributor to IAS defects. In adults treated by anal
dilatation for anal fissures, fecal incontinence is a known complication [105], and IAS defects have also been described [106].

AES proved to be a useful research tool adding knowledge to the pathophysiology of postoperative fecal incontinence after TEPT and LEPT. We also demonstrated that AES can be performed in children without sedation. However, AES examinations have limited value in the clinical setting for these patients because half of the children with IAS defects had good fecal continence while one fourth of the children with intact IAS still were incontinent. Thus, the predictive value of the AES findings regarding continence was low.

7.1.3 Risk factors for sphincter defects and poor bowel function

In Study IV, IAS defects were seen significantly more frequently after TEPT than after LEPT. This effect of operative approach on IAS defects remained evident after controlling for background characteristics such as patient age. TEPT procedure was the only significant predictor for IAS defect in the multiple logistic regression model. The principal difference between the TEPT and LEPT procedures is that the dissection of the colon and rectum is performed transanally or transabdominally, respectively [101]. In most patients, the transanal dissection during TEPT involves longer and more extensive anal dilatation than LEPT. We believe this contributed to more IAS defects and thereby higher risk of fecal incontinence after TEPT. Ideally, the transanal dissection during endorectal pull-through should be performed with minimal or no anal dilatation [19,101]. Our results indicate that too much dilatation of the anal canal may occur even if there is focus on avoiding this. In addition, incorrect endorectal dissection may also damage the IAS [10]. The transanal endorectal dissection in our department was intended to be initiated 5-10 mm oral to the dentate line, and thus the IAS should be preserved. However, one can wonder whether some children with postoperative fecal incontinence had their dissection started too low. This was supported of the finding of shorter distance between the dentate line and the anastomosis in some patients during postoperative rectal inspection (unpublished data).

The total rate of fecal incontinence at last follow up were nearly similar for TEPT and LEPT in Study I However, daily episodes of fecal incontinence were reported more frequently after TEPT than after LEPT, in line with the endosonographic findings, although not significant. In a recent meta-analysis of 5 retrospective studies comparing TEPT and LEPT [91] the frequency of fecal incontinence did not differ between the two approaches. However, the included studies were all retrospective and of low quality score. Thus, the authors of the meta-analysis concluded that further long term follow-up studies were warranted.

In children with idiopathic constipation, the width of IAS has been reported to correlate with the severity of symptoms [39,107]. This correlation could not be reproduced in HD
patients, indicating that other factors than IAS hypertrophy causes persistent constipation in HD patients. Internal sphincter achalasia, bowel dysmotility, intestinal neuronal dysplasia or reduced numbers of interstitial cells of Cajal in the ganglionic bowel have been proposed as explanations for persistent constipation [3,10,16,54,62–64].

7.1.4. Anal manometry
The median maximum anal resting and squeeze pressures were within the range previously described in HD patients and healthy children [38,41,55,56,63,108,109]. In one small series, manometry was performed in five children after TEPT and seven children after transabdominal Soave procedure. Like us, they found similar resting pressures in the two groups [52]. In study IV, the presence of IAS defects was not associated with lower resting pressure, contrary to previous findings after the Duhamel procedure for HD, where the numbers of IAS disruptions were inversely correlated to resting pressure [41]. Previous studies have demonstrated associations between anal sphincter pressures and fecal incontinence [54,55]. This was not reproduced in our study. Normal anal manometry findings have also previously been reported both in HD patients with fecal incontinence and with persisting obstructive symptoms [3,41,63]. Thus, the value of anal manometry in the assessment of anorectal function after endorectal pull-through procedures for HD may be questioned.

7.1.5. Hirschsprung associated enterocolitis (HEC)
The occurrence of HEC was lower than what was usually reported [17,66]. The pathogenesis of HEC is unknown [66]. One hypothesis is that HEC is associated with postoperative outlet obstruction. It has been stated that after surgery for HD, there will be a risk of either obstructive complications or fecal incontinence, but hardly ever both in the same patient [6]. Our postoperative findings of frequent fecal incontinence and few cases of constipation and HEC support this theory. However, the occurrence and severity of HEC in Norway is low also before surgery [65]. Thus, there might be genetic, microbiological or other factors contributing to the lower occurrence of HEC in Norway.

7.2. Late diagnosed HD
Study II reminds us that HD should be considered also in older children with severe constipation. Nearly 500 cases of late diagnosed HD in older children and adults have been described in the literature [67]. Interestingly, most patients in the present study had been hospitalized for severe constipation at least once before they were diagnosed. This delayed diagnosis caused prolonged suffering for the constipated children and their families. Furthermore the risk of postoperative complications was higher after delayed diagnosis.
While the incidence of early complications in study I was low, and comparable to previous reports after one stage endorectal pull-through [79,85,88], study II revealed frequent early postoperative complications in children with late diagnosis. Studies of HD diagnosed in adults [110–113] support our findings of more postoperative complications when surgery for HD is performed beyond infancy.

The most striking difference between children with early and late definitive treatment was the rate of anastomotic leakage and abscess. A plausible explanation for leakage in late diagnosed HD may be problems associated with a severely dilated colon [85,111,114,115]. This contributes to difficult dissection as well as anastomosis incongruence if the dilated bowel is not resected. Furthermore, the consequences of a minor anastomotic leakage may be more severe in older patients. In one study, anastomosis dehiscence was identified by routine investigation under general anesthesia 1 - 2 weeks after one stage transanal pull-through in 8 out of 34 infants and toddlers [116]. Only two of these children had symptoms of leakage. Thus, minor anastomosis dehiscence may occur frequently in infants as well, not necessarily leading to clinical symptoms.

Because of the dilated colon in older HD patients, several authors recommend a preoperative colostomy [68,85,101,114,117–119] to decompress the colon prior to the pull-through. Our two incidents of anastomotic leakage in study III occurred in patients without a preoperative stoma. However, they had followed a preoperative bowel management program with laxatives and weekly enemas for four to six months. The effect and optimal duration of preoperative bowel management is unknown. Interestingly, the child in study III who was given extensive laxative treatment for 19 months before surgery obtained markedly reduced diameter of the sigmoid colon and had an uneventful postoperative course. Thus, non surgical bowel management may be useful. Rectal wash-outs are usually warranted for sufficient bowel emptying in untreated HD patients, but repeated rectal procedures may cause psychological trauma [120]. Therefore, a preoperative stoma should be considered in older children with severe colon dilatation. The different alternatives for reduction of colon dilatation before definitive surgery; extended laxative treatment, rectal wash-outs, colostomy or ileostomy, should be discussed individually in collaboration with the patient and the parents.

A protective stoma the first weeks after surgery has been proposed after a coloanal anastomosis in adult HD to prevent abscesses due to anastomosis dehiscence [121,122]. Also in older children, a protective stoma may be indicated [68]. We believe the severe complications of anastomotic leakage in two children in the present study could have been avoided if they had a protective stoma. Recently, delayed anastomosis, as in the original Soave procedure, has been proposed as an alternative to protective stoma in adult HD patients [123].
7.3. Endosonographic evaluation of sphincters in healthy children

The measured IAS thickness of approximately one millimeter was in good agreement with recent reports [36,37]. Children seem to have a thinner IAS than adults [30,32,124,125].

The mean EAS thickness of 5.3 mm corresponds well with previous results in children as well as in adults [30,32,36,124,126]. EAS thickness was positively correlated with age. This has also previously been described [36,38]. We believe this reflects general normal growth of body structures during childhood. As in previous studies in children, no significant correlation between the thickness of EAS and sex were noted [36].

No sphincter defects were detected in healthy children. However, differences in reflectivity were observed in most children, and an apparent anterior discontinuity of the EAS was frequently seen in girls. In adults, a gender difference in the anterior part of the EAS has been reported, and the EAS is known to be shorter anteriorly in women. Thus, there may be an apparent anterior discontinuity of the EAS in transverse images from the mid anal canal from a woman with an intact EAS [45,46]. This is also described in children [37]. We observed hyporeflective areas in the EAS in the midline adjacent to the perineal body, and also anterolaterally adjacent to the transverse perineal muscles. The latter finding has been briefly discussed in previous reports in adults, never in children [30,46,127]. The lower reflectivity has been explained by transverse perineal muscle fibers crossing the EAS. The hyporeflective area in the posterior midline of EAS has been well documented and has been regarded to represent the anococcygeal ligament [30,36,37]. When AES is performed in children to assess sphincter integrity after surgery or trauma, it is important to differentiate these hyporeflective areas of the normal EAS from real sphincter defects.

7.4. Methodological considerations and limitations

7.6.1. Study design

HD patients were included in the study at the time of operation, and were prospectively followed from 1998 to 2011. The long term bowel function data and AES and manometry results from patients were collected during a limited time period (2008-2011). Therefore this study has some of the limitations seen in cross-sectional and retrospective studies.

Study IV was designed to seek correlations between the endosonography and manometry findings and the bowel function, and not to compare results after endorectal pull-through with transanal vs. transabdominal approach. Age at operation and age at follow-up were different in the two groups, and several selection biases may be identified. Some studies have indicated improved bowel functions in older patients.
and in Study I we first assumed that age difference between the groups could explain the tendency for more severe soiling after TEPT. However, the evidence for age effect on bowel function is weak, and contradicted by some studies [96]. In study IV, the effect of operative approach on IAS defects remained evident after controlling for possible confounders, including age. Therefore, this association cannot be ignored.

7.6.2. Scoring clinical bowel function

There is no international consensus on any scoring system to describe bowel function after HD surgery. Furthermore, different authors use various definitions of constipation, soiling and fecal incontinence. In this thesis, we used Krickenbeck score [27] (table 4.4.1), which was defined for anorectal malformations. Since HD patients suffer from many of the same problems as patients with anorectal malformations, and Krickenbeck score is the most novel system developed by international consensus for functional results after anorectal surgery in children, we decided to apply this score for HD patients. Krickenbeck is not a validated scoring system for overall bowel function. Like other scoring systems, Krickenbeck does not differentiate between genuine incontinence and overflow incontinence due to constipation.

Ideally, bowel function should be reported by the patients themselves, because proxy reported outcome, as well as doctor reported outcome, may differ from patient reported outcome [129]. A strength of this theses is that clinical bowel function was not doctor reported. However, most patients were young and were interviewed with their caregivers present, and we did not differentiate between patient reported and proxy reported outcome.

7.6.3. Anal endosonography

We found good or excellent inter rater reliability for EAS thickness measurement and IAS defect detection. These inter rater analyzes were based on two investigators assessing the same set of images. Ideally, two investigators should have performed independent AES examination of each child to evaluate inter rater reliability, but we wanted to save the children from this additional examination. Some HD patients had AES performed twice by two different investigators, and the sphincter defect detection was reproducible (not published).

In contrast to studies in adults; exact measurements of the IAS was difficult in most children, and the inter rater reliability for IAS measures was fair. The assessment of IAS thickness is complicated by the fact that the 19 mm probe used in Study III most likely stretches the anal sphincters in a small child and thereby makes the sphincter appear thinner. Some authors have discussed whether the size of the probe affects the sphincter thickness in adults [130,131], but the results are not consistent. One recent study in women have shown that the IAS volume appears smaller when measured by
anal endosonography with a 17 mm diameter probe compared to vaginal endosonography with no probe in the anal canal [5]. In study IV, we used a thinner ultrasound probe surrounded by an expandable balloon, and unpublished data indicated that the IAS tended to appear thinner and more difficult to define when the anal canal was more dilated. This may also explain why exact IAS measurements tended to be more difficult in younger children in study I. However, difficulties in defining the IAS in the youngest children have also been reported with a smaller anal probe (diameter 8 mm), which unlikely dilates the anal canal [36].

The moderately reflective band surrounding IAS has generally been denoted EAS, and in this thesis, EAS thickness was defined as the thickness of this moderately reflective band. However, a considerable proportion of this ring represents the LM [30,33,43]. The EAS is a contributor of the anal canal pressure, and the squeeze pressure in particular. The function of the LM is still unknown. Therefore, EAS measures without LM would be preferable, and such results are published in adults [30]. However, in adults, the LM is the most difficult layer to measure because of variations in interface reflections. In our study the inner part of what we assessed as EAS in some children had lower reflectivity than the outer part (Fig 6.4 a). We could, however, not repeatedly define any interface reflection between LM and EAS. In adults, the interface reflection is thought to represent a fat plane. In children, the amount of visceral fat is less than in adults. This may even be so in the anal canal and contribute to the difficulties in defining the interface reflections and the margins of the LM in children.

In five children of Study III, the measured EAS thickness differed more than 0.8 mm between the two observers. When we reviewed these five cases, we easily defined the outer border of EAS. It turned out that EAS thickness varied around the circumference within each image. As the sphincter borders sometimes are poorly defined at the exact 3 or 9 o’clock positions, we allowed measurements to be taken in the sectors 2-4 o’clock and 8-10 o’clock; and we believe that the investigators measured different parts of the EAS in these cases.

All children were examined while under general anesthesia. Diagnostic endosonography is often performed without sedation. We believe that the thickness and endosonographic appearance of the sphincters are unaffected by anesthesia even though general anesthesia with muscle relaxants may cause a relaxation of the sphincters. Recently, Keshtgar et al. measured similar IAS thicknesses in patients with and without ketamine anesthesia [51].

7.6.4. Anorectal manometry
In paper IV, the manometry results were not correlated to either IAS defects or fecal incontinence, and we stated that the value of anal manometry in the assessment of anorectal function after endorectal pull-through procedures for HD may be questioned.
However, associations between anal resting pressure and fecal incontinence have been described by others after different operations for HD when the patients were examined with different manometry systems and ketamine anesthesia [54,55]. In study IV, the examination was performed without sedation. Even though most children cooperated well, the anal resting pressure results may be less reliable because the conditions for examining were not as standardized as under ketamine anesthesia. The high pressure zone in children is short, and small movements can cause a significant displacement of the probe and a drop in the measured pressure. We used a microtip catheter because these catheters are thin and easily accepted by small children. Others have used water perfused catheters or water filled sensor balloons. These systems are more likely to produce artifacts in small children due to expansion of the anal canal or rectal ampoule and the unpleasant feeling of soiling of water. Microtip catheters are considered to have the same reliability as water perfusion systems or water filled sensor balloons [56,132]. Multiple channel vector manometry provides a 3-dimensional graphic image of the sphincteric pressure profile along the anal canal, and may be a better alternative in these patients [53]. When manometry has been used for HD diagnostics in neonates, sleeve manometry and high resolution manometry has been used to overcome the problems with probe displacement and short high pressure zone [47,49]. These techniques might also be useful postoperatively.

7.7. Clinical implications and future perspectives

These studies have proven that postoperative fecal incontinence is a more frequent problem than previously believed. Fecal incontinence has a negative impact on social life and mental health [120]. These patients need long term follow-up by a multidisciplinary team including pediatric surgeon and specialized nurse, in some cases in collaboration with pediatrician, pediatric psychologist or psychiatrist, and social worker. Some patients need close follow-up into adulthood.

The high frequencies of IAS defects and fecal incontinence after endorectal pull-through, especially after TEPT, are worrying. Correct surgical technique is crucial for postoperative outcome. Therefore, we propose that TEPT are compared to LEPT or other operative HD procedures in studies with larger numbers of patients before TEPT again is performed as a routine procedure. Our research group is a collaborator in the Nordic Pediatric Surgery Study Consortium who are now running a retrospective Scandinavian multi center study in which these operative techniques will be explored. Ideally, a randomized controlled trial should be performed. The preferred techniques in our department are now laparoscopy assisted transanal endorectal pull through or laparoscopic Duhamel procedure. Furthermore, when performing transanal endorectal dissection, we have special focus on preservation of the dentate line and of minimal dilatation of the anal canal.
Because of the higher risk of early complications in children with late diagnosis, we now consider a peri-operative diverting stoma in older children with severe colon dilatation. A stoma will secure preoperative decompression of the dilated colon and may reduce the risk of postoperative dehiscence and abscess. Furthermore, older children should be prepared for the possibility of temporary frequent, loose stools and incontinence the first weeks after surgery. If an older child experience postoperative incontinence, close follow-up and support to handle the problems must be instituted.

8. CONCLUSIONS

Fecal incontinence occurs more frequently after endorectal pull-through procedures for HD than previously believed. Half of the patients have IAS defects after the procedure, and we believe IAS defects contribute to fecal incontinence in many patients. IAS defects were seen more often after completely transanal procedures. Therefore, laparoscopy assisted procedures are now preferred in our department.

Complications, especially related to anastomosis dehiscence, occurred more frequently in HD patients operated after the age of 3 years than in younger children. Therefore, older patients should be handled differently from the neonates and toddlers.
9. REFERENCES


10. ERRATA

p 8 DEFINITIONS, EAS thickness:
... interface reflection at the outer margin of the EAS (Fig. 2.1.1) (Fig. 2.1)

p 26, paragraph 3.5.1, last line:
The technique is more thoroughly described in chapter 5.3. 4.3.

p 32 paragraph 5.5, second line:
... interviews in all outpatient visits after the age of three years (Appendix). (Appendix A)

Study IV, p 1343, paragraph 2.2., third line:
Resting pressure showed a weak positive correlation...
## 11. Appendix

### Langtidsresultater

**Pasienter operert for Hirschsprung med transanal endorektal pullthrough**

**Barn over 3 års alder**

<table>
<thead>
<tr>
<th>Navn</th>
<th>Personnr</th>
<th>Pas ID</th>
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<tbody>
<tr>
<td>Slektning med Hirschsprung</td>
<td>Ja</td>
<td>Nei</td>
</tr>
<tr>
<td>Slektning med inflammatorisk tarm</td>
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**Operasjonsdato:**

**Allmennsymptomer**

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<td></td>
</tr>
<tr>
<td>Kvalme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magesmerter</td>
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<td></td>
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<tr>
<td>Annet</td>
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**Dato for utfylling:**

**Fylt ut av:**

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### Krickenbeck score

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<tbody>
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<tr>
<td>Sier fra om avføringstrang</td>
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<td>Klarer å holde igjen</td>
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<table>
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<tr>
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</tr>
<tr>
<td>Bremsespor (Grad 0)</td>
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</tr>
<tr>
<td>Lekkasje ukentlig (Grad 1)</td>
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<tr>
<td>Lekkasje daglig, ikke sosialt problem (Grad 2)</td>
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<td>Konstant, sosialt problem (Grad 3)</td>
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<table>
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<td>Velregulert med laxantia (Grad 2)</td>
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<td>Ikke tilstrekkelig effekt av laxantia (Grad 3)</td>
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<td>4-6 pr dag</td>
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<tr>
<td>7-10 pr dag</td>
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<tr>
<td>&gt;10 pr dag</td>
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<tr>
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<td>Stoppende medisin^3:</td>
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<tr>
<td>Laxantia (dose)^3:</td>
</tr>
<tr>
<td>Skylling/ACE/Klyster^3:</td>
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**Episoder med Hirschsprung Enterocolitt^6 eller vedvarende diarre?**

**Kommentarer:**
Veiledning for utfylling av skjema "Langtidsresultater pasienter operert for Hirschsprung med transanal endorektal pullthrough"

Oppdatert 17.02.2010

Skjemaet fylles ut av sykepleier ved kontroller i avdelingen av Hirschsprungs pasienter som er 3 år eller eldre. Skjemaet scannes under B3 Spesialjournal, og originalen legges til Stensrud.

Der det reelle svaret ligger mellom to rubrikker, bes foreldrene velge hva som passer best.

1 Krickenbeck score brukes på barn over 3 år uten pågående behandling. Man angir om barnet har avføringskontroll, og avføringslekkasje og forstoppelse graderes 0-3. De som bruker skylling eller klyx, skal scores ut i fra hvordan de ville hatt det uten denne behandlingen. Bruk kommentarfeltet til å angi hvorfor de skyller, og hvordan de fungerer etter skylling.

2 F.eks hvis avføringen bare kommer ved skylling, bruk kommentarfeltet.

3 Med lekkasje (soiling) menes avføringslekkasje (med eller uten avføringstrang) som gir luktplager og/eller behov for klesskift eller bleier/ truseinnlegg.

4 Avføringskonsistens beskrives fortrinnsvis med begrepene løs, grøtet, normal, seig eller hard

5 Angi type og dose/frekvens

6 Begrepet Hirschsprungs Enterokolitt (HEC) brukes om episoder med feber, oppblåst buk og diarre som har krevet antibiotikabehandling. Angis med dato. Episoder med diarre uten feber og oppblåst buk noteres også.
- Pappa, kan brennesle brenne deg når den er død?
- Se Pappa, der er en brennesle, og den er død
... Nei, jeg kan ta på bladene, og den brenner ikke!
- Dette burde du ta med i doktorgraden, Pappa!

Kristian 7 år, 2014