CLINICAL AND PATHO-PHYSIOLOGICAL STUDIES
OF IDIOPATHIC MEGACOLON AND MEGARECTUM

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Abstract

Constipation associated with dilatation of the rectum and/or colon, in the absence of demonstrable organic disease, is an uncommon and poorly characterised condition. The aim of the work reported in this thesis was to characterise idiopathic megarectum and megacolon clinically and to investigate the pathophysiology of this condition.

Idiopathic megarectum (with or without more proximal colonic dilatation) has been shown to be clinically and epidemiologically distinguishable from idiopathic megacolon (where the rectum is of normal diameter). A small number of patients had spinal dysraphism which may be of aetiological importance.

Upper and lower gastrointestinal radiology and transit studies were used to determine if there was a panenteric disorder. There was no upper gut dilatation. There were abnormalities of late gastric emptying, but small bowel transit was unremarkable and delay in colonic transit was mainly confined to the regions of dilated gut.

There was no intrinsic abnormality of the internal or external anal sphincters in patients with idiopathic megarectum or idiopathic megacolon. However, manual disimpaction under general anaesthetic was associated
with iatrogenic sphincter damage.

The use and adverse effects of drugs used in the management of constipation have been reviewed. Some patients require a colostomy in their management. I investigated physiologically the value of different irrigation techniques.

Archive (formalin fixed and processed into paraffin wax) and fresh frozen tissue were studied using a variety of histological techniques, including immunohistochemistry with antibodies raised against neural tissue, neurotransmitters and contractile proteins.

In patients with idiopathic megarectum the muscularis externa and mucosae were thickened and there was a decreased density of innervation of the longitudinal muscle. In rectal longitudinal muscle of these patients there was a decrease in nonadrenergic noncholinergic nerve fibres. Abnormalities of the smooth muscle contractile proteins have been demonstrated in one patient with idiopathic megarectum.

The abnormalities of the enteric innervation in patients with idiopathic megarectum have been shown not to be attributable to the neurotropic effects of herpes viruses.
# Table of Contents

1. Title page
2. Abstract
4. Table of contents
5. Acknowledgements
6. Collaborative work and patients' consent
8. List of publications
10. List of Tables
11. List of Figures
13. Chapter 1. Introduction
29. Chapter 2. Clinical features
57. Chapter 3. The anal sphincter
73. Chapter 4. Gastrointestinal transit
101. Chapter 5. Pathology
122. Chapter 6. Enteric innervation
147. Chapter 7. Contractile proteins, neural markers and electron microscopy
157. Chapter 8. DNA viruses
164. Chapter 9. Adverse effects of laxatives
194. Chapter 10. Colostomy irrigation
211. Chapter 11. Discussion
222. References
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Collaborative Work

Much of the work presented in this thesis would not have been possible without the collaboration of a number of senior colleagues. I have personally conducted all the clinical work, including anorectal physiological testing, and all the isotope transit studies including the formal assessment of gastric emptying and small and large bowel transit. The anal ultrasound scans were done by Dr Clive Bartram and Dr Steve Halligan (St Mark's Hospital, London), reported blindly by Dr Halligan, and reviewed by Dr Bartram and myself. The contractile protein immunohistochemistry and electron microscopy were performed by Dr Virpi Smith (Great Ormond St, London) on tissue provided by myself. The polymerase chain reaction techniques looking for herpes virus DNA were done by Dr Henry Debinski, again on tissue provided by myself. All the other histological work, including cutting frozen sections, processing and assessment was done personally after appropriate training and validation by Dr Ian Talbot (St Marks' Hospital, London), Dr CHV Hoyle and Dr P Milner (Department Developmental Biology, UCL).

Patient's Consent

For each of the clinical studies approval was obtained from either the Ethical Committee of the City and Hackney Health Authority (1989 and 1990) or the Barts NHS Group
Ethics Committee (1993) and each patient gave fully informed written consent. All the histological material was obtained from the resection specimens of patient's undergoing surgery at St Mark's Hospital. All patients at St Mark's sign a standardised consent form which specifically states that any resected tissue that is not used for diagnostic purposes may be used for research purposes. All patients signed such a consent form. Even if patients were undergoing investigations at another clinician's request as part of their normal routine work up, consent was always formally obtained and the patient fully aware that the results would be included in a research project.

**Statement of originality**

All the published series to date looking at the clinical features of idiopathic megarectum and megacolon are retrospective. To my knowledge this is the first study to include prospective data. This study distinguishes between patients who have a megacolon in contrast to patients who have a megarectum with or without more proximal colonic dilatation. This is a key issue as such patients require different management. For the first time the different epidemiology of patients with idiopathic megarectum compared to idiopathic megacolon has been characterized. This is the first time that non-large bowel disease has been investigated in these patients. The histological techniques used have not been previously applied to such a large archive of material in such well defined groups. The work on fresh tissue is innovative and there is no other published work on the potential role of viruses in the aetiology of this condition. The work on colonic pressures and colostomy irrigation has not been reported elsewhere.
List of publications

The following publications, based on the work in this thesis, have been published.

Reviews:

Gattuso JM, Kamm MA. [1994] Adverse effects of drugs used in the management of constipation and diarrhoea. DRUG SAFETY 10: 47-65

Gattuso JM, Kamm MA. [1993] The management of constipation in adults. ALIMENTARY PHARMACOLOGY AND THERAPEUTICS 7: 487-500

Original articles:


Gattuso JM, Kamm MA, Talbot IC. [1996] Pathology of idiopathic megarectum and idiopathic megacolon. (submitted)

Communications: (first author = presenter)

Gattuso JM, Talbot IC, Abassi M, Kamm MA. [1994] First description of the pathology of idiopathic megarectum and megacolon. GUT S48
Debinski HS, Gattuso JM, Kangroe HD, Jeffries D, Kamm MA. [1994] Idiopathic megacolon - search for a viral or neuropathic aetiology. GUT S4: A216

Halligan S, Gattuso JM, Kamm MA, Bartram CI. [1994] Occult anal sphincter damage following manual disimpaction demonstrated by anal endosonography. CLINICAL RADIOLOGY 49: 768


Book chapter:

Table 1. Age of onset of symptoms and age at surgery in patients having surgery over a 23 year period (1968-1991), for idiopathic megarectum and / or megacolon.

Table 2. Symptoms in patients prospectively studied with idiopathic megarectum or idiopathic megacolon.

Table 3. Anorectal physiological testing in 22 patients with idiopathic megarectum and 6 patients with idiopathic megacolon prospectively studied.

Table 4. The results of repeated anal manometry in five patients with idiopathic megarectum.

Table 5. Gastric emptying of the liquid phase of a meal in patients with idiopathic megarectum and normal controls.

Table 6. Gastric emptying of the solid phase of a meal in patients with idiopathic megarectum and normal controls.

Table 7. Small intestinal and colon transit in patients with idiopathic megarectum and normal controls.

Table 8. Results of radio-isotope and radio-opaque marker colonic transit studies indicating sites of regional delay and regions of dilated gut as demonstrated on contrast studies.

Table 9. The diameters of the 3 smooth muscle layers, the muscularis mucosa (mm) and the circular (cm) and longitudinal muscle (Im) of the muscularis externa, of controls and patients with idiopathic megarectum and idiopathic megacolon.

Table 10. Ratio of circular to longitudinal muscle thickness in controls and in patients with idiopathic megarectum and idiopathic megacolon.

Table 11. Density of innervation in regions of the rectum in controls and in patients with idiopathic megarectum.

Table 12. Density of innervation in regions of the sigmoid colon in controls and in patients with idiopathic megarectum and idiopathic megacolon.

Table 13. Density of innervation in regions of the proximal colon in controls and in patients with idiopathic megarectum and idiopathic megacolon.
Table 14. Density of innervation in regions of the sigmoid colon in samples from patients with non-obstructive carcinoma (controls) and in patients with idiopathic megarectum or megacolon.

Table 15. Density of innervation in regions of the rectum in samples from patients with non-obstructive carcinoma (controls) and in patients with idiopathic megarectum.

Table 16. Levels of calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP) in the muscularis externa and mucosal regions in samples of the distal sigmoid colon obtained from five control patients and four patients with idiopathic megabowel.

Table 17. The details of 3 patients with idiopathic megarectum and 3 with idiopathic megacolon.

Table 18. Drugs used in the management of constipation.

Table 19. Patient details in colostomy irrigation study.

Table 20. The median number of high pressure propagated waves, before and after infusion of 500 and 1500 ml of tap water in 18 studies performed in 5 individuals.

LIST OF FIGURES

Figure 1. Gastrografin enema on unprepared bowel showing rectal dilatation extending proximally from the pelvic floor, with no distal narrow segment, characteristic of idiopathic megarectum.

Figure 2. Anal ultrasound scan showing 2 defects in the internal anal sphincter and an intact external anal sphincter.

Figure 3. Radio-isotope transit studies: regions of interest.

Figure 4a. Gastric emptying of the liquid phase of a test meal in patients with idiopathic megarectum.

Figure 4b. Gastric emptying of the solid phase of a test meal in patients with idiopathic megarectum.

Figure 5a. The colonic isotope transit study in one patient (JH) with idiopathic megarectum. The time activity curves for each region of interest are shown.
Figure 5b. The colonic isotope transit study in one patient (FC) with idiopathic megarectum. The time activity curves for each region of interest are shown.

Figures 6. Photomicrographs of H&E stained sections of normal control tissue (a) and from a patient with idiopathic megarectum (b), taken at the same magnification (x15). Figures 6c (x40) and 6d (x100) are photomicrographs showing PGP 9.5 immunoreactivity in rectal tissue of a patient with idiopathic megarectum.

Figure 7. Intramural innervation of the large intestine of patients with non-obstructive carcinoma (control) and idiopathic megarectum or megacolon.

Figure 8. Intramural innervation in a patient with idiopathic megarectum stained for immunoreactivity to PGP 9.5.

Figure 8a: Cryostat sections of normal control tissue (a) and from a patient with idiopathic megarectum (b) immunostained for beta cytoplasmic actin.

Figure 9: Typical baseline manometric recording over a 30 minute period.

Figure 10: One of the few pre-infusion high pressure propagated waves.

Figure 11: Example of the effect of the infusion on baseline colonic pressure.

Figure 12: Changes in intralumenal pressure produced by infusion of 500 and 1500 ml.

Figure 13: Example of a high pressure propagated wave in the post infusion phase, induced by irrigation.
CHAPTER 1

Introduction

Constipation is a heterogeneous condition. It is symptom not a diagnosis; when a patient complains of constipation the patient may mean infrequent bowel actions, hard stools, excessive straining at stool, sensation of incomplete rectal evacuation or even abdominal 'bloating' (Goodhart 1902, Hinton and Lennard-Jones 1968, Devroede 1992).

Different pathophysiological processes result in constipation. It may be caused by an intrinsic gut abnormality ('primary constipation') or secondary to systemic disease such as hypothyroidism or hypercalcaemia. A comprehensive review of the causes of constipation can be found in standard texts (Kamm 1991). Patients with primary intractable constipation can be divided into those who have a normal diameter large bowel and those who have gut dilatation.

Primary constipation without gut dilatation.

Constipation is common in pregnancy and may be secondary to the increase in circulating progesterone and decreased levels of motilin (Christofides et al 1982). The pathogenesis of constipation in the elderly is multifactorial. The call to stool may be ignored because
of apathy, confusion, dementia, depression or physical weakness. In the elderly rectal sensation may be decreased and a normal call to stool may not occur (Read et al 1985, Varma et al 1988) and they are more likely to be taking anti-cholinergic or other constipating drugs (anti-Parkinsonian drugs, opiates, phenothiazines and anti-depressants).

Patients with intractable, severe idiopathic constipation can be divided into two groups on the basis of radio-opaque marker studies (Evans et al 1992): those with slow colonic transit and those with normal colonic transit. There is a marked female preponderance in both groups.

**Idiopathic slow transit constipation:** These patients may open their bowels every 1-4 weeks, have difficulty with rectal evacuation, and abdominal pain and bloating (Preston and Lennard-Jones 1986). The rectum is usually empty and the colonic diameter is normal on contrast studies. Up to 50% of these patients may have abnormalities of gastric emptying and small bowel transit (Kumar et al 1989a, Van der Sijp et al 1993a).

Idiopathic slow transit constipation is a distinct clinical syndrome, but there may be a variety of underlying aetiologies. Abnormalities of the colonic enteric innervation have been found in resection specimens from such patients (Preston et al 1983,
Many women with slow transit constipation have poor pelvic floor coordination, known as "anismus" or "paradoxical contraction on defaecatory straining", which can be demonstrated electromyographically or by measuring anal canal pressures. Biofeedback is a successful treatment in some of these patients (Kamm 1993b).

**Cerebral factors:** Psychological problems may also be aetiologically significant in constipation. The brain can be a potent inhibitor of colonic function (Klauser et al 1990, Tucker et al 1981) and a significant number of patients may have a history of childhood bereavement, emotional, sexual or physical abuse (Preston, Pfeiffer and Lennard-Jones 1984, Devroede 1992, Rex et al 1992).

**Defaecatory disorder with normal transit constipation:** Rectal evacuation may be abnormal and prolonged straining over many years may worsen pelvic floor weakness (Kamm, Bartram and Lennard-Jones 1989). Proctography may show a significant rectocele and surgical repair may then improve symptoms (Kamm, Bartram and Lennard-Jones 1989) but the majority are usually managed medically.

**Internal anal sphincter myopathy:** Kamm et al (1991) reported a familial myopathy of the internal anal
sphincter associated with proctalgia fugax and constipation. The latter characterized by difficulty in rectal evacuation. The internal anal sphincter was abnormally thick clinically and on anal endosonography. Internal anal sphincter strip myectomy is the treatment of choice. The prevalence of this condition is unknown.

**Primary constipation with gut dilatation.**

This includes those with Hirschsprung's disease, chronic (idiopathic) intestinal pseudo-obstruction (CIP), and idiopathic megarectum and idiopathic megacolon.

**Hirschsprung's disease:** Hirschsprung's disease classically presents in the neonatal period with delayed passage of meconium. There is a distal aganglionic segment which causes a functional obstruction. The distal narrow segment, which extends from the anal canal proximally, may be long or short and can be seen with a contrast enema. The diagnosis can be confirmed on rectal biopsy. Treatment is surgical.

Hirschsprung's disease should be considered in an adult presenting with chronic constipation who has a dilated large bowel and whose symptoms started in childhood (Todd 1977, McCready and Beart 1980, Barnes et al 1986). In adult Hirschsprung's disease there is rarely any history of faecal soiling and the rectum is empty on examination.
The narrow segment may be seen on a contrast study. The diagnosis can be confirmed by demonstrating the absence of the recto-anal inhibitory reflex and by full thickness rectal biopsy. The biopsy must include tissue from 2 cm above the dentate line as there can be hypoganglionic and aganglionic segments at the normal recto-anal junction. Aganglionosis is diagnostic of Hirschsprung's disease. Acetyl cholinesterase staining of fresh, unfixed tissue will show an increased staining in the aganglionic segment due to extrinsic nerve hypertrophy.

**Chronic intestinal pseudo-obstruction:** CIP can be defined as the occurrence of symptoms and signs of intestinal obstruction without mechanical blockage. CIP is rare, it is characterized by recurrent attacks of abdominal pain and distension, vomiting and weight loss culminating in multiple hospital admissions for obstructive episodes. If the colon is the primary site involved patients present with intractable constipation and colonic dilatation on radiological studies.

CIP may be sporadic or familial (autosomal recessive, autosomal dominant or sex-linked). In familial cases the phenotypic expression of the gene is variable. CIP is caused either by a visceral neuropathy or visceral myopathy, but within each group there is a wide range of nerve and muscle disorders (Smith et al 1992, Lowsky et al 1993).
There is no specific treatment for CIP. Surgery has a limited role and should be tailored to demonstrable physiological abnormalities. If a laparotomy has been performed there is then a diagnostic difficulty in differentiating between an episode of acute pseudo-obstruction and an obstruction secondary to adhesions.

**Chagas' disease:** Chagas' disease is a common cause of dilated gut in South America. It is caused by Trypanosoma cruzi. It was first recognised in 1955 (Raia 1955). Inflammatory changes are seen around the enteric ganglia and neuronal degeneration results in bowel dilatation. Colonic involvement results in severe constipation.

**Idiopathic megarectum and megacolon:** Some constipated patients have a megarectum or megacolon of unknown cause. The bowel is of increased diameter and sometimes length. There is no definitive diagnostic test for idiopathic megarectum or megacolon. Symptoms may start in childhood or as an adult and these may represent different disorders. Patients complain of intractable constipation, intermittent abdominal pain and abdominal distension.

Idiopathic megarectum and idiopathic megacolon are uncommon and poorly characterised. The aim of this thesis was to define these conditions and investigate their pathophysiology.
Historical aspects of idiopathic megarectum and megacolon

Megacolon can be defined as dilatation of a part or of the whole colon in the absence of an obstructive lesion. The term 'idiopathic megacolon' included Hirschsprung's disease ("congenital megacolon") until it was recognised that a distal aganglionic segment of large bowel was pathognomonic of Hirschsprung's disease (Whitehouse and Kernohan 1948, Bodian, Stephens and Ward 1949, Lee and Bebb 1951, Swenson, Fisher and Gherardi 1959). The term "idiopathic megacolon" then lacked clarity as it was often unclear as to whether the conditions described included Hirschsprung's disease or whether the term implied all cases of dilated gut in which Hirschsprung's disease had been excluded. Hirschsprung's disease was also known as 'aganglionic megacolon' or 'neurogenic megacolon', non-Hirschsprung's megacolon was also referred to as 'acquired functional megacolon', 'atonic megacolon', 'psychogenic megacolon' and 'pseudo-Hirschsprung's disease' and reports of Chagasic megacolon as "acquired megacolon" (Raia 1955, Netto et al 1962) added to the confusion.

By the 1960s Hirschsprung's disease and Chagasic megacolon were well defined as separate and discrete entities, but Goligher (1961) still lamented 'the diagnostic "dump heap" of idiopathic megacolon'. There remains considerable confusion in the terminology of

Hirschsprung's disease and idiopathic megacolon were clearly distinguished clinically and radiologically by Bodian, Stephens and Ward (1949). These authors also described two types of idiopathic megacolon, one in which the dilatation was confined to the rectum and sigmoid colon ('terminal reservoir') and one in which a longer dilated segment was noted ('tubular dilatation') and in whom, on radiological criteria, the boundary between normal and abnormal was ill defined.

**Clinical feature of idiopathic megarectum and megacolon.**

Idiopathic megarectum and megacolon affect both sexes and symptoms, including intractable constipation, abdominal pain and distension and faecal incontinence, may start in early or late childhood or in adulthood (Bodian, Stephens and Ward 1949, Tobon and Schuster 1974, Lane and Todd 1977, Barnes 1985, Kamm and Stabile 1991,
Relationship between childhood and adult megarectum.

Meunier, Louis and Jaubert de Beaujeu (1984) found that an enlarged rectum and colon is common in children with severe constipation. In that study a single contrast barium enema was done after a standard bowel preparation. They felt that the presence of a megarectum did not reveal any useful information about the pathophysiology of constipation in children and did not predict outcome.

The majority of children with idiopathic megarectum are successfully managed with drug treatment, with presumed resolution of the dilated gut. The relationship between late adolescent and adult patients with idiopathic megarectum and such children is unknown. If medical management in childhood fails it may be that the megarectum has been present since birth or that the rectum has become irreversibly dilated secondarily to behavioural abnormalities (Clayden 1989). Many adult patients with idiopathic megarectum are successfully managed with drugs, but there is no information as to whether there is any significant resolution of often gross rectal and sigmoid dilatation.

Soiling and the anal sphincter in idiopathic megarectum
Callaghan and Nixon (1964) reported the results of their physiological observations on children with non-Hirschsprung's megarectum. They distinguished 3 groups with increasing functional abnormalities of the rectum, the 'enlarged rectum', the 'expanded rectum' and the 'inert rectum'. In the first group, 'enlarged rectum', larger rectal volumes than normal produced otherwise normal sphincter relaxation, whereas in the latter, 'inert rectum' group, sphincteric inhibition occurred before any conscious rectal sensation. The 3 groups appeared to be related to increasing clinical severity and duration of symptoms. Inhibition of the anal sphincters before the onset of rectal sensation was postulated to be related to soiling.

Similarly, Meunier, Mollard and Marechal (1976) reported that in children with idiopathic megarectum rectal sensitivity to balloon distension was much reduced compared to controls. The incidence of faecal incontinence increased proportionally with the decrease in rectal sensitivity. Meunier, Mollard and Marechal (1976) postulated that the aetiology was originally psychological, with faecal retention occurring to such a degree that faecal impaction and subsequent overflow faecal incontinence occurs.

In patients with idiopathic megarectum who have a weak anal sphincter the associated faecal incontinence has
been attributed to the presence of stool in the rectum inhibiting anal tone, to stool distending the anal canal, or to the underlying disorder. Some patients remain incontinent after disimpaction, even when they achieve regular and satisfactory bowel evacuation.

**Gut function in idiopathic megarectum and idiopathic megacolon.**

In patients with idiopathic megarectum it is unknown whether the abnormality of gut function is limited to the dilated large bowel. The upper gut could be structurally and functionally abnormal, as in some forms of chronic intestinal pseudo-obstruction (Kamm 1994, Christensen et al 1990), or just functionally abnormal as occurs in some patients with severe idiopathic slow transit constipation (Kumar et al 1989a, Reynolds et al 1987, Stivland et al 1991, Van der Sijp et al 1993a).

**Histopathology of idiopathic megarectum and idiopathic megacolon.**

In contrast to the well defined histological abnormalities in Hirschsprung's disease (Whitehouse and Kernohan 1948, Bodian, Stephens and Ward 1949, Lee and Bebb 1951) and chronic primary intestinal pseudo-obstruction (Krishnamurthy and Schuffler 1987, Milla and Smith 1994, Smith and Lake 1994), the pathological basis
underlying both idiopathic megarectum and idiopathic megacolon is unknown. In particular, it is unknown if there are abnormalities involving the extrinsic nerves, the enteric nerve plexuses, or the intestinal smooth muscle. Abnormalities of any of these components could lead to gut dilatation and impaired motility.

**Short and long term adverse effects of laxatives.**

The majority of patients with idiopathically dilated bowel are managed medically. Such patients are dependent on oral laxatives or rectal preparations to achieve a bowel action. They use a variety of laxative preparations, often starting in childhood, and will consume large doses of laxatives for many years. These patients are vulnerable to adverse effects, especially as most laxatives are not recommended for sustained, long term use. I reviewed the literature on the adverse effects of laxatives [Gattuso and Kamm 1994] with the aim of providing data for informed prescribing.

**Surgical treatment of idiopathic megarectum and idiopathic megacolon.**

In some patients with idiopathic megarectum or idiopathic megacolon medical therapy fails and surgery is required. Some reported studies do not specifically differentiate between idiopathic megarectum, idiopathic megacolon,
secondary causes of dilated large bowel or idiopathic slow transit constipation. The latter are often reported as having a 'redundant colon' and can be categorised as idiopathic megacolon (Watkins and Oliver 1965, Belliveau et al 1982).

(i) Colectomy. Roy (1968) reported the success of extended left hemicolectomy (mid-transverse colon to lower rectum) in patients with "idiopathic megacolon". All 5 patients had a dilated rectum and sigmoid colon, with dilatation extending more proximally in 3, but all had a normal diameter right colon. Palmer and McBirnie (1967) reported similar results with colectomy and caecorectal anastomosis. More recently colectomy and ileorectal anastomosis would appear to be the operation of choice as lesser resections may result in post-operative constipation (Lane and Todd 1977, McCready and Beart 1979, Belliveau et al 1982. Stabile et al 1991a, Stabile and Kamm 1991).

(ii) Duhamel operation. This operation was devised for patients with Hirschsprung's disease (Duhamel 1964). It is also used in patients with idiopathic megarectum who have a rectum so dilated that an ileorectal anastomosis is not feasible. However, the outcome is not as good as it is in patients with Hirschsprung's disease (Stabile et al 1991b).

(iii) Coloanal anastomosis. Resection of the dilated bowel only and coloanal anastomosis would appear to be a
better option. However, there are only 3 reports in the literature of a total of 10 patients (Vernava, Robbins and Brabbee 1989, Stabile et al 1992b, Stewart, Kumar and Keighley 1994). One patient had gross incontinence, one died after anastomotic dehiscence and one had a completion colectomy and formation of an end ileostomy for persistent constipation.

(iv) **Restorative proctocolectomy.** This procedure is at greater risk of anastomotic complications but can produce a good functional outcome (Hosie, Kmiot and Keighley 1990, Ecker, Kreisler-Haag and Lindemann 1994, Stewart, Kumar and Keighley 1994).

(v) **Pelvic floor surgery.** It is unknown whether abnormalities of the anal sphincter are aetiologically important in idiopathic megarectum and megacolon. An anorectal (strip) myectomy has been reported to produce good results in children (Nissan and Bar-Maor 1971, Hata, Sasaki and Uchino 1988) but this has not been a consistent finding. Division of the puborectalis muscle has not been shown to be of therapeutic benefit (Kamm, Hawley and Lennard-Jones 1988).

(vi) **Formation of a stoma (end colostomy or end ileostomy).** This may be done following failed reconstructive surgery or as a primary procedure without bowel resection. An ileostomy would appear to relieve constipation, as does a colostomy provided the colon used is of normal diameter (Stabile et al 1992a).
Colostomy irrigation.

Some patients with idiopathic megarectum will have an end colostomy, either as a primary procedure or after failed reconstructive surgery. An abdominal stoma can be a source of considerable distress as one form of incontinence is exchanged for another. The aim of colostomy irrigation is to restore faecal continence.

The colon is 'irrigated' every 24 to 48 hours with tap water, the aim is to wash out the bowel in one controlled session so that there is no faecal leakage in between irrigations. However, colostomy irrigation can be time consuming and ineffective in preventing faecal leakage.

There is little information in the literature regarding the ideal volumes to be infused or whether the rate of infusion influences the efficacy of colostomy irrigation. I therefore studied a group of colostomates, who had no known gastrointestinal motility disorder, to ascertain the ideal rate and volume of infusion, and whether an infusion pump would be useful.

Aims of this thesis.

The aims of the work presented in this thesis were:
(i) to characterise the clinical features of idiopathic megarectum and megacolon.
(ii) to assess treatment and clinical outcome.

(iii) to study the function and morphology of the anal sphincter in patients with idiopathic megarectum and megacolon.

(iv) to determine if there is a panenteric defect by assessing the structural and functional integrity of the upper gut as well as colonic and anorectal function.

(v) to identify neural or smooth muscle abnormalities.

(vi) to see if a viral infection is a cause of idiopathic megarectum or idiopathic megacolon.

(vii) to review the safety of laxative treatment.

(viii) to investigate parameters affecting colostomy irrigation.
CHAPTER 2.

Clinical Features of

Idiopathic Megarectum and idiopathic megacolon

Idiopathic megarectum and/or idiopathic megacolon appear to be clinically heterogenous, are very uncommon, and hence are often poorly managed. The work reported in this chapter aimed to characterise these conditions clinically.

A large series of patients was defined precisely from the clinical, operative and pathological aspects, by retrospectively studying all patients who underwent surgery at one hospital for these conditions over a 23 year period. To establish the clinical spectrum of all patients with this condition, including outcome, and to evaluate them consistently, we have also prospectively studied all patients with idiopathic megarectum or megacolon referred to the same hospital over a three year period.

PATIENTS AND METHODS

In both the retrospective and prospective part of this study patients were divided into those with (i) idiopathic megarectum (which included a variable degree of sigmoid colon dilatation), (ii) total rectal and colonic dilatation or (iii) megacolon with a normal size
rectum (Bodian, Stephens and Ward 1949, Lane and Todd 1977).

RETROSPECTIVE STUDY OF OPERATED PATIENTS

The notes of patients classified as having idiopathic megarectum or megacolon who had surgery between 1968-1991 were reviewed. Patients were included only if the gut was dilated on preoperative contrast studies and at operation, and if other causes of gut dilatation such as Hirschsprung's disease had been excluded. The extent of gut dilatation was determined from the written reports of pre-operative contrast studies and the intra-operative findings. Sixty three patients fulfilled these criteria.

Symptoms at presentation to our hospital, treatment before referral and at our hospital, and past medical, surgical and family history were reviewed. The histology reports of biopsies and resection specimens were also reviewed.

PROSPECTIVE STUDY

All 29 patients with idiopathic megarectum or megacolon, attending St Mark's Hospital between 1992 and 1995, were prospectively investigated according to protocol.

Hirschsprung's disease was excluded by the characteristic
clinical features of soiling and faecal impaction down to the pelvic floor (both characteristic of idiopathic megarectum in contrast to Hirschsprung's disease), dilatation of the rectum down to the pelvic floor on contrast studies, and the demonstration of the rectoanal inhibitory reflex (Lawson and Nixon 1967, Ustach, Tobon and Schuster 1969, Aaronson and Nixon 1972, Tobon and Schuster 1974, Meunier, Marechal and Mollard 1978). If the diagnosis remained uncertain full thickness rectal biopsies were obtained to demonstrate the presence of intramural ganglia. The histology of the resection specimens of all patients who had surgery was also reviewed to ensure Hirschsprung's disease or an intestinal neuropathy or myopathy had not been missed.

(i) Questionnaire

A detailed questionnaire was completed, in the presence of a parent or carer where appropriate. This included information about the duration and severity of symptoms, other illnesses, family history, and treatments.

(ii) Radiology

All patients had lower gastrointestinal contrast studies performed, usually a water soluble contrast (Gastrografin) enema on unprepared bowel. A rectal diameter of greater than 6.5 cm in the lateral view, as
measured on a line extending perpendicular to S2, was regarded as abnormally enlarged (Preston, Lennard-Jones and Thomas 1985).

To exclude upper gut dilatation, and therefore chronic idiopathic intestinal pseudoobstruction, 21 patients also had an upper gastrointestinal barium study (Kamm 1994). Upper gut dilatation is uncommon without duodenal dilatation. As we wished to minimise the radiation exposure in these predominantly young patients radiological investigation was limited to one radiograph, at 15 minutes after ingestion, as this was most likely to reveal any upper gut dilatation. In a further 2 patients a complete contrast study of the upper gut had been performed at the referring hospital.

An abnormality of the extrinsic innervation to the hindgut could be a cause of dilated gut. Lumbar spine X-Rays were performed in 23 patients to look for evidence of spinal dysraphism.

(iii) Anorectal physiological tests

Anorectal physiological tests were performed in 29 patients. They were performed when the patients' bowel was as empty as possible, having been emptied either with enemas and laxatives or after manual disimpaction under general anaesthetic. If studies were performed after
disimpaction, those reported here were undertaken a minimum of 10 days after the procedure, with the rectum having been kept empty by the use of laxatives or enemas. The normal range for these tests was derived from a prospective study of age and sex matched healthy volunteers, using identical techniques in our laboratory (Jameson et al 1994).

A perineometer was used to measure the position of the perineum relative to the ischial tuberosities at rest and during straining and the degree of perineal descent calculated (Henry, Parks and Swash 1982). Perianal light touch and pin prick (pain) sensation were tested. Anorectal manometry was performed with a closed water-filled 3 mm microballoon and a station pull through technique. The following measurements were made: maximum resting anal pressure, functional anal canal length, maximum voluntary contraction increment and maximum cough increment (mean of 3 measurements for each). Rectal sensation was assessed by inflating a rectal balloon with air at 60 ml per minute to measure the threshold of sensation (first sensation), the volume at which the patient first had the urge to defaecate (urge volume) and the maximum tolerated volume. The mean of 3 such measurements was recorded. The presence or absence of the rectoanal inhibitory reflex (Denny-Brown and Robertson 1935, Schuster 1975) was determined and the volume needed to elicit it recorded. The mucosal electrosensory
threshold was assessed in the rectum 6 cm above the anal canal and in the centre of the anal canal with a bipolar ring electrode (Dantec, UK) mounted on a Foley urinary catheter (Roe, Bartolo and Mortensen 1986, Kamm and Lennard-Jones 1990). This electrode was connected to a constant current stimulator (Neuromatic 2000 M\C, Dantac, UK). Patients were asked to expel a simulated stool (50 ml water filled balloon) whilst in the left lateral position. Any paradoxical contraction on defaecatory straining while attempting to expel a balloon filled with 50 ml water (Preston and Lennard-Jones 1985, Kuijpers and Bleijenberg 1985) was recorded with either a concentric needle electrode sited within the external anal sphincter or with perianal self-adhesive surface electrodes. Right and left pudendal nerve latencies were measured with a St Mark's pudendal nerve stimulating electrode.

The rectoanal inhibitory reflex was further studied in 9 patients using electrical stimulation applied to the rectal wall (Kamm, Lennard-Jones and Nicholls 1989, Nagasaki et al 1984), to assess its possible value as an additional diagnostic test when the reflex cannot be induced with rectal distension. Nagasaki et al (1984) have shown in constipated children that electrical stimulation of the rectal mucosa can induce the rectoanal inhibitory reflex. This reflex is dependent on an intact intramural enteric innervation and independent of the extrinsic rectal innervation (Lubowski et al 1987, Kamm,
(iv) Clinical Outcome

The response to laxatives and enemas, and the need for surgery, was recorded. The laxatives most commonly employed in the management of these patients are osmotic laxatives, usually magnesium sulphate or lactulose, taken once or twice per day in a dose titrated to achieve regular daily bowel actions without excessively liquid stools and urgency. The use of these drugs is based on previous experience trying different laxative regimes in these patients.

The need for surgery was based on the failure of medical therapy, either because of an unwillingness of the patients to continue taking laxatives or using enemas, or because of the failure of these substances to prevent recurrent faecal impaction. A further indication for surgery in patients with an idiopathic megacolon was the occurrence of volvulus.

RESULTS

RETROSPECTIVE STUDY

Of the 63 patients studied 22 had idiopathic megarectum (7 female, median age 20 years, range 12-69 years), 23
had megarectum and megacolon (7 female, median age 27 years, range 12-69 years) and 18 had megacolon only (12 female, median age 40 years, range 22-66 years). Patients with idiopathic megacolon (and a normal diameter rectum) were significantly \((p=0.0009)\) older than patients with idiopathic megarectum. Five patients with a megacolon, comprising three also with a megarectum and two with a megacolon only, had had a previous sigmoid volvulus, and one further patient with idiopathic megacolon had had a volvulus of the splenic flexure.

Most patients presented with constipation, but documented bowel habit was very variable, from five times per day to only once every 3 months. The normal or greater than normal bowel frequency in some patients related to impaction with overflow, repeated attempts to defaecate, and a genuine high frequency in a small proportion.

Faecal incontinence was always associated with rectal faecal impaction and occurred in 17 patients (77%) of those with isolated megarectum and 13 patients (57%) of those with a megarectum with megacolon. Most patients \((n=14, 82\%)\) with idiopathic megarectum alone, and approximately half \((n=6, 46\%)\) of those with associated proximal colonic dilatation, had undergone manual disimpaction under general anaesthetic.

Abdominal distension was more common than abdominal pain,
occurring in 60 percent and 40 percent of patients respectively, and occurred in all 3 patient groups. No patient experienced vomiting. Table 1 shows the age of onset of symptoms and the age at operation in the 3 patient groups. Ninety percent of patients with idiopathic megarectum were dependent on laxatives, almost all starting in childhood. In contrast 55 percent of patients with idiopathic megarectum and megacolon and 72 percent of patients with megacolon alone used laxatives, often intermittently.

No formal intelligence or psychological testing had been undertaken in these patients. However 4 patients with idiopathic megarectum and 2 with megarectum and megacolon were noted to have marked mental retardation. The majority of patients appeared to be within the normal intelligence range. Seven patients, all with a megarectum, with or with out megacolon, had documented depression, often associated with schooling difficulties. No such history was noted in the patients with idiopathic megacolon only.

Most patients had no significant family history. In 4 patients there was a family history of constipation, none of which required hospital admission. One patient with idiopathic megarectum and megacolon had a brother with Hirschsprung's disease. Isolated congenital abnormalities were present in 3 patients with idiopathic megarectum: 1
had congenital heart disease, 1 agenesis of one ear and 1 agenesis of one iris.

A rectoanal inhibitory reflex was elicited in 9 of 18 (50%) of patients with idiopathic megarectum, in 12 of 16 (75%) patients with idiopathic megarectum and megacolon, and in 9 of 10 (90%) patients with idiopathic megacolon. In all 63 patients histology of pre-operative full-thickness rectal biopsies and the resection specimens were reported as showing idiopathic megabowel and did not show any features of Hirschsprung's disease or of an intestinal myopathy or neuropathy.

PROSPECTIVE STUDY

Twenty two patients (7 female) had idiopathic megarectum, with a dilated rectum of median diameter 10 cm (range 7-15 cm), no distal narrow segment, and variable dilatation of the sigmoid colon (Figure 1). Six patients (3 female) had idiopathic megacolon, with a dilated sigmoid and proximal colon but a normal diameter rectum, and 1 patient had total colonic and rectal dilatation (rectum 9.5 cm diameter).

(i) Questionnaire

Patients with idiopathic megarectum presented to our hospital at a median age of 19 (range 13-36) years. Of
these patients, 12 became symptomatic in infancy, 9 between the ages of 5-10 years and 1 at age 18 years. The six patients with idiopathic megacolon were significantly (p=0.0007) older (median 42, range 37-59 years) than the patients with megarectum. Three patients with megacolon had constipation requiring laxatives in childhood, the other three having no bowel related symptoms until adulthood.

Table 2 summarises the presenting symptoms. Faecal incontinence, that is passive soiling, associated with rectal faecal impaction, occurred in all patients with idiopathic megarectum. Eight of these patients denied faecal incontinence on direct questioning, despite it being obvious on clinical examination.

In patients with idiopathic megarectum abdominal pain and distension was associated with faecal impaction and relieved by bowel evacuation. Bowel evacuation also relieved abdominal pain and distension in three of the patients with idiopathic megacolon, but in two patients there were no obvious initiating or relieving factors for their pain. A variety of laxatives, including suppositories and enemas, had been tried by all the patients with idiopathic megarectum. Symptoms in patients with idiopathic megacolon were more variable, including constipation, increased bowel frequency, abdominal pain and bloating; a constant need for laxatives was not seen.
in these patients.

Three patients with idiopathic megarectum experienced nocturia, although it occurred infrequently in one patient. No patient had urinary incontinence or a history of urinary tract infections.

No formal IQ tests or psychological profiles were performed. However, 5 patients with idiopathic megarectum were mentally retarded, and one had severe autism. Another patient had a history of manic depression controlled by lithium.

The only significant medical or surgical history in any of the patients was manual disimpaction under general anaesthetic in patients with idiopathic megarectum. No patient had a history of physical or sexual abuse, a history of precipitating event such as anal fissure, or a relevant family history. Thyroid function tests and calcium levels were normal in all patients.

(ii) Radiology

Seventeen of the 22 patients with idiopathic megarectum, 5 of the 6 patients with idiopathic megacolon, and the one patient with combined megacolon and megarectum had upper gastrointestinal contrast studies. No duodenal dilatation was seen in any patient.
Twenty three patients had lumbar spine X-Rays. Of these two of 18 with idiopathic megarectum, and two of four with idiopathic megacolon, had spina bifida occulta. The patient with colonic and rectal dilatation had normal spine radiographs.

(iii) Anorectal Physiological Testing

There was no abnormal perineal descent in any of the patients studied.

The results of anorectal physiological testing are shown in Table 3. The maximum resting anal pressure was lower than normal in 12 patients with idiopathic megarectum. The voluntary contraction increment was normal in all except 3 patients with idiopathic megarectum. Two had a low or absent voluntary contraction increment, but normal cough increment, suggesting an intact external anal sphincter but lack of voluntary effort.

Perianal sensation was normal in all patients. Rectal sensation to electrical stimulation, a useful marker of possible neurological abnormality (Kamm and Lennard-Jones 1990) was elevated in most patients with idiopathic megarectum, 5 having no rectal sensation at maximal stimulation and only 6 being within the normal range. Rectal electrosensation was within normal limits in patients with idiopathic megacolon. Rectal sensation to
balloon distension was diminished in both patients with idiopathic megarectum and idiopathic megacolon.

In the two patients with a megarectum and occult spina bifida the rectal sensory threshold was well above the normal range (43 and 99 mA). In the two patients with a megacolon and occult spina bifida the rectal sensory threshold to electrical stimulation was normal.

The rectoanal inhibitory reflex was elicited by balloon distension in 14 of 22 (64%) patients with idiopathic megarectum and in 5 of the 6 patients with idiopathic megacolon.

Only 1 patient with idiopathic megarectum was able to expel the simulated stool, but 4 of the 6 patients with idiopathic megacolon were able to do so. Paradoxical contraction of the external anal sphincter on attempted rectal evacuation was seen in half of the patients with idiopathic megarectum but in only 1 of those with idiopathic megacolon. Pudendal nerve latencies were normal in all patients.

Elicitation of the rectoanal inhibitory reflex using electrosimulation
The rectoanal inhibitory reflex could be elicited in four of seven patients with an idiopathic megarectum using a rectal inflation volume of 50 ml air. In the other three it could not be elicited using volumes up to the maximum tolerated volume. It was only possible to elicit the
reflex using electrical stimulation in 1 of these seven patients; in four of these patients the stimulus caused pain without reaching a level necessary required to induce sphincter relaxation. Of two patients with idiopathic megacolon, both with normal rectoanal inhibitory reflexes on balloon insufflation and a normal rectal electrosensory threshold, a reflex was induced by electrical stimulation in only one.

(iv) Clinical Outcome

Of the 22 patients with an idiopathic megarectum 15 were successfully established and maintained on maintenance laxatives, and / or enemas. Seven patients (3 female) required surgery (colectomy and ileorectal anastomosis (2), Duhamel procedure (2) or ileostomy formation (1), and 2 patients booked for surgery elsewhere). The type of surgery was determined by the rectal diameter, with colectomy and ileorectal anastomosis being the preferred procedure but only being possible if the rectal diameter was small enough (Duhamel 1964, Kamm and Stabile 1991, Stabile et al 1991a&b).

One patient with idiopathic megacolon, which was associated with radiologically documented recurrent sigmoid volvulus, had a left hemicolectomy. The other patients with idiopathic megacolon were successfully managed with intermittent laxative use. The patient with
idiopathic megarectum and megacolon had a colectomy with ileorectal anastomosis, which successfully relieved intractable abdominal pain and bloating.

**DISCUSSION**

Idiopathic megarectum and idiopathic megacolon are rare conditions. To recruit a large series therefore required examining a defined group who had been treated over a prolonged period. Patients who had required surgery provided such an opportunity, and also provided the advantage of supportive documented operative and pathology findings. In contrast it was necessary to study patients prospectively to obtain uniform measurements of function, investigate possible aetiological factors such as spinal dysraphism, and to determine the proportion of patients with different clinical outcomes. The second part of the study would appear to be the first unselected series of patients studied, the literature consisting mainly of retrospective surgical series.

Although this study comprised patients referred to a tertiary centre, patients with these conditions appear likely to find their way to such centres because of their rarity and the difficulties in their management. They are therefore likely to be representative of patients with these disorders, although it possible that patients with milder forms of these conditions remain unrecognised and
untreated in the community. The true prevalence of these disorders is unknown.

**Idiopathic megarectum**

We have shown that patients with idiopathic megarectum, with or without more proximal colonic dilatation, form a clinically distinct group. We have used radiological criteria to separate the patient groups in this study, although this appeared to correlate well with the clinical presentation. In contrast Verduron and colleagues (1988) used rectal volume-pressure testing to classify a group of patients they studied.

These patients with idiopathic megarectum are clinically different from patients who have a dilated large bowel with a normal diameter rectum, the latter being more appropriately labelled as having idiopathic megacolon.

Barnes (1985) and Barnes et al (1986) distinguished 2 groups of patients with idiopathic megacolon, one with childhood onset and one with onset in 'adulthood' (>10 years old). The former were more likely to have a megarectum in keeping with our findings. However, there was an overlap with rectal or colonic dilatation occurring in both age groups. Classification on the basis of the degree of large bowel dilatation would appear to offer a more rational approach, as symptoms and
management would appear to depend on this.

In Hirschsprung's disease there is a male predominance of approximately 2:1 (Hawley and Ritchie 1994) to 4:1 (Orr and Scobie 1983), although Tobon and Schuster (1974) reported a male:female ratio of 9:1. In this study patients with idiopathic megarectum had a male predominance of 2:1, as in Tobon and Schuster's (1974) report on non-Hirschsprung's megacolon.

Two thirds of patients presenting to our hospital were able to be restored to good health with drug therapy, but a third required surgery. In these patients surgery was required for failed medical treatment, either because the rectum was too large to keep empty or because of failure to comply with drug treatment. Many of these patients do benefit from surgical therapy (Kamm and Stabile 1991).

Almost all patients with idiopathic megarectum developed symptoms in childhood or adolescence, and it occurred more commonly in males. Only a minority of our patients appeared to have a marked intellectual deficit, although others have recognised the association of a dilated bowel with intellectual impairment and psychiatric disease (Ehrentheil 1955, Watkins and Oliver 1965) or neurogenic disorders (Lewitan, Nathonson and Slade 1951). Whether these associations are due to a shared abnormality of brain and gut neurological development, to long term use
of psychotropic drugs, or to the effects of suppressed defaecation, remain unknown.

In patients with idiopathic megarectum the symptoms started in childhood or adolescence, and were due to rectal faecal impaction. In most patients this was associated with marked faecal incontinence, a symptom which at this age can have profound psychological and social consequences.

It is likely that patients with idiopathic megarectum have a number of differing underlying aetiologies, including behavioural and neurophysiological. In contrast to patients with chronic idiopathic intestinal pseudo-obstruction (Christensen et al 1990) and slow transit idiopathic constipation (Bannister et al 1988, MacDonald et al 1991, Lemieux, Kamm and Fowler 1993, Van der Sijp 1993a) this condition appears to be an isolated abnormality, with no upper gastrointestinal or urinary abnormalities. Upper gut radiological studies were normal and patients responded clinically to keeping the rectum empty. Further evidence comes from radioisotope transit studies from the stomach and small bowel in these patients, which have not revealed major disturbances of function (see chapter 4, Gattuso et al 1996).

Rectal sensation to distension was impaired in these patients, but this is to be expected when the rectum is
dilated. However the rectal sensory threshold to electrical stimulation was also elevated, raising the possibility of an underlying neurological disorder. This test, which probably conveys sensation via unmyelinated type C afferent fibres and extrinsic pelvic afferent nerves, is a useful marker of extrinsic denervation (Kamm and Lennard-Jones 1990). This raised threshold may be related to retained stool in the rectum, although the presence of stool usually blocks conduction completely, preventing any measurement from being obtained. Although an abnormality of extrinsic innervation may be aetiologically important in some patients, only two of our patients with idiopathic megarectum had spinal dysraphism, suggesting that this condition is not simply related to occult spina bifida.

The presence of a rectoanal inhibitory reflex in most of these patients indicates an intact intramural enteric innervation. We could not elicit the reflex by electrostimulation despite patients feeling the stimulus, ensuring the electrodes mucosal contact, and the known intact architecture of the intrinsic enteric innervation in this condition (Gattuso, Kamm and Talbot 1994, see chapters 5 and 6). This may reflect altered responsiveness of the intrinsic nerves, as is seen in idiopathic constipation (Kamm, Lennard-Jones and Nicholls 1989, Kamm and Lennard-Jones 1990). The value of electrical stimulation as a diagnostic test in patients
with a dilated rectum was not confirmed.

The low resting anal canal pressure in these patients is an indicator predominantly of impaired internal anal sphincter function (Frenckner and Epler 1975, Read and Sun 1992). This may relate to damage caused by manual disimpaction under general anaesthetic (see chapter 3), an inhibitory effect of large volume of rectal stool, although these patients were studied with as empty a rectum as possible, or an intrinsic abnormality of the sphincter itself (possibly shared with a smooth muscle abnormality of the rectum). The role, if any, of prolonged rectal distension in lowering anal tone is unknown, although Read and Abouzekry (1986) showed that in elderly patients rectal faecal impaction was not associated with any lowering of the anal pressures.

The external anal sphincter was functionally intact, as reflected in the normal voluntary contraction (Read and Sun 1992) and cough increments.

Of those patients managed medically, anorectal physiological assessment did not distinguish between those patients who would successfully use oral laxatives and establish a 'normal' defaecatory pattern, without undue faecal urgency and full continence, and those who would be dependent on regular phosphate enemas to empty the rectum of formed stool. Paradoxical contraction on
defaecatory straining and inability to expel a simulated stool has been reported in these patients before (Barnes and Lennard-Jones 1985, 1988); its presence did not predict the outcome of medical management as has been found in other conditions (Jones et al 1987). Unlike patients with functional bowel disorders and a non-dilated gut (Drossman et al 1990, Talley, Helgeson and Zinsmeister 1992) we found no history of sexual or physical abuse.

These patients needed continuous use of oral laxatives or enemas to prevent reimpaction. Faecal incontinence was mainly associated with rectal impaction, and was not a refractory 'psychological' problem. Maintenance treatment for these patients is lifelong (Barnes et al 1986), and this needs to be impressed on the patient and their carers.

**Idiopathic megacolon**

In contrast to patients with idiopathic megarectum, patients with idiopathic megacolon had the onset of symptoms either in childhood or adulthood. There may be a difference in aetiology between those who develop symptoms at these two different times in life. In contrast to patients with idiopathic megarectum, idiopathic megacolon is more common in women, although numbers in the prospective study are small.
Megacolon remains relatively poorly defined from the morphological point of view. Normal values for proximal and sigmoid colon diameters on single contrast enemas (Patriquin, Martelli and Devroede 1978) and double contrast enemas (Preston, Lennard-Jones and Thomas 1985) have been reported. However, there is a wide normal range and the diagnosis of megacolon remains subjective. During the prospective study we saw very few of these patients, whose condition appears to be rarer than idiopathic megarectum.

Rectal sensation to distension was impaired in the patients with a megacolon despite a lack of radiological rectal enlargement, suggesting increased rectal wall compliance, as part of an abnormal propensity to dilatation throughout the large bowel.

Two of the patients with a megacolon had spinal dysraphism. This suggests that abnormal extrinsic innervation may be aetiologically important in this condition, although the numbers were too small to be certain statistically of the importance of this finding. The normal rectal electrosensory threshold in these 2 patients suggest that if extrinsic denervation is aetiologically important, the colon, and not the rectum, is affected.

Drug treatment was sometimes successful, and sometimes
was only needed intermittently. Surgery is clearly indicated if there is evidence of volvulus, and colectomy with ileorectal anastomosis should be considered in those with disabling symptoms. Volvulus may not be an uncommon complication of this condition. It is well established that some patients with sigmoid volvulus have an underlying megacolon which should be a factor when the extent of bowel resection to be performed is considered (Caplan et al 1965, Shepherd 1969, Hughes 1980, Ryan 1982).
Figure 1. Gastrografin enema on unprepared bowel showing rectal dilatation extending proximally from the pelvic floor, with no distal narrow segment, characteristic of idiopathic megarectum. a: AP view (below), b: lateral view (see over page)
Table 1. Age of onset of symptoms and age at surgery in patients having surgery over a 23 year period (1968-1991), for idiopathic megarectum and / or megacolon.

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Idiopathic megarectum n=22</th>
<th>Idiopathic megarectum and megacolon n=23</th>
<th>Idiopathic megacolon n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age at onset</td>
<td>Age at operation</td>
<td>Age at onset</td>
</tr>
<tr>
<td>&lt;5</td>
<td>11 (50%)</td>
<td>0</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>5-10</td>
<td>7 (32%)</td>
<td>0</td>
<td>8 (35%)</td>
</tr>
<tr>
<td>11-20</td>
<td>1 (5%)</td>
<td>13 (59%)</td>
<td>5 (22%)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>2 (2%)</td>
<td>9 (41%)</td>
<td>6 (26%)</td>
</tr>
</tbody>
</table>
Table 2. Symptoms in patients prospectively studied with idiopathic megarectum or idiopathic megacolon.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Idiopathic Megarectum (n=22)</th>
<th>Idiopathic Megacolon (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faecal incontinence</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Faecal impaction</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Previous manual disimpaction under general anaesthetic</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Sense of incomplete evacuation</td>
<td>16 (of 18)*</td>
<td>3</td>
</tr>
<tr>
<td>Digital extraction of faeces</td>
<td>1 (f)</td>
<td>1 (f)</td>
</tr>
<tr>
<td>Nocturia</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

*: only 18 patients able to fully understand the question

f = female
Table 3. Anorectal physiological testing in 22 patients with idiopathic megarectum and 6 patients with idiopathic megacolon prospectively studied.

<table>
<thead>
<tr>
<th></th>
<th>Idiopathic megarectum</th>
<th>Idiopathic megacolon</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>maximum resting anal</td>
<td>56 (20,110)</td>
<td>100 (36,136)</td>
<td>97 (74,132)</td>
</tr>
<tr>
<td>pressure (cm H$_2$O)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>voluntary contraction</td>
<td>91 (0,160)</td>
<td>102 (41,200)</td>
<td>119 (56,189)</td>
</tr>
<tr>
<td>increment (cm H$_2$O)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cough increment (cm H$_2$O)</td>
<td>86 (20,160)</td>
<td>90 (67,140)</td>
<td>xxxxxxxxxxxx</td>
</tr>
<tr>
<td>anal canal length (cm)</td>
<td>3.6 (2.5,5)</td>
<td>3.8 (3.5,4.5)</td>
<td>4 (3.4,4.6)</td>
</tr>
<tr>
<td>1st sensation (ml)</td>
<td>215* (20,680)</td>
<td>103 (50,180)</td>
<td>46 (29,72)</td>
</tr>
<tr>
<td>urge volume (ml)</td>
<td>244** (90,633)</td>
<td>239 (143,433)</td>
<td>92 (70,125)</td>
</tr>
<tr>
<td>maximum tolerated (ml)</td>
<td>518*** (150,950)</td>
<td>411 (250,683)</td>
<td>188 (145,234)</td>
</tr>
<tr>
<td>anal sensation (mAmp)</td>
<td>7 (3,11)</td>
<td>6 (3,8)</td>
<td>5 (3,8)</td>
</tr>
<tr>
<td>rectal sensation (mAmp)</td>
<td>39**** (17,78)</td>
<td>28 (20,35)</td>
<td>24 (15,35)</td>
</tr>
</tbody>
</table>

Control values from the normal range prospectively determined in age and sex matched healthy volunteers in our laboratory (Jameson et al 1994). Data were normally distributed and results are given as mean with range in parentheses. [Controls = mean and 95% confidence intervals.]

* 1 patient no sensation on inflation with >1000 ml
** 4 patients had no urge sensation, *** 4 patients had no sensation of discomfort with >1000 ml, **** 5 patients had no sensation at maximal stimulation (99.9 mAmp)
CHAPTER 3

The anal sphincter in patients with idiopathic megarectum and idiopathic megacolon

Patients with idiopathic megarectum, adolescents or young adults, both male and female, have intractable constipation, faecal incontinence associated with faecal impaction, abdominal distension and pain. The aim of treatment in these patients is to prevent faecal impaction, either by inducing a semi-liquid stool using osmotic laxatives, or by the regular use of enemas (Kamm and Stabile 1991). A prerequisite for successful long term treatment is to start with an empty rectum. A manual disimpaction under general anaesthetic is often needed to achieve this. In contrast patients with idiopathic megacolon do not develop rectal faecal impaction and rarely suffer from faecal incontinence (chapter 2).

In patients with idiopathic megarectum faecal incontinence has been attributed to the presence of stool in the rectum inhibiting anal tone, to stool distending the anal canal, or to the underlying disorder (Callaghan and Nixon 1964, Meunier, Mollard and Marechal 1976). Some patients remain incontinent after disimpaction, even when they achieve regular and satisfactory bowel evacuation.

The purpose of this study was to investigate the function and morphology of the anal sphincter in patients with idiopathic megarectum and idiopathic megacolon.
PATIENTS AND METHODS

Seventeen patients with idiopathic megarectum (8 female, median age 18 years, range 13-36) and 6 patients with idiopathic megacolon (3 female, median age 52 years, range 37-73) were studied with anal endosonography and manometry.

The diagnosis of idiopathic megarectum was made on the characteristic clinical, physiological and radiological findings (Kamm 1993a, Preston, Lennard-Jones and Thomas 1985, chapter 2). The rectoanal inhibitory reflex was demonstrated in 9 patients and in 6 patients enteric ganglia were demonstrated on rectal biopsy excluding Hirschsprung's disease. In 2 patients no rectoanal inhibitory reflex was elicited but the clinical and radiographic findings were characteristic of idiopathic megarectum and both patients were successfully managed medically. Water soluble contrast studies without bowel preparation were used to determine the extent of rectal and colonic dilatation.

The diagnosis of idiopathic megacolon was made on the clinical and radiological findings (see chapter 2). A normal rectoanal inhibitory reflex was present in all patients and in 3 patients normal enteric ganglia were demonstrated on rectal biopsy.
Idiopathic megarectum

Of the 17 patients with idiopathic megarectum, 14 had undergone manual disimpaction under general anaesthetic. Of these, eleven patients had had documented manual disimpaction only, and three patients had undergone manual disimpaction combined with an intentional 'anal stretch'. All the manual disimpactions first started during the patients' teenage years.

The majority of the manual disimpactions, including the patients who had an 'anal stretch' as part of the procedure, were performed in district general hospitals, prior to referral to St Mark's Hospital. All were performed under general anaesthetic.

Fifteen patients with idiopathic megarectum gave a history of passive faecal incontinence for formed stool, including two patients who had not undergone manual disimpaction under general anaesthetic. Faecal incontinence was usually associated with rectal faecal impaction and in all patients was present prior to any manual disimpaction under general anaesthetic. Twelve patients had had more than one manual disimpaction under general anaesthetic, the most being 10 over 2 years, while two had had only one disimpaction.

Idiopathic megacolon
Five of the 6 patients with idiopathic megacolon complained of constipation (<2 bowel actions per week), one had frequent stools, but all complained of abdominal pain and distension. These symptoms were often intermittent. None of these patients had ever had rectal faecal impaction or needed manual evacuation under general anaesthetic. One patient had very occasional passive leakage of liquid stool only, but none of the others had any form of faecal incontinence.

**Anal endosonography**

All patients were examined using a Bruel and Kjaer ultrasound scanner Type 1846 (Bracknell, UK) with a 7-MHz transducer which rotates to provide a 360 degree cross-sectional image. The technique and interpretation of the image have been described previously (Law, Kamm and Bartram 1991, Sultan et al 1993). Both sphincter muscles are well seen with this transducer, and the images have been extensively validated (Sultan et al 1993, Sultan et al 1994a,b,c). The presence of defects in the external and internal anal sphincters, and whether they were single, multiple or the muscle was fragmented were recorded (Speakman et al 1991). All scans were performed by one of two radiologists, SMH or CIB, and all were then reviewed and reported by SMH with no knowledge of the patients clinical status and previous surgical procedures.
Anal manometry

The maximum resting and voluntary contraction anal canal pressures were recorded using a stationary pull-through technique with a water-filled latex balloon 4 mm in diameter connected to a pressure transducer. The voluntary contraction pressure was recorded as the incremental rise above the resting pressure. The technique has been previously described (Barnes and Lennard-Jones 1988).

The resting anal canal pressure is indicative predominantly of internal anal sphincter function (Read and Sun 1992). Previous studies have established that passive faecal incontinence, or soiling, is associated with internal anal sphincter dysfunction and a low resting pressure (Delechenaut et al 1992, Engel et al 1995). The voluntary contraction incremental rise is indicative of external anal sphincter function (Read and Sun 1992). Poor external anal sphincter function is associated with urge faecal incontinence and a low voluntary contraction incremental pressure rise (Delechenaut et al 1992, Engel et al 1995).

Manometry was performed when the patients were not impacted, usually several weeks after manual disimpaction under general anaesthetic. Five patients with idiopathic megarectum had repeated anal manometry, soon after and
many weeks after manual disimpaction under general anaesthetic.

RESULTS

The patients with idiopathic megarectum had a rectal diameter of more than 6.5 cm on a pelvic radiograph (Preston, Lennard-Jones and Thomas 1985) [median 10 cm, range 7-15 cm]. In all patients the dilatation extended down to the pelvic floor without a distal narrow segment (Figure 1). All patients with idiopathic megacolon had had barium enemas, the films were not available for review in 2 and reliance was placed on the original report of the films. The 6 patients with idiopathic megacolon had a normal sized rectum and a dilated colon (median 8.5 cm, range 7-10 cm) with no evidence of a distal narrow segment.

Anal endosonography in patients with idiopathic megarectum

In the 3 patients who had not undergone a manual disimpaction under general anaesthetic both the internal and external anal sphincters appeared normal in texture and thickness, and were structurally intact.

Of the 14 patients with a history of manual disimpaction under general anaesthetic, 9 patients had disruption of
one or both of the anal sphincter muscle rings. Four patients had a fragmented internal anal sphincter, but normal external anal sphincter (Figure 2). One patient had a single defect of the external sphincter only. Four patients had multiple defects in both the internal and external anal sphincters. In all the patients the texture of the remaining internal and external sphincter muscles appeared normal. None of the patients with sphincter disruptions had had a previous vaginal delivery.

Anal Endosonography in patients with idiopathic megacolon

In all 6 patients the internal and external anal sphincters appeared to be normal.

Anal Manometry in patients with idiopathic megarectum

There was no significant difference in the resting anal pressure between patients who had an intact and those who had a disrupted internal anal sphincter on the ultrasound scan (median 56 (range 40-110, n=9) v median 45 (range 20-80, n=8), intact v disrupted internal sphincter, p=0.21, Mann Whitney U test). When considered individually, 5 of 8 patients with an internal sphincter defect had a resting pressure below the normal range for their age and sex, as defined in our laboratory (Jameson et al 1994), compared to 4 of 9 patients without a defect who fell below the normal range.
There was also no significant difference in the resting anal pressure between patients who had or had not had a manual disimpaction under general anaesthetic (median 47 (range 20-88, n=14) v median 60 (range 40-110, n=3), disimpacted v not disimpacted, p=0.24, Mann Whitney U test). When considered individually, 8 of 14 patients who had been disimpacted under general anaesthetic had a resting pressure below the normal range, compared to 1 of 3 patients who had not been disimpacted.

There was no significant difference in the voluntary contraction incremental pressure between patients who had an intact and those who had a disrupted external anal sphincter on the ultrasound scan (median 120 (range 40-160, n=12) v median 92 (range 47-147, n=5), intact v disrupted external sphincter, p=0.11, Mann Whitney U test). When considered individually, no patient had a voluntary contraction pressure below the normal range for their age and sex, as defined in our laboratory (Jameson et al 1994).

**Anal manometry in patients with idiopathic megacolon**

Manometry was normal in 4 patients (resting anal canal pressure 108,100, 120, 136 and voluntary contraction increment 133, 88, 200, 100 respectively). In 2 patients (1f) resting anal canal pressure (36 and 50) and
voluntary contraction increment (40 and 45) was low.

Clinical Outcome in patients with idiopathic megarectum

Of the 17 patients, 9 patients achieved regular bowel actions and full continence with either regular oral magnesium sulphate, phosphate enemas, or a combination. Four patients required surgery, with two having a colectomy and ileorectal anastomosis, one an ileostomy, and one a Duhamel procedure. This last patient has required further manual disimpactions under general anaesthetic even after surgery, but is now achieving regular bowel actions and full continence with daily laxatives. One patient declined follow up, and one patient is waiting for surgery. Two patients are poorly compliant with daily laxatives and remain incontinent when impacted.

In some patients it was possible to undertake anal manometry repeatedly: before, soon after and a long time after disimpaction under general anaesthetic. When possible anal endosonography has also been performed before and after disimpaction. In one of these patients (OT) we could make these observations around the time of their first manual disimpaction under general anaesthetic. Table 4 shows the results in five such patients. In 3 patients the resting pressure was very low soon after manual evacuation, but progressively
recovered. The voluntary contraction increment also improved. Patients QD, NX, and OT were successfully treated with either osmotic laxatives or phosphate enemas after manual disimpaction, did not reimpact, and became fully continent. Patients RS and RO underwent colectomy with ileorectal anastomosis after a prolonged, but unsuccessful, trial of medical therapy. Six months post-operatively patient RO had daily passive faecal incontinence of liquid stool, while patient RS was fully continent.

Clinical outcome in patients with idiopathic megacolon

Two patients (If) had a documented sigmoid volvulus, both initially successfully managed conservatively. One of these has had a left hemicolectomy, which has cured the intermittent episodes of volvulus and the persistent constipation but abdominal pain and bloating persists. The other patients have all been managed on a symptomatic basis to good effect.

DISCUSSION

The major finding in this study is that a majority of patients who have had a manual disimpaction under general anaesthetic have an anatomically disrupted sphincter, as identified on anal endosonography. The sphincter appears to have been damaged by stretching, in a manner similar
to the damage sustained during an anal dilatation (Speakman et al. 1991, Nielsen et al. 1993).

Of the 8 patients with idiopathic megarectum who had defects in the internal anal sphincter, 3 had also had an anal stretch performed at the time of manual disimpaction under general anaesthetic. Some surgeons deliberately or inadvertently include anal dilatation as part of a manual disimpaction; this report highlights the risk to the sphincter inherent in this practice.

Of the two sphincter muscles, the internal anal sphincter appears to be particularly at risk during a manual disimpaction, and damage to this muscle may account for some of the passive leakage of stool by these patients.

Three patients with idiopathic megarectum had not had a manual disimpaction under general anaesthetic when first seen, and all had a structurally intact sphincter. It could be argued that as these patients had not required manual disimpaction the severity of their condition was milder. However, two had a typical idiopathic megarectum with recurrent faecal impaction and overflow incontinence, but had avoided disimpaction under general anaesthetic by successful use of rectal preparations. These patients appeared to have been more compliant with drug treatment, rather than having had a less severe condition.
There is no evidence to suggest that patients with an idiopathic megarectum have a fragmented sphincter prior to intervention. In healthy subjects without a history of anal trauma or surgery sphincter defects are not observed (Burnett and Bartram 1991). One patient who was scanned before and after disimpaction demonstrated further structural damage. The changes demonstrated in these patients are very similar to those previously reported in patients with faecal incontinence after deliberate anal dilatation (Speakman et al 1991). It is likely that the changes described are caused by the trauma of disimpaction, rather than being due to the underlying disorder.

In the patients with idiopathic megarectum there was no difference in the resting pressure, either between those with endosonographic sphincter damage and those without, or between those who had been disimpacted under general anaesthetic and those who had not. Several factors are likely to underlie this finding. The range of normal resting pressure is great, so that damage to a sphincter with a previously high pressure may not reduce that pressure to below the normal range. Secondly, it is likely that less severe internal sphincter damage can occur related to disimpaction, without endosonographic changes, but still resulting in a fall in the anal pressure. There may also be a residual abnormality of internal sphincter function related to many years of
rectal distension. For a rare condition this is a large series, but it may have been too small to identify a true correlation of pressure changes with structural damage. There are few adult patients with a megarectum who have not undergone manual disimpaction under general anaesthetic.

The 6 patients with idiopathic megacolon had endosonographically intact anal sphincters. Manometry was normal in 4 patients. In 1 patient with low pressures rare episodes of minor soiling of faecal liquid was reported, in the other patient, who had very similar pressures, there was never any incontinence.

Patients may differ in their degree of continence even with identical endosonographic and manometric abnormalities (Bennett and Duthie 1964, McHugh and Diamant 1987, Delechenaut et al 1992). This was observed in two patients RS and RO. Stool consistency and rectal sensation are other relevant factors which will influence the ability to remain continent.

The aim of both medical and surgical treatment of megarectum is the production of a liquid or semi-liquid stool to prevent further impaction (Kamm and Stabile 1991). If impaction does occur, it is possible to perform repeated manual disimpactions under general anaesthetic without traumatising the anal sphincters. Three patients
had had more than 4 disimpactions each, without sustaining any endosonographic evidence of sphincter disruption.

In summary, in patients with idiopathic megacolon the internal and external anal sphincters would appear to be functionally and structurally intact. Manual disimpaction under general anaesthetic appears to structurally damage the anal sphincter in some patients. This damage may contribute to the incontinence that patients with a megarectum experience, particularly when they are not impacted. Sphincter damage from previous manual disimpaction under general anaesthetic is likely to compromise the outcome of medical or surgical treatment, making persistent incontinence more likely.
Figure 2. Anal ultrasound scan showing 2 defects in the internal anal sphincter [i], defects marked by arrows, and an intact external anal sphincter [E]. Two fragments of internal sphincter, which appear dark, remain. This patient had undergone multiple manual evacuations under general anaesthetic, but no documented anal stretches. On manometry, the resting pressure was 36 (low) and voluntary contraction increment was 160 (normal).
Table 4. The results of repeated anal manometry in five patients with idiopathic megarectum. RP = maximum resting pressure, VCI = voluntary contraction increment, both in cm H$_2$O.

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>Days after manual disimpaction under general anaesthetic</th>
<th>RP</th>
<th>VCI</th>
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<td></td>
<td>85</td>
<td>75</td>
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<td>44</td>
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<td>11</td>
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CHAPTER 4

Gastrointestinal transit in patients with idiopathic megarectum and idiopathic megacolon

In patients with idiopathic megarectum and idiopathic megacolon it is unknown whether the functional abnormality is limited to the dilated large bowel. The upper gut could be structurally and functionally abnormal, as in some forms of chronic intestinal pseudo-obstruction (Kamm 1994, Christensen et al 1990), or just functionally abnormal as occurs in some patients with severe idiopathic slow transit constipation (Kumar et al 1989a, Reynolds et al 1987, Stivland et al 1991, Van der Sijp et al 1993a).

There are no published data pertaining to upper gut transit in patients with idiopathic megarectum or idiopathic megacolon, or to the functional significance of delayed colonic transit. In particular it is not known if the functional abnormality is confined to the dilated colonic region or whether it is panenteric. The extent of the intestinal abnormality has important implications if surgery is being contemplated.

Patients with idiopathic megarectum and idiopathic megacolon may have a functional abnormality of gut function which is more extensive than the segment of dilated bowel suggests. The morphology and function of
the upper and lower gastrointestinal tract was assessed by examining gut diameter and transit in a group of these patients.

**PATIENTS AND METHODS**

(A) PATIENTS

*Idiopathic megarectum*

Ten patients (4 female, median age 18, range 17-26 years) with idiopathic megarectum were studied. In 8 patients constipation started in infancy, at the age of 9 in one patient, and the age of 10 in one.

Patients were included in this study because the intractable nature of their symptoms made them candidates for surgical treatment. All patients had used multiple laxatives without success throughout childhood. In all ten patients the use of phosphate or other enemas was unsuccessful or the patient had failed to comply with their use. Eight of these patients were dependent on repeated manual disimpaction under general anaesthesia and the other two patients experienced daily overflow incontinence.

Seven patients complained of abdominal pain and bloating, one complained of abdominal pain only, and 2 patients had neither. These symptoms were relieved in all patients by rectal evacuation.
In all the patients it was possible to palpate the rectum as an abdominal mass prior to disimpaction, and all had a loaded or impacted dilated rectum on sigmoidoscopy.

Hirschsprung's disease was excluded in all patients by the demonstration of the rectoanal inhibitory reflex, by histological examination of a full thickness rectal biopsy, or by radiological examination and clinical response to treatment. Six patients had a normal rectoanal inhibitory reflex; 3 of these patients had had a rectal biopsy, which was normal. The rectoanal reflex could not be demonstrated in the other four patients. Two of these had had rectal biopsies which were normal. The remaining two patients had not had a biopsy but had clinical features in keeping with idiopathic megarectum, with the onset of constipation only in late childhood and radiological dilatation of the rectum down to the anal sphincter. The latter radiological feature does not exclude a short segment Hirschsprung's disease, but the clinical features at presentation and the clinical outcome were consistent with a diagnosis of idiopathic 'idiopathic megacolon' megarectum rather than Hirschsprung's disease.

Three patients with idiopathic megacolon (1 female, ages 37, 42, 53 years) were studied. In the female patient symptoms started in childhood, in the male patients as adults. One patient (male) had had a documented sigmoid volvulus successfully managed by colonoscopic decompression. All complained of abdominal pain, abdominal distension, and constipation which were intermittent and variable in severity. In one patient
bowel frequency varied from 1 per week to 3-4x per day, in irregular cycles.

Abdominal examination and sigmoidoscopy were unremarkable. The rectoanal inhibitory reflex was normal in all 3 patients. One patient (female) had a full thickness rectal biopsy which had shown normal enteric ganglia.

(B) HEALTHY CONTROL SUBJECTS

The control group have been reported previously (Van der Sijp et al 1993a,b) and provide the normal range for our laboratory. Twelve healthy volunteers (8 men, median age 33 years, range 19 to 50 years) were studied as controls. No control subject had any past or present gastrointestinal symptoms, and their spontaneous bowel frequency was 5 to 7 bowel actions per week.

METHODS

All patients had barium and water soluble contrast studies of the upper and lower gut, radio-isotope measurement of gastric, small bowel and colonic regional transit, and radio-opaque marker colonic transit studies. Prior to the start of the transit studies the bowel was emptied. Digital examination and rigid sigmoidoscopy then confirmed the absence of faecal impaction. No oral laxatives, rectal preparations or other drugs which could
affect gut transit were then taken until the studies were completed.

Each control subject had a radio-isotope and a radio-opaque marker transit study, the results of which have been previously published (Van der Sijp et al 1993a,b).

(A) CONTRAST STUDIES

Prior to the start of the isotope and radio-opaque marker studies, all 10 patients with idiopathic megarectum had a water soluble contrast (gastrografin) enema performed on unprepared bowel to determine the rectal diameter and the proximal extent of large bowel dilatation. The presence of a megarectum was defined as a rectal diameter of greater than 6.5 cm at the pelvic brim on a lateral view (Preston, Lennard-Jones and Thomas 1985).

The 3 patients with idiopathic megacolon had had barium enemas prior to referral to St Mark's Hospital, no further lower gut contrast studies were done as it was not felt appropriate to expose these patients to further radiation.

A limited upper gastrointestinal barium meal contrast study, with a single film taken at 15 minutes, was done to look for duodenal and upper gut dilatation. Duodenal dilatation is the most sensitive radiological means of
diagnosing chronic intestinal pseudo-obstruction (Kamm 1994). The study was limited in order to assess duodenal diameter while minimising radiation exposure.

(B) RADIO-ISOTOPE TRANSIT STUDIES

A specifically designed radio-labelled meal was used to study solid and liquid gastric emptying, small bowel and colonic transit (Krevsky et al 1986, Read et al 1986, Kamm 1989, 1992, Mather et al 1991). The full protocol including data analysis methodology has been published previously (Van der Sjip 1993a,b, Mather et al 1991). Technetium [Tc-99m] was used to label the liquid phase of orange juice. The solid phase consisted of a 570 kcal pancake containing indium [In-111] labelled resin microspheres.

(i) Gastric emptying

Time-activity curves were created for solid and liquid radio-isotope gastric emptying. Data were analyzed to determine the percentage of radio-isotope remaining in the stomach at a given time (Figure 3). The lag phase for solid and liquid emptying was defined as the time taken between the end of the test meal and for 5% of the solid or liquid phase to leave the stomach. The time taken to empty 25%, 50%, and 75% of both liquid and solid phases, and the amount of liquid and solid phase remaining in the
stomach at 180 and 360 minutes, were determined.

(ii) Small bowel transit.

The 'head of the meal' small bowel transit time was determined by visual on-screen assessment as the time difference between first arrival of the solid phase radio-isotope in the duodenum and the caecum.

(iii) Colonic transit.

Colonic scans were obtained on the first day of the study from the time of first radio-isotope entry into the colon. Scans were subsequently obtained three times each day until either all the radio-isotope had been excreted or all the isotope had reached the rectosigmoid region and failed to progress further over a 7 day period.

Eight regions of interest were created (see Figure 3): region 1 - small bowel, region 2 - caecum and ascending colon, region 3 - hepatic flexure, region 4 - transverse colon, region 5 - splenic flexure, region 6 - descending colon, region 7 - rectosigmoid, region 8 - faeces. The total abdominal radio-isotope count, corrected for radio-isotope decay, remains constant throughout the study if no radio-isotope is excreted in the stools. Any decrease in the corrected total abdominal radio-isotope count allows for the proportion of radio-isotope passed in the
stool to be calculated.

Colonic transit of radioisotope was assessed in three ways: transit through each colonic region, the "front" of radioisotope, and progression of the "centre of mass" of radioisotope.

Time activity curves were created for each region of interest, enabling the sites of regional colonic delay to be determined. Secondly, the "fastest colonic transit time" was the time difference between first arrival of the isotope [indium] in the caecum and its first appearance in the rectum. The first appearance of indium 111 in the stool, which corresponds with a fall in intra-abdominal radio-isotope count (Van der Sjip 1993b), could not be used in this study as most patients with idiopathic megarectum do not defecate without the aid of laxatives or enemas. All patients were required to keep a record of bowel movements, and these were reviewed in conjunction with the corrected [for radio-active decay] total intra-abdominal radio-isotope count. Lastly, the centre of mass of the radio-isotope of each colonic scan was calculated to assess the effectiveness of colonic transit (Krevsky et al 1986). The centre of mass was defined as the point lying ahead of 50% of the radio-isotope mass.

(C) RADIO-OPAQUE MARKER COLONIC TRANSIT STUDY.
Three sets of radiographically distinguishable markers, comprising 20 circles, 20 rods and 20 cubes, were taken at the same time each morning on three consecutive days. A plain abdominal Xray was taken 120 hours after the start of the study. The position and number of remaining markers were documented (Evans et al 1992). In 6 patients with idiopathic megarectum and in all 3 patients with idiopathic megacolon this study started on the first day of the radio-isotope study. In the other 4 patients with idiopathic megarectum the marker transit study had already been performed prior to the isotope study, under identical conditions.

RESULTS

(A) CONTRAST STUDIES.

Idiopathic megarectum and idiopathic megacolon

No patient had upper gut dilatation, but all had dilated large bowel. Of the 10 patients with idiopathic megarectum, four had a megarectum only, five had dilatation of the rectum and sigmoid colon, and one patient had dilatation of the rectum and whole colon. In all patients with a megarectum the rectal dilatation extended down to the pelvic floor with no distal narrow segment. The median rectal diameter was 11 cm, ranging from 8 - 15 cm at the pelvic brim on the lateral view. The 3 patients with idiopathic megacolon had a normal looking rectum on the double contrast barium studies, but
were reported as having a dilated and elongated colon (7 and 8.5 cm diameter descending colon on the films available for review).

(B) RADIO-ISOTOPE TRANSIT STUDIES.

Idiopathic megarectum

The results of the radio-isotope and radio-opaque marker transit studies and the colonic contrast studies in patients with idiopathic megarectum are summarised in Tables 5 to 8.

(i) Gastric emptying

Gastric emptying of the liquid and solid phases of the test meal are graphically presented in Figure 4a & b. The quantitative analysis is seen in Tables 5 and 6.

When considered individually, four patients with idiopathic megarectum had entirely normal gastric emptying of liquid and solid. The other 6 patients with idiopathic megarectum had abnormally slow gastric emptying, either throughout the study or more commonly in the later stages of gastric emptying.

For the patients as a whole there was no statistical difference between patients with idiopathic megarectum and controls for the lag phases and gastric emptying time for 25%, 50%, and 75% of either liquid or solid phases.
However, late gastric emptying was abnormally slow for a number of patients, as illustrated in Figures 4a and 4b. As a result the patients with idiopathic megarectum had a significantly increased proportion of both the solid and liquid meal remaining at 360 minutes (p < 0.001 for both liquid and solid phases).

(ii) Small bowel transit

Data from one patient with idiopathic megarectum were lost through a technical error. As a group the patients with idiopathic megarectum had significantly faster "head of the meal" small bowel transit than controls [medians, 35 v 55 mins, megarectum v controls, p=0.04, Table 7]. However, when considered individually all but one patient with idiopathic megarectum fell within the normal range.

(iii) Colonic transit

All the patients' colonic isotope scans were abnormal, as illustrated in Figure 5. The region(s) of delay corresponded to the region(s) of dilated gut as demonstrated on contrast studies in 9 of the 10 patients with idiopathic megarectum. One patient refused to continue with the study at 72 hours, when the head of the radioisotope was in the descending colon.
As a group the patients with idiopathic megarectum had a significantly slower 'fastest' colonic transit time than the controls [p=0.006] (Table 7). However, when considered individually seven patients had fastest colonic transit times within or just outside the normal range, providing further evidence that there was not substantially delayed transit in the undilated colon.

The progression of the centre of mass of radioisotope in most patients with idiopathic megarectum was prolonged, with a spectrum of abnormal transit. No patient with idiopathic megarectum defecated during the study, and the centre of mass remained within the rectosigmoid region in 8 patients in the latter part of the study (72-192 hours). In 2 patients with idiopathic megarectum there was very slow initial transit, with the centre of mass remaining at the level of the transverse colon at 72 hours. In one of these patients there was then rapid progress into the rectosigmoid region where no further progress occurred; the other patient declined to continue with the study. In the patient with a megacolon as well as a megarectum, progression of the centre of mass was very slow throughout the colon. In this patient the centre of mass had not progressed beyond the splenic flexure by 144 hours when the study ended. In one patient progression of the centre of mass was initially normal followed by stasis within the descending colon and then the rectosigmoid region. In 6 patients progression of the
centre of mass was initially normal, some delay occurring in the transverse and descending colon, but the centre of mass reaching the rectosigmoid region just within normal limits.

**Idiopathic megacolon**

As there were only 3 patients in this group, the results will be considered individually.

(i) Gastric emptying

Two patients with idiopathic megacolon had normal gastric emptying for liquid and solid phases of the test meal. One patient (female) had abnormally slow late gastric emptying, with an increased proportion of both the liquid and solid phases remaining in the stomach at 6 hours (17 and 20% respectively).

(ii) Small bowel transit

The "head of the meal" small bowel transit was slightly fast in 1 patient (25 minutes) but was otherwise within the normal range.

(iii) Colonic transit

The colonic isotope scans were abnormal in all 3 patients with idiopathic megacolon. In one patient no isotope had reached the rectosigmoid region by 168 hours, despite the patient reporting x3 bowel actions during the study. It should be noted that this patient had had a sigmoid...
volvulus a few weeks prior to this study.

The patients with idiopathic megacolon had a slow 'fastest' colonic transit time (38, 79 and 168 hours). The delay was most marked in the left colon (predominantly the descending colon) in 2 patients with idiopathic megacolon, and in the right colon in the patient who had had a sigmoid volvulus.

The progression of the centre of mass of radioisotope was prolonged. All 3 patients reported at least 2 defaecations during the transit study, but in only one patient was there any loss of isotope before 125 hours, and this patient retained 50% of the isotope load at 96 hours (all figures corrected for radioactive decay).

(C) RADIO-OPAQUE MARKER COLONIC TRANSIT STUDY

Idiopathic megarectum
In patients with idiopathic megarectum, the site of delay of the radio-opaque markers was the same as the dilated segment of gut, which was similar to the site of delay of radio-isotope. All 10 patients had markedly slow transit with the majority of radio-opaque markers retained after 120 hours. In 6 patients all the retained markers were within the rectosigmoid region. In 2 patients most of the markers were located within the rectosigmoid region. In one patient the majority of markers were within the
descending colon, and in the one patient with a megacolon 55 of the 60 shapes were reported as retained, but the X-Ray film was subsequently lost and therefore unavailable for review.

**Idiopathic megacolon**

Two patients with idiopathic megacolon had normal radio-opaque marker colonic transit studies (6 and 7 retained markers). The other retained the majority of the markers (50), distributed throughout the colon with the majority in the rectosigmoid region. In this patient, the radioisotope had not reached the rectosigmoid region at 120 hours.

**DISCUSSION**

Patients with idiopathic megarectum and idiopathic megacolon have a normal calibre upper small intestine. Although the upper gut appears normal in calibre, our results show that some patients with idiopathic megarectum have abnormalities of gastric emptying. Most commonly a delay occurred in the late phase of gastric emptying, a finding similar to patients with idiopathic slow transit constipation (Stivland et al 1991, Van der Sijp et al 1993a. However, unlike the latter group, patients with idiopathic megarectum did not complain of bloating and abdominal distension after the test meal.
Six patients with idiopathic megarectum retained excessive solid, liquid or both components of the test meal at 6 hours. The significance of these abnormalities of gastric emptying is uncertain. All the patients started the isotope transit study with an empty colon, to avoid a possible inhibitory effect on gastric emptying by rectal (Youle and Read 1984) or colonic distension. Although the gastric emptying study started 48 hours after any laxative agent, it is unlikely that any inhibitory affect of colonic loading occurred. The delayed late gastric emptying may be related to altered interdigestive gut motility.

One patient with idiopathic megacolon had abnormal late gastric emptying, but as only 3 such patients were studied the significance of this finding is unknown.

Although a distended rectum may alter small bowel transit (Youle and Read 1984) no patient with idiopathic megarectum had slow small bowel transit. This is in contrast to patients with severe idiopathic constipation, many of whom have abnormalities of gastric emptying and small bowel transit (Stivland et al 1991, Van der Sijp 1993a). Small bowel transit tended to be faster than normal in patients with idiopathic megarectum, but this in itself is unlikely to be of clinical significance. In contrast, Bassotti et al (1987) reported disordered small bowel motility in a 10 year old Iranian child with
idiopathic megarectum and megacolon. The child presented with constipation, faecal incontinence and vomiting, which resolved with magnesium salts. None of the patients with idiopathic megarectum had vomiting as a symptom despite very infrequent bowel actions.

Patients with idiopathic megarectum have rectal dilatation down to the pelvic floor, with no distal narrow segment. Proximal colonic dilatation commonly extends to the sigmoid colon and occasionally the whole colon is involved. All the colonic isotope scans showed abnormal colonic transit. In most patients the region(s) of delay corresponded to the region(s) of dilated bowel, with retention in the rectosigmoid region in all patients in whom the study was completed [n=9]. In normal controls the descending colon and rectosigmoid regions are thought to function mainly as conduits whereas the transverse colon appears to be an important storage site (Krevsky et al 1986, Proano et al 1990). This storage function of the transverse colon is exaggerated in some patients with idiopathic megarectum, but the caecum and ascending colon, descending colon, and rectosigmoid regions have also been demonstrated to be 'storage sites'. The delayed transit through the more proximal colon may, despite adequate bowel preparation prior to these transit studies, be a consequence of many years of rectosigmoid stasis rather than a primary abnormality. In those patients with a megacolon, with or without a megarectum,
retention of isotope is seen throughout the colon, suggesting that the major motility disorder resides within the dilated gut. The results of surgery would tend to support this observation. If a stoma is brought out proximal to dilated gut its function is normal, whereas function is abnormal if dilated gut is used to form a stoma (Stabile et al 1992a).

In patients with idiopathic megarectum the radio-opaque marker transit study produced similar results to the radio-isotope study. Radio-opaque markers would therefore appear adequate in clinical practice for defining the region of delayed transit in patients with idiopathic megarectum. In contrast in patients with idiopathic megacolon with a normal diameter rectum, the radio-isotope scans demonstrated markedly abnormal colonic motility which the radio-opaque marker study failed to detect.

Defining the site of delayed transit may be especially important if surgery is being contemplated in these patients. A stoma brought out proximal to the dilated large bowel is usually effective (Stabile et al 1992a), and a simple transit study should be able to predict this in patients with idiopathic megarectum. More specialist investigations may be needed in patients with idiopathic megacolon. The patient with idiopathic megacolon and sigmoid volvulus had marked delay in transit through the
right colon. This was thought to be secondary to a recent sigmoid volvulus and he had a left hemicolecctomy for recurrent volvulus. Surgery resolved the symptoms associated with volvulus and constipation, however intermittent abdominal pain and bloating recurred after surgery and persisted at 3 years follow up. These symptoms were not associated with any abnormalities on X-Ray studies and suggest possible motility abnormalities in the residual large bowel.

Other procedures, such as a coloanal anastomosis (Stabile et al 1992b, Stewart, Kumar and Keighley 1994) should also be preceded by a study of gut transit to be certain the dilated segment is the only part of the colon which is functionally deficient.
Table 5. Gastric emptying of the liquid phase of a meal in patients with idiopathic megarectum and normal controls*.

<table>
<thead>
<tr>
<th>LIQUID GASTRIC EMPTYING</th>
<th>Megarectum</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>lag phase (min)</td>
<td>6 (1-15)</td>
<td>7 (2-16)</td>
<td>NS 0.70</td>
</tr>
<tr>
<td>time to empty 25% (min)</td>
<td>33 (10-55)</td>
<td>29 (6-55)</td>
<td>NS 0.46</td>
</tr>
<tr>
<td>time to empty 50% (min)</td>
<td>115 (45-160)</td>
<td>90 (27-115)</td>
<td>NS 0.09</td>
</tr>
<tr>
<td>time to empty 75% (min)</td>
<td>221 (105-328)</td>
<td>175 (105-230)</td>
<td>NS 0.29</td>
</tr>
<tr>
<td>% remaining at 180 minutes</td>
<td>30 (10-45)</td>
<td>25 (12-39)</td>
<td>NS 0.48</td>
</tr>
<tr>
<td>% remaining at 360 minutes</td>
<td>10 (3-22)</td>
<td>0 (0-7)</td>
<td>S 0.0005</td>
</tr>
</tbody>
</table>

*Data presented as MEDIAN with range in parentheses
p values using Mann Whitney unpaired, two-tailed test
NS = not significant
S = significant
Table 6. Gastric emptying of the solid phase of a meal in patients with idiopathic megarectum and normal controls.

<table>
<thead>
<tr>
<th>SOLID GASTRIC EMPTYING</th>
<th>Megarectum</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>lag phase (min)</td>
<td>35 (10-135)</td>
<td>41 (17-80)</td>
<td>NS 0.83</td>
</tr>
<tr>
<td>time to empty 25% (min)</td>
<td>108 (63-185)</td>
<td>103 (65-150)</td>
<td>NS 0.97</td>
</tr>
<tr>
<td>time to empty 50% (min)</td>
<td>154 (105-360)</td>
<td>153 (110-210)</td>
<td>NS 0.72</td>
</tr>
<tr>
<td>time to empty 75% (min)</td>
<td>266 (170-360)</td>
<td>200 (180-270)</td>
<td>NS 0.39</td>
</tr>
<tr>
<td>% remaining at 180 minutes</td>
<td>36 (26-77)</td>
<td>41 (27-65)</td>
<td>NS 0.92</td>
</tr>
<tr>
<td>% remaining at 360 minutes</td>
<td>15 (5-50)</td>
<td>0 (0-5)</td>
<td>S 0.0002</td>
</tr>
</tbody>
</table>

Data presented as MEDIAN with range in parentheses
p values using Mann Whitney unpaired, two-tailed test
NS = not significant
S = significant
Table 7. Small intestinal and colon transit in patients with idiopathic megarectum and normal controls.

<table>
<thead>
<tr>
<th></th>
<th>Megarectum</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small bowel solid transit time [min]</td>
<td>35 [5-60] n=9</td>
<td>55 [30-68] n=11</td>
<td>S 0.04</td>
</tr>
<tr>
<td>Colon solid fastest transit time [min]</td>
<td>48 [26-144] n=10</td>
<td>31 [27-38] n=11</td>
<td>S 0.006</td>
</tr>
</tbody>
</table>

*Data presented as MEDIAN with range in parentheses
p values using Mann Whitney unpaired, two-tailed test
S = significant
Table 8. Results of radio-isotope and radio-opaque marker colonic transit studies indicating sites of regional delay and regions of dilated gut as demonstrated on contrast studies.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Radio-isotope colonic transit study</th>
<th>Radio-opaque marker study</th>
<th>Contrast study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Region of delay</td>
<td>Fastest transit (hours)</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>TC</td>
<td>&gt;72</td>
<td>recsig</td>
</tr>
<tr>
<td>PC</td>
<td>recsig (C&amp;AC, TC)</td>
<td>71</td>
<td>recsig</td>
</tr>
<tr>
<td>TC</td>
<td>recsig</td>
<td>26</td>
<td>recsig</td>
</tr>
<tr>
<td>BD</td>
<td>rectum</td>
<td>47</td>
<td>rectum</td>
</tr>
<tr>
<td>JH</td>
<td>recsig</td>
<td>49</td>
<td>rectum</td>
</tr>
<tr>
<td>KH</td>
<td>recsig</td>
<td>40</td>
<td>rectum</td>
</tr>
<tr>
<td>JM</td>
<td>rectum</td>
<td>34</td>
<td>recsig</td>
</tr>
<tr>
<td>TN</td>
<td>recsig</td>
<td>37</td>
<td>recsig</td>
</tr>
<tr>
<td>RN</td>
<td>recsig &amp; DC</td>
<td>51</td>
<td>DC (TC, SF, recsig)</td>
</tr>
<tr>
<td>RS</td>
<td>C&amp;AC, TC</td>
<td>&gt;144</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Key: C&AC: caecum and ascending colon; TC: transverse colon; SF: splenic flexure; DC: descending colon; recsig: rectum and sigmoid colon; colon: all colon including sigmoid colon; >: did not reach rectosigmoid region in time given; if region of gut in parentheses: delay in transit occurred but not as marked as elsewhere.
Figure 3. Radio-isotope transit studies. (a) The stomach was "outlined" on screen to create a region of interest enabling the percentage of isotope remaining in the stomach to be calculated. The pictures to the right illustrate progressive emptying of the stomach and accumulation of isotope in the small intestine. (b) Similarly the colon was divided into 6 regions of interest (see text) and the percentage of isotope in each region was calculated. The views obtained at 48, 72, 96 and 192 hours in one patient with idiopathic megarectum are shown in Figure 3c. Nearly all the isotope was in the rectum by 72 hours, despite the patient's protestations to the contrary, effective defaecation did not occur. By 192 hours the patient had overflow faecal incontinence and radio-isotope was seen in the anal canal. Phosphate enemas successfully evacuated the rectum.
Figure 3. Gastric emptying of the liquid phase of a meal in patients with ileocecal resection (in 10).

I.L. : Colonic Transit Study

48 hours

72 hours

96 hours

192 hours

PA View
Figure 4a. Gastric emptying of the liquid phases of a test meal in patients with idiopathic megarectum (n=10). The shaded area represents the normal range (mean +/- 2 standard deviations). Each line represents a patient with idiopathic megarectum.
**Figure 4b.** Gastric emptying of the solid phases of a test meal in patients with idiopathic megarectum (n=10). The shaded area represents the normal range (mean +/- 2 standard deviations). Each line represents a patient with idiopathic megarectum.
Figure 5a. The results of the colonic isotope transit study in a patient with idiopathic megarectum (JH). Transit is within normal limits to the rectosigmoid region where significant delay occurs. The patient had not spontaneously defaecated for many years. At 142 hours a phosphate enema was given which emptied the rectum. The time activity curves for each region of interest are shown.

Figure 5a
**Figure 5b.** The results of the colonic isotope transit study in a patient with idiopathic megarectum (FC). Some delay occurs proximally in the caecum and ascending colon, and more markedly in the transverse colon, as well as in the dilated rectosigmoid region. Rectal evacuation was achieved by manual evacuation. The time activity curves for each region of interest are shown.
CHAPTER 5

Pathology of idiopathic megarectum and megacolon

The pathological basis underlying both idiopathic megarectum and idiopathic megacolon is unknown. In particular it is unknown if there are abnormalities involving the extrinsic nerves, the enteric nerve plexuses, or the intestinal smooth muscle. Abnormalities of any of these components could lead to gut dilatation and impaired motility.

Most reports on the pathology of these conditions relate to one or two patients only. The muscle layers have been reported as normal (Duhamel 1966, Watkins 1966, Palmer and McBurnie 1967, Nissan and Bar-Maor 1971, Barnes et al 1986, Scott 1988, Stabile 1992b), atrophic (Kune 1966, Barnes et al 1986, Morson et al 1990) and hypertrophic (Kune 1966, Palmer and McBurnie 1967, Roy 1968, Smith 1972a, Smith, Grace and Todd 1977, Barnes et al 1986, Stabile 1991b, 1992b). The intrinsic innervation has been reported as normal (Duhamel 1966, Watkins 1966, Palmer and McBurnie 1967, Roy 1968, Nissan and Bar-Maor 1971, Barnes et al 1986, Scott 1988, Stabile 1991ab 1992b), but decreased numbers of ganglion cells have also been reported (Palmer and McBurnie 1967). Most of these reports have included assessment by haematoxylin and eosin staining only, although silver staining has shown some neuronal abnormalities (Smith 1972a, Smith, Grace

In this chapter the results of a detailed histological study of 30 patients with idiopathic megarectum and idiopathic megacolon is reported. The aim was to identify neural or smooth muscle abnormalities.

PATIENTS AND METHODS

TISSUE STUDIED

(i) Patients
Tissue was obtained from the colon and/or rectum of 30 patients (9 female, median age 24, (range 12-66) years) who had undergone surgery for either idiopathic megarectum or idiopathic megacolon. These two groups of patients were defined based on the criteria presented in chapter 2.

Twenty four patients had a megarectum which was associated with a variable degree of proximal colonic dilatation: 4 patients had a dilated rectum only (all men, median age 21 (range 15-32) years), 9 had a megarectum and a megasigmoid with a normal diameter proximal colon (2 female, median age 18 (range 12-24) years, 11 patients had rectal and total colonic dilatation (4 female, median 27 (range 20-58) years).

Six patients had a normal sized rectum with a dilated
total colon (3 female, median 39 (range 34-66) years).

In all cases Hirschsprung's disease and other known causes of a dilated gut were excluded on the basis of either an intact rectoanal inhibitory reflex or a full thickness rectal biopsy showing the presence of ganglion cells, prior to definitive surgery.

The following full thickness specimens were obtained: rectum from 16 patients, 15 of whom had a typical megarectum; sigmoid colon from 26 patients, all of whom had a megasigmoid; and more proximal colonic specimens from 18 patients, 16 of whom had a megacolon.

(ii) Controls
Control tissue was obtained from the resection specimens of 17 patients (6 female, median age 58 (range 39-91) years) who had non-obstructing colonic or rectal cancer. None of these patients had any other known colonic pathology. The full thickness control specimens were taken at least 5 cm from the tumour and included rectum from 11 patients, sigmoid colon from 15, and more proximal colon from 3 patients.

In both patients and controls all tissue included the taenia coli.

HISTOLOGICAL PREPARATION
(i) Histology

Longitudinally orientated blocks of the full thickness of the bowel wall were taken for processing into paraffin wax after fixation in 10% formal saline. Sections were cut at 6 μm and stained with Haematoxylin and Eosin (H&E), periodic acid Schiff (PAS), Martius Scarlet Blue (MSB) and Phosphotungstic Acid Haematoxylin (PTAH).

(ii) Immunohistochemistry

Neural and glial tissue were immunostained with primary rabbit polyclonal antibodies raised against S100 protein, a glial and Schwann cell marker (Lowe 1990), and protein gene product 9.5 (PGP 9,5) a nerve cell body and axon marker (Wilson et al 1988, Lowe 1990).

Sections from the same blocks used for routine histology were dewaxed in xylene and immersed in 0.3% hydrogen peroxide for 20 minutes to block any non-specific hydrogen peroxidase. Sections to be immunostained by S100 antibodies were incubated with 0.1% chymotrypsin for 8 min at 37°C. All sections were then incubated with the primary antibody (1 in 250: PGP 9.5, Ultraclone, Isle of Wight, UK and S100, DAKO, Copenhagen, Denmark) for 1 hr.

Sections were thoroughly washed with phosphate buffered saline, incubated with the second layer antibody (1 in
200, biotinylated affinity-isolated swine immunoglobulins to rabbit immunoglobulins (DAKO) for 1 hour. The sections were washed with phosphate buffered saline and incubated for 45 min with the third layer, streptavidin (1 in 200, Streptavidin antibody, avidin biotin complex, Amersham, Amersham, UK).

After washing with phosphate-buffered saline the sections were 'developed' with diaminobenzadine (DAB, Vector, Peterborough, UK) with 0.03% hydrogen peroxide solution. The reaction was ended by washing in tap water and the sections were counterstained with Haematoxylin and Eosin.

HISTOLOGICAL ANALYSIS

On the H&E stained sections the presence of melanosis coli or other histological features were noted. On the same sections the diameter of the muscularis mucosae and of the circular and longitudinal muscle of the muscularis externa were measured using a graded graticle. For each smooth muscle layer 3 separate measurements were made across the section and the mean calculated. Inclusion bodies on the PAS stained sections and the presence of any fibrosis in the smooth muscle layers on the MSB and PTAH stained sections were recorded.

The density of S100 and PGP 9.5 immunoreactivity was assessed on a numeric scale of 0-5 (absent to very dense)
in the layers of the gut from lumenal to serosal surface. The presence of the 3 divisions of the submucosal plexus, that is Meissner's plexus, the Intermediate plexus and Henle's plexus (Hoyle and Burnstock 1989a, Crowe et al 1992) were documented.

STATISTICAL ANALYSIS

Two-tailed Mann-Whitney tests were carried out for statistical comparison between patients and controls for sections from the same colonic regions. Analysis of the results from patients with idiopathic megarectum was performed separately from those with idiopathic megacolon.

RESULTS

Patients with idiopathic megacolon and a normal diameter rectum were older than patients with idiopathic megarectum (39 (34-66) v 21 (12-58), median (range) years, p=0.002), in keeping with the clinical pattern of these two conditions. Patients with idiopathic megarectum who had distal gut dilatation only (ie megarectum with or without a dilated sigmoid colon) were younger than those with megarectum and total colonic dilatation (18 (12-32) v 27 (20-57), p=0.005).

HISTOLOGY

106
Mild melanosis coli was seen in 1 control patient (6%), in 8 patients (33%) with idiopathic megarectum, and 2 of 6 patients (33%) with idiopathic megacolon. Mild 'obstructive colitis', that is a mild chronic inflammatory cell infiltrate in the lamina propria, was seen in one control patient (6%), 10 patients (42%) with idiopathic megarectum and 3 patients (50%) with idiopathic megacolon. Hypertrophy of the muscularis externa was reported in 8 patients with idiopathic megarectum, including 1 patient who had a thickened muscularis mucosae, and in 2 patients with idiopathic megacolon. Slight fibrosis of the muscularis externa was seen in 1 patient with idiopathic megarectum.

In one control patient mild diverticular disease, without any evidence of inflammation, was noted.

The diameters of the smooth muscle layers of patient and control rectum, sigmoid colon and proximal colon are shown in Table 9.

**Idiopathic Megarectum**

In patients with idiopathic megarectum the rectal muscularis mucosae and both the circular and longitudinal muscle of the muscularis externa were thickened (see Figure 6). In dilated sigmoid colon the muscularis
mucosae was abnormally thick, but the muscularis externa was within normal limits. All 3 smooth muscle layers were of normal thickness in dilated proximal colon.

**Idiopathic megacolon**

There was no measured thickening of any of the smooth muscle layers at any level in patients with idiopathic megacolon.

The ratio of thicknesses of the circular to longitudinal muscle in the rectum, sigmoid colon and proximal colon in patients and controls are shown in Table 10. This shows that in the rectum of patients with an idiopathic megarectum there was proportionately significantly greater thickening of the longitudinal muscle compared to the circular muscle layer.

**PERIODIC ACID SCHIFF (PAS)**

Inclusion bodies were not seen in tissue from either the control patients or from patients with idiopathic megarectum or idiopathic megacolon.

**MARTIUS SCARLET BLUE (MSB) and PHOSPHOTUNGSTIC ACID HAEMATOXYLIN (PTAH)**

With MSB staining 1 control patient showed a slight increase in connective tissue in the muscularis externa
Idiopathic Megarectum

(i) MSB staining showed some fibrosis of the longitudinal muscle in 14 patients (58%) with idiopathic megarectum. With MSB a similar increase in fibrosis was seen in the circular muscle of 9 patients (38%) and in the muscularis mucosae of 7 patients (29%).

(ii) Using PTAH staining an increase in fibrosis was seen in 5 patients (21%) in the longitudinal muscle, in 4 patients (17%) in the circular muscle and in 1 patient in the muscularis mucosae.

There was a variable relationship between increased connective tissue within the smooth muscle layers (fibrosis) and increased thickness of smooth muscle. In patients with idiopathic megarectum fibrosis of the longitudinal muscle of the rectum was always associated with hypertrophy, but only about 50% of patients with a thickened longitudinal muscle had evidence of fibrosis. There was thickening of rectal muscularis mucosae in 13 patients with idiopathic megarectum but this was associated with fibrosis in only 1 patient.

Idiopathic Megacolon
Using MSB staining fibrosis of the longitudinal muscle was seen in 2 patients (33%), of the circular muscle in 1 patient, and in the muscularis mucosae of 3 patients (50%).

PTAH staining showed some fibrosis in 1 patient in the muscularis mucosae and in 1 patient in the longitudinal muscle.

**IMMUNOHISTOCHEMISTRY**

Although reproducible staining was obtained within the muscularis externa and adjacent Henle's plexus it was difficult to achieve the same quality of staining within the lamina propria, mainly due to an excess of background staining.

The density of innervation in different layers of the rectum, sigmoid and proximal colon is shown in Tables 11-13. The density of neural tissue within the circular muscle was uniform across a section from the inner to the outer margins, but the density in the longitudinal muscle varied across a section in both controls and patients.

PGP 9.5 and S100 immunoreactivity of the circular muscle appeared normal (Figure 6). There appeared to be a decrease in the density of neural tissue of the longitudinal muscle in all the regions of the large bowel.
studied in patients with idiopathic megarectum, although this reached statistical significance only in the sigmoid colon.

Henle's and Meissner's plexuses were identified in more than 95% of patients but the Intermediate plexus was not seen in all patients (71-93% varying with gut region), due to technical reasons rather than any intrinsic abnormality in patients. The observed ganglia were normal in appearance (Figure 6).

**DISCUSSION**

The major finding in this study was thickening of the muscle layers of the gut in patients with idiopathic megarectum. The marked thickening of the muscularis externa in the rectum involved both the circular and longitudinal muscle, hypertrophy of the latter being most marked. In patients with idiopathic megarectum atrophy of the smooth muscle layers of the gut was not seen, despite gut dilatation. The muscularis mucosae was also thickened.

A decrease in the density of innervation of the longitudinal muscle of the rectum was also seen. This change may relate to the hypertrophy of this smooth muscle layer or may be part of the primary pathological process. However, in the sigmoid colon of patients with idiopathic megarectum the decreased density of neural
tissue within the longitudinal muscle was not associated with muscle hypertrophy, suggesting that this neural abnormality may be primary.

There was no clear association between muscle thickening and fibrosis. Patients with idiopathic megarectum with thickened muscularis propria or mucosae did not necessarily have associated smooth muscle fibrosis. Similarly, fibrosis of normal diameter enteric muscle was seen.

The architecture of the enteric nervous system appeared to be preserved in patients with idiopathic megarectum and idiopathic megacolon. No focal abnormality was found in either the myenteric or submucosal plexuses. The amount of neural tissue within the circular muscle was greater than that in the longitudinal muscle in both controls and patients, as has been reported previously in healthy subjects (Howard, Garrett and Kidd 1984).

Although the architecture of the enteric nervous system in patients with idiopathic megarectum and megacolon appeared to be intact, abnormalities of neurotransmission involving important inhibitory neurotransmitters such as VIP and nitric oxide (Burleigh 1992, Huizinga, Tomlinson and Pintin-Quezada 1992, Stark and Szurszewski 1992, Keef et al 1993, O'Kelly, Brading and Mortensen 1993, Boeckxstaens et al 1993) may have a role in the
aetiopathogenesis of this condition. Abnormalities of distribution of vasoactive intestinal polypeptide (VIP), a putative inhibitory neurotransmitter (Couture et al 1981, Gershon and Erde 1981, Furness and Costa 1987, Hoyle and Burnstock 1989b, Huizinga, Tomlinson and Pintin-Quesada 1992), have been found in the resection specimens of patients with idiopathic megacolon (Koch et al 1992), severe idiopathic chronic constipation (Koch et al 1988, Milner et al 1990) and in patients with Hirschsprung's disease.

The control tissue was obtained from patients undergoing surgery for non-obstructing colonic adenocarcinoma. These patients were older than those with idiopathic megarectum and idiopathic megacolon but were thought to offer more appropriate reference tissue than from patients, albeit of a more similar age group, undergoing surgery for inflammatory bowel disease or familial adenomatous polyposis. Changes in enteric innervation have been reported in patients with inflammatory bowel disease (Koch, Carney and Go 1987, Koch et al 1988b, Kubota et al 1992). There would appear to be no evidence to suggest that changes in enteric muscle thickness occur with age.

The two patients groups differed in their mode of clinical presentation, extent of bowel dilatation, and age. Patients with idiopathic megarectum alone were significantly younger than patients with colonic
dilatation and a normal diameter rectum (idiopathic megacolon). This is in keeping with the clinical impression that idiopathic megarectum and idiopathic megacolon are different conditions, although there is some clinical overlap.

Other minor histological changes were noted. Melanosis coli, a marker of chronic excessive anthraquinone intake (see chapter 9), was seen in a third of patients with idiopathic megarectum or idiopathic megacolon, although it was advanced in only 1 patient. Mild inflammation, so called 'obstructive colitis', was seen in half the patients and may relate to a chronic functional obstruction.

In summary, there is marked thickening of the enteric smooth muscle in patients with idiopathic megarectum. This does not appear to be associated with any marked abnormality of the architecture of the enteric innervation. However, functional abnormalities of the enteric innervation remain a possible cause for this smooth muscle hypertrophy.
Table 9. The diameters of the 3 smooth muscle layers, the muscularis mucosa (mm) and the circular (cm) and longitudinal muscle (lm) of the muscularis externa, of controls and patients with idiopathic megarectum and idiopathic megacolon.

<table>
<thead>
<tr>
<th></th>
<th>Rectum</th>
<th>Sigmoid colon</th>
<th>Proximal colon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=11</td>
<td>n=15</td>
<td>n=3</td>
</tr>
<tr>
<td>mm</td>
<td>33(21-61)</td>
<td>25(17-48)</td>
<td>21(15-30)</td>
</tr>
<tr>
<td>cm</td>
<td>633(333-1670)</td>
<td>877(593-1667)</td>
<td>360(167-700)</td>
</tr>
<tr>
<td>lm</td>
<td>303(183-643)</td>
<td>460(160-1092)</td>
<td>250(45-808)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic Megarectum</td>
<td>n=21</td>
<td>n=21</td>
<td>n=10</td>
</tr>
<tr>
<td>mm</td>
<td>78(23-144)**</td>
<td>44(21-165)**</td>
<td>26(13-48)</td>
</tr>
<tr>
<td>cm</td>
<td>1000(375-3410)**</td>
<td>801(287-3500)</td>
<td>668(312-1592)*</td>
</tr>
<tr>
<td>lm</td>
<td>1083(233-3200)**</td>
<td>379(102-1643)</td>
<td>233(150-1600)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic Megacolon</td>
<td>n=1</td>
<td>n=5</td>
<td>n=6</td>
</tr>
<tr>
<td>mm</td>
<td>73</td>
<td>41(15-57)</td>
<td>29(23-53)</td>
</tr>
<tr>
<td>cm</td>
<td>840</td>
<td>808(43-1178)</td>
<td>479(393-1033)</td>
</tr>
<tr>
<td>lm</td>
<td>570</td>
<td>357(90-727)</td>
<td>403(145-767)</td>
</tr>
</tbody>
</table>

Values given are the median diameters (in um) with the range in parentheses. In all patients with idiopathic megarectum the gut dilatation extended for a variable extent proximally. The values given in this group are from **dilated** bowel only.

n: refers to number of patients
*: p=<0.05
**: p=<0.005

In the proximal colon more than one colonic region was available in some patients (ie ascending, transverse or descending colon), the 3 control patients provided 5 specimens, the 16 patients provided 30 specimens.
Table 10. Ratio of circular to longitudinal muscle thickness in controls and in patients with idiopathic megarectum and idiopathic megacolon.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Idiopathic Megarectum</th>
<th>Idiopathic Megacolon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>2.28 (1.36)</td>
<td>1.44 (0.96)*</td>
<td>1.47</td>
</tr>
<tr>
<td>n=11</td>
<td>n=21</td>
<td>n=1</td>
<td></td>
</tr>
<tr>
<td>Sigmoid</td>
<td>2.41 (1.14)</td>
<td>2.17 (0.97)</td>
<td>2.63 (1.12)</td>
</tr>
<tr>
<td>n=15</td>
<td>n=21</td>
<td>n=5</td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>2.04 (1.35)</td>
<td>2.31 (1.10)</td>
<td>1.76 (0.63)</td>
</tr>
<tr>
<td>n=3</td>
<td>n=10</td>
<td>n=6</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean with standard deviation in parentheses.

All measurements from patients with idiopathic megarectum are taken from dilated segments of gut.

n = number of patients
* p=<0.05
Table 11. Density of innervation in regions of the rectum in controls and in patients with idiopathic megarectum.

<table>
<thead>
<tr>
<th></th>
<th>Longitudinal muscle</th>
<th>Circular muscle</th>
<th>Muscularis mucosae</th>
<th>Lamina propria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td>1(0,2)</td>
<td>4(4)</td>
<td>2(0,2)</td>
<td>2(0,3)</td>
</tr>
<tr>
<td>PGP 9.5</td>
<td>2(1,2)</td>
<td>4(4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Idiopathic Megarectum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td>1(0,3)</td>
<td>4(3,5)</td>
<td>2(0,3)</td>
<td>2(0,3)</td>
</tr>
<tr>
<td>PGP 9.5</td>
<td>1(0,2)</td>
<td>3(3,4)</td>
<td>3(0,3)</td>
<td>3(0,3)</td>
</tr>
</tbody>
</table>

Values given are the median score with the range in parentheses. Scoring system: 0=absent, 1=very sparse, 2=sparse, 3=moderate, 4=dense, 5=very dense. Tissues from 11 control patients and 15 patients with idiopathic megarectum.

- = too much background staining for accurate scoring
Table 12. Density of innervation in regions of the sigmoid colon in controls and in patients with idiopathic megarectum and idiopathic megacolon.

<table>
<thead>
<tr>
<th></th>
<th>Longitudinal muscle</th>
<th>Circular muscle</th>
<th>Muscularis mucosae</th>
<th>Lamina propria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td>1(0-3)</td>
<td>4(4)</td>
<td>3(0-3)</td>
<td>3(0-3)</td>
</tr>
<tr>
<td>PGP9.5</td>
<td>2(0-3)</td>
<td>4(4)</td>
<td>3(0-3)</td>
<td>3(0,3)</td>
</tr>
<tr>
<td><strong>Idiopathic Megarectum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td>1(0-3)</td>
<td>4(3-5)</td>
<td>2(0-3)</td>
<td>2(0-3)</td>
</tr>
<tr>
<td>PGP9.5</td>
<td>1(0-2)*</td>
<td>4(3-5)</td>
<td>3(0-3)</td>
<td>3(0-3)</td>
</tr>
<tr>
<td><strong>Idiopathic Megacolon</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td>1(0-2)*</td>
<td>4(3-5)</td>
<td>3(0-3)</td>
<td>3(0-3)</td>
</tr>
<tr>
<td>PGP9.5</td>
<td>1(0-3)</td>
<td>3.5(3-4)</td>
<td>3(2-3)</td>
<td>3(2-3)</td>
</tr>
</tbody>
</table>

Values given are the median score with the range in parentheses. Scoring system: 0=absent, 1=very sparse, 2=sparse, 3=moderate, 4=dense, 5=very dense. Tissues from 13 control patients and patients with idiopathic megarectum and with idiopathic megacolon, all of whom had a dilated sigmoid colon.

*p=<0.05
Table 13. Density of innervation in regions of the proximal colon in controls and in patients with idiopathic megarectum and idiopathic megacolon.

<table>
<thead>
<tr>
<th></th>
<th>Longitudinal muscle</th>
<th>Circular muscle</th>
<th>Muscularis mucosae</th>
<th>Lamina propria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td>1(0-3)</td>
<td>4(4)</td>
<td>3(3)</td>
<td>2(0-3)</td>
</tr>
<tr>
<td>PGP 9.5</td>
<td>1.5(0-3)</td>
<td>4(4)</td>
<td>3(3)</td>
<td>3(0-3)</td>
</tr>
<tr>
<td><strong>Idiopathic Megarectum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td>1(0-3)</td>
<td>4(3-5)</td>
<td>2(0,3)*</td>
<td>3(0-3)</td>
</tr>
<tr>
<td>PGP 9.5</td>
<td>1(0-2)</td>
<td>4(3-4)</td>
<td>2(0-3)</td>
<td>3(0-3)</td>
</tr>
<tr>
<td><strong>Idiopathic Megacolon</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td>1(0-3)</td>
<td>4(3-4)</td>
<td>2(0-3)*</td>
<td>2(0-3)</td>
</tr>
<tr>
<td>PGP 9.5</td>
<td>2(0-3)</td>
<td>4(3-4)</td>
<td>2(0-3)</td>
<td>3(0-3)</td>
</tr>
</tbody>
</table>

Values given are the median score with the range in parentheses. Scoring system: 0=absent, 1=very sparse, 2=sparse, 3=moderate, 4=dense, 5=very dense. Tissues from 3 control patients and patients with idiopathic megarectum and patients with idiopathic megacolon, all of whom had a dilated proximal colon.

*: p=<0.05
Figure 6.

Figures 6a and 6b are photomicrographs of H&E stained sections of normal control tissue (a) and from a patient with idiopathic megarectum (b), taken at the same magnification (x15). In the patient with idiopathic megarectum a thickened muscularis externa is present.

Figures 6c (x40) and 6d (x100) are photomicrographs showing PGP 9.5 immunoreactivity in rectal tissue of a patient with idiopathic megarectum. The dense staining of the circular muscle is in contrast to the sparse staining within the longitudinal muscle (c). The ganglia illustrated in 6d are from Henle's plexus (H), the Intermediate plexus (I) and Meissner's plexus (M).

cm: circular muscle
lm: longitudinal muscle
Figure 6
CHAPTER 6

Enteric Innervation in idiopathic megarectum and megacolon

Decreased levels of vasoactive intestinal peptide (VIP), a putative inhibitory neuropeptide (Furness and Costa 1980, Hoyle and Burnstock 1989b, Huizinga, Tomlinson and Pintin-Quezada 1992) have been found in patients with idiopathic megacolon using radioimmunoassay (Koch et al 1992). Acetylcholinesterase activity was decreased in the muscularis externa of all resection specimens of the descending colon of 6 patients with idiopathic megacolon, indicating that excitatory neuromuscular transmission might also be affected (Koch et al 1992).

Decreased numbers of VIP immunoreactive nerve fibres have also been demonstrated in the oligoganglionic and aganglionic segments of colon obtained from patients with Hirschsprung's disease (Tsuto et al 1985, Larsson and Sundler 1990). Similarly in patients with idiopathic chronic constipation decreased levels of VIP have been demonstrated by immunoassay as well as decreased density of VIP immunoreactive nerve fibres by immunohistochemistry (Koch et al 1988a, Milner et al 1990).

Nitric oxide has an important role as an inhibitory neurotransmitter in the human gastrointestinal tract (Huizinga, Tomlinson and Pintin-Quezada 1992, Burleigh
1992, Boeckxstaens et al 1993, O'Kelly, Brading and Mortensen 1993, Stark and Szurszewski 1992, Keef et al 1993). In Hirschsprung's disease nitric oxide synthase-containing neurones are absent from the aganglionic regions of the intestine (Larsson et al 1995), and this may be a significant factor in the aetiology of this obstructive disorder.

The work reported in this chapter examines the intramural innervation of the large intestine in samples of tissue obtained from patients with idiopathic megarectum or idiopathic megacolon. The distributions of VIP and CGRP immunoreactivity and NADPH-diaphorase activity were assessed. NADPH-diaphorase activity can be regarded as a marker for nitric oxide synthase (NOS) in neurones in formaldehyde fixed tissue (Lincoln, Hoyle and Burnstock 1995).

PATIENTS AND METHODS

TISSUE STUDIED

(i) Patients

Tissue was obtained from five patients who had surgery for idiopathic megarectum and megacolon (1 female: age 18 years, 4 male: ages 18, 21, 25 and 37 years).

Two patients had dilatation of the rectum (rectal diameter at the pelvic brim on the lateral view 9.5 cm
and 11.5 cm) and entire colon (7-10 cm) as seen on preoperative x-ray contrast studies, 2 patients had a gross megarectum (10.5 cm and 14 cm) with dilatation of the sigmoid colon (8.5 cm and 10 cm) but a normal diameter colon (3.5 cm), 1 patient did not have gross rectal dilatation (4 cm) but did have marked sigmoid (10 cm) and colonic dilatation (6-10 cm).

Full thickness specimens that included the taenia coli were obtained from the sigmoid colon in all patients, and from the rectum and proximal colon in 3 patients.

(ii) Controls
Control tissue was obtained from the resection specimens of 10 patients (6 male, median age 52 years, range 43-91) who had non-obstructing colonic or rectal cancer (the same controls as used in chapter 5). None of these patients had any other underlying colonic pathology. The control tissue was taken at least 5 cm from the tumour. The routine histology was reviewed on all controls to ensure no unsuspected pathology had been present. Full thickness specimens were obtained from rectum (4), sigmoid colon (8) and proximal colon (1).

HISTOLOGICAL PREPARATION

(i) Immunohistochemistry
Samples were fixed in paraformaldehyde (4% in 0.1 M phosphate buffered saline, PBS, pH 7.3) for 1.5 to 2 h immediately after resection. After 3 ten min washes with PBS, samples were stored overnight in 7% w/v sucrose (for cryoprotection) with 0.1% w/v sodium azide. The samples were trimmed, blocked onto cork, mounted in Tissue-Tek embedding medium (OTC), frozen in crystallising isopentane (-158 °C) and stored in liquid nitrogen (approximately -200 °C).

Cryostat (-26 °C) sections cut at 10 μm were immunostained with primary rabbit polyclonal antibodies raised against S100 protein, a glial cell marker (Lowe 1990), protein gene product 9.5 (PGP 9.5) a nerve cell body and axon marker (Wilson et al 1988, Lowe 1990), VIP and CGRP. The sections were incubated with the primary antibodies (1 in 1000 dilution) at room temperature for 18 h. Preparations were then washed in PBS and incubated with the secondary antibody which was biotinylated donkey antirabbit IgG (1 in 250 dilution) for 1 h at room temperature. Preparations were then washed in PBS and incubated with a third layer of fluorescein isothiocyanate-conjugated streptavidin (1 in 250 dilution), for 1 h at room temperature. They were then washed with PBS, incubated with pontamine sky-blue (PBS/0.05% pontamine sky-blue/1% dimethylsulphoxide) for 5 - 10 min to reduce background fluorescence, rinsed in PBS and mounted in Citifluor (City University, London).
Stained sections were stored at 4-8 °C.

No neuronal staining was observed when the primary antibody was omitted. There was no specific staining when the anti-VIP serum was preadsorbed with VIP (0.3 μM) or the anti-CGRP serum with CGRP (0.3 μM) for 1 h at room temperature.

(ii) Histochemistry

Sections were also stained for reduced nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase activity. Sections were incubated with 0.7 mM nitroblue tetrazolium (NBT) and 1 mM NADPH made up in 0.1 M PBS pH 7.3 for 15 - 30 min. NADPH diaphorase activity, localized histochemically in paraformaldehyde fixed tissue, has been shown to colocalise extensively with nitric oxide synthase (NOS) immunoreactivity (Saffrey et al 1992, Ward et al 1992, Vanderwinden et al 1993), thus this technique is believed to demonstrate neurones capable of nitric oxide synthesis. There was no visible reaction product in the sections if the NADPH was omitted from the staining solution.

HISTOLOGICAL ANALYSIS

The density of innervation by nerves containing immunoreactivity or NADPH-diaphorase activity was
assessed subjectively on a numeric scale of 0 to 5 in the different layers of the gut from the luminal to the serosal surface. The presence of the three divisions of the submucosal plexus, namely Henle's plexus, Meissner's plexus and the Intermediate plexus (Hoyle and Burnstock 1989a, Crowe et al 1992) were documented. The presence or absence of VIP and CGRP immunoreactive cell bodies and NADPH diaphorase positive cell bodies in the ganglionic layers were also documented. At least four sections from each sample, stained for each substance, were examined on separate occasions.

This method of analysis is adequate for localising the peptides and for determining possible gross differences in patterns of innervation that might appear between the two groups of patients. However, such a method of analysis does not provide an adequate reflection of the peptide levels and cannot be used for a meaningful comparison of amounts of peptides present in the two samples. Immunoassays were carried out to measure peptide levels.

(iii) Immunoassay

Samples of the distal sigmoid colon from 5 control patients and 4 patients with idiopathic megarectum were processed for quantification of levels of VIP and CGRP by an inhibition enzyme-linked immunosorbent assay (ELISA)
Samples were frozen in liquid nitrogen until being dissected when the mucosa was separated from the muscularis externa along the plane of the submucous plexus. Neuropeptides were extracted by placing the tissue samples in 0.5 M acetic acid in a boiling water bath for 15 min. Samples were then homogenised and centrifuged at 3,500 g for 15 min. The supernatant was lyophilised and stored at -20°C.

Polystyrene 96-well microtiter assay plates were coated with the appropriate neuropeptide in 0.1 M bicarbonate-carbonate buffer containing 0.02% (w/v) sodium azide, pH 9.6, and stored overnight in a refrigerator. The plates were then washed with PBS containing 0.05% v/v Tween and 0.02% w/v sodium azide (PBS-TA). 150 ul of PBS-TA containing 0.1% w/v gelatin (gel-PBS-TA) was then added to each well and left for 1 h at room temperature.

The lyophilised samples were reconstituted with gel-PBS-TA containing 0.001% w/v aprotinin. Neuropeptide standards were prepared in the same buffer to produce a range of 0 to 10,000 pg per well. Neuropeptide antibodies were prepared in the following dilutions VIP 1:50,000 and CGRP 1:12,500. 50 µl of standard or sample and 50 µl of antibody were put into wells in triplicate and left overnight in a refrigerator at 4°C.
All plates were washed 3 times with PBS-Tween. 100 μl of anti-rabbit IgG conjugated to alkaline phosphatase in gel-PBS-TA (1:20,000) was added to each well, and the plates were incubated in a humid chamber at 37°C for 2 h. The plates were then washed 3 times with PBS-Tween and then with 0.1 M glycine buffer (pH 10.4). 100 μl of p-nitrophenyl phosphate in glycine buffer (1 mg. ml⁻¹) was then added to each well. The plates were read on a Titertek spectrophotometer at 405 nm.

RESULTS

In the patients with idiopathic megarectum, despite the gross dilatation, there was no muscle atrophy. In rectal tissue, hypertrophy of the muscularis mucosae was seen in 3 patients and of the muscularis externa in 2 patients. One patient had hypertrophy of both the muscularis mucosae and muscularis externa in the sigmoid colon and of the muscularis externa only in the proximal colon.

In sections stained with haematoxylin and eosin, mild obstructive colitis (an increase in chronic inflammatory cells in the lamina propria) was seen in all patients, mild melanosis coli in 2 patients, but no other abnormalities of the enteric nerves or muscle layers.

The immunohistochemical, NADPH-diaphorase histochemical and immunoassay results are summarised in Tables 14 - 16.
The gross pattern of distribution of S100 protein and PGP 9.5 immunoreactivity was similar in all sections from both control and patient groups. The inner circular muscle had a uniform density of innervation, whereas that of the longitudinal muscle varied across a section from regions with little or no neural tissue to regions of dense innervation (Figures 7 and 8). This local variation was most marked in the taenia of the sigmoid colon, although it also occurred in the longitudinal muscle of the rectal tissue.

An occasional ganglion or lone immunoreactive cell body was seen in the lamina propria, close to the muscularis mucosae, or embedded within the circular muscle in sections from the controls. No ganglia were seen embedded within the longitudinal muscle in sections from controls.

In tissue from the sigmoid colon of one patient, who had marked sigmoid colon and rectal dilatation, there was only a sparse innervation of the outer longitudinal muscle but normal, dense, innervation of the circular muscle. In the samples of tissue from the sigmoid colon of the other 4 patients, the innervation of the muscularis externa appeared to be within normal limits. There was nothing unusual about the appearance of myenteric ganglia in four of the five patients. However, in one patient some ectopic myenteric ganglia were
demonstrated within the longitudinal muscle (Figure 7). S100 and PGP 9.5 immunoreactivity in the submucous plexus were normal in this patient. There was a tendency towards a denser innervation of the lamina propria and muscularis mucosae in all patients compared to controls (Tables 14 and 15).

In the samples of rectal tissue from the patients with megarectum, the density of innervation of the longitudinal muscle was less than that of controls (Table 15). The myenteric and submucosal plexuses were unremarkable. As in the sigmoid colon there was a tendency for an increased number of nerve fibres in the lamina propria and the muscularis mucosae compared to controls (Figures 7 and 8).

In the proximal colon the pattern of innervation was similar to that of the sigmoid colon, and there were no obvious differences between the groups of tissues.

VIP- immunoreactive nerve fibres were found in all the gut wall layers in tissues from both groups of patients (Figure 7). VIP-positive immunoreactive cell bodies were seen in all three layers of the submucosal plexus in both control and patient tissue. In the myenteric ganglia occasional immunoreactive nerve cell bodies were found in most, but not all, of the control specimens and there was dense network of nerve fibres within the myenteric
plexus. A similar picture was seen in the myenteric plexus of all specimens from 3 of the patient group, but in two patients (one male and one female, both gross megarectum and distal megasigmoid) no VIP-immunoreactive nerve cell bodies were seen in the myenteric plexus of the sigmoid colon, but immunoreactive nerve fibres were plentiful. In both of these patients some VIP immunoreactive cell bodies were found in each layer of the submucosal plexus in the same tissue region.

There appeared to be a lower density of VIP-immunoreactivity in the longitudinal muscle of rectal tissue obtained from the patients with megabowel. There was a tendency towards a denser VIP-immunoreactivity of the muscularis mucosae and the lamina propria in tissue from both rectal and sigmoid tissue in the patient group compared to controls (Tables 14 and 15).

CGRP-immunoreactive nerve fibres were only seen in the myenteric plexus, in all sections from both groups (Figure 7). No CGRP-immunoreactive cell bodies were seen.

In all patients the neural distribution of NADPH-diaphorase paralleled that of the distribution of enteric nerves as demonstrated by immunoreactivity for PGP 9.5 or the glial cell marker S100 protein. There was a moderate to dense distribution of NADPH-diaphorase-positive nerve
fibres in the muscularis externa in all control and the majority of patient tissue. Numerous positive cell bodies as well as positive nerve fibres were seen in the myenteric ganglia of tissue from both controls and patients. In tissue from both groups of patients NADPH-diaphorase positive nerve fibres were demonstrated in all three layers of the submucosal plexus. The staining for NADPH-diaphorase was densest in Henle's plexus, which contained many positive cell bodies, but the staining was sparse in Meissner's plexus and the Intermediate plexuses, and positive cell bodies were not always present in these regions. Positive nerve fibres were sparse in the lamina propria and muscularis mucosae, but present in both control and patient tissue.

VIP and CGRP were detected by immunoassay in both the mucosal and muscular layers of sigmoid colon in both controls and patients (Table 16). There was no significant difference between controls and patients in either tissue layer for either of the neuropeptides studied.

**DISCUSSION**

The results show that there may be abnormalities in the enteric intramural innervation, by nerves containing PGP 9.5, VIP, and NADPH-diaphorase, of patients with idiopathic megarectum and megacolon. In the rectum, the
density of innervation of the muscularis mucosae and lamina propria appeared to be increased and in the longitudinal muscle layer the density of innervation was decreased. These changes were observed when the neurones were stained for PGP 9.5, VIP or NADPH-diaphorase.

In tissue from the proximal and sigmoid colon from patients with idiopathic slow transit constipation, an increase in the innervation in the muscularis externa has been reported (Benson et al 1992). Benson et al (1992) looked at S100 and neuron-specific enolase immunoreactivities, however the circular and longitudinal muscles were not differentiated in this study. Those results contrast with the finding here where there is no suggestion of increased innervation in the longitudinal muscle, but more likely a decrease.

The overall distribution of VIP-immunoreactivity is similar to that described by others in human control tissue (Ferri et al 1983, Milner et al 1990, Crowe et al 1992) and in a range of mammalian species (Furness and Costa 1980 and 1987). A rich VIP-containing nerve supply in human intestinal mucosa has been reported by Ferri et al (1982) and was also seen in this study. Regional colonic differences in concentrations of VIP have been demonstrated in human mucosal specimens (Calman et al 1989). In this study VIP-positive immunoreactivity did not vary greatly between colonic regions.
In addition to being an inhibitory neurotransmitter, VIP increases intestinal secretion in humans (Krejs et al 1980). The mucosal nerve fibres are thought to have a role in the control of blood flow and vascular permeability, transport across the gut lining, endocrine secretion and also a sensory function (Furness and Costa 1987). There is no known functional abnormality of the mucosa in patients with idiopathic megarectum and megacolon.

In patients with idiopathic megarectum and megacolon marked hypertrophy of the muscularis externa was observed in some cases. This may suggest a functional obstructive aetiology such as pelvic floor incoordination, inappropriate enteric excitatory motor input, or loss of inhibitory motor pathways, as postulated by Koch et al (1992).

In tissues from both groups of patients, from all gut regions, CGRP-positive immunoreactivity was seen only in the myenteric plexus, and no positive cell bodies were seen at all. Larsson, Malmfors and Sundler (1988) described CGRP-positive immunoreactivity in six patients with Hirschsprung's disease. In the normal ganglionic gut CGRP-positive immunoreactive nerve fibres were reported as 'few' in three patients and 'moderate' in three. Furthermore, in only one case was any CGRP-positive immunoreactivity seen in the muscularis externa.
and none was seen in the submucosa or mucosa, nor were CGRP-positive immunoreactive nerve cell bodies found. This is consistent with other published work on human tissue (Crowe et al 1992). In a review of the literature Larsson and Sundler (1990) reported that CGRP-positive immunoreactivity had been demonstrated in nerve fibres innervating the muscle and ganglia, but absent in the mucosa. In contrast, in human ileum Dhatt and Buchan (1994) showed CGRP-immunoreactive cell bodies in all three zones of the submucous plexus as well as in the myenteric ganglia. Few CGRP-immunoreactive nerve fibres were seen outside the ganglia. Dolk et al (1990) found little or no CGRP-immunoreactivity in normal human proximal and sigmoid colon, but an increased CGRP-positive immunoreactivity in the myenteric ganglia in 7 patients with slow transit constipation.


The density of NADPH-diaphorase staining tended to be less in the muscularis externa of patients with
idiopathic megarectum and megacolon when compared with controls, and this paralleled decreased neural density as shown by PGP 9.5 immunoreactivity. NADPH diaphorase-positive cell bodies were seen in the submucosal plexus of both control and study tissue in contrast to an absence of such positively stained cell bodies in human ileum (Dhatt and Buchan 1994). In patients with idiopathic megarectum and megacolon the nitric oxide inhibitory motor system appears to be present but with a smaller number of nerve fibres.

The variation in density of innervation across sections of the longitudinal muscle, most markedly in the sigmoid colon could have important implications for any quantitative study in terms of selecting appropriate microscopic fields. As far as we are aware this variation has not been reported before. Nevertheless it was a consistent finding, being observed in every section.

In conclusion, patients with idiopathic megabowel appear to have a decreased inhibitory innervation of the longitudinal muscle layer of the rectum, as labelled with VIP-immunoreactivity and NADPH-diaphorase (nitric oxide synthase) activity. This is a situation common to other motility disorders such as severe chronic idiopathic constipation and Hirschsprung's disease. Abnormalities in VIP and nitric oxide inhibitory systems may contribute to
abnormal gut function and subsequent gut dilatation.
Table 14. Density of innervation in samples of sigmoid colon from patients with non-obstructive carcinoma (controls) and in patients with idiopathic megarectum or megacolon (megabowel).

<table>
<thead>
<tr>
<th></th>
<th>Longitudinal muscle</th>
<th>Circular muscle</th>
<th>Muscularis mucosae</th>
<th>Lamina propria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td>3(0-5)</td>
<td>5(5)</td>
<td>3(1-5)</td>
<td>3(0-5)</td>
</tr>
<tr>
<td>PGP 9.5</td>
<td>2.5(0-5)</td>
<td>5(4-5)</td>
<td>2(0-5)</td>
<td>3(1-5)</td>
</tr>
<tr>
<td>VIP</td>
<td>2(0-5)</td>
<td>4(0-5)</td>
<td>3(0-4)</td>
<td>3(0-5)</td>
</tr>
<tr>
<td>CGRP</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NADPH-d</td>
<td>2(0-5)</td>
<td>5(3-5)</td>
<td>2(1-3)</td>
<td>2(1-3)</td>
</tr>
<tr>
<td><strong>Megarectum/megacolon</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td>2(0-5)</td>
<td>5(3-5)</td>
<td>4(3-5)</td>
<td>3(1-5)</td>
</tr>
<tr>
<td>PGP9.5</td>
<td>3(0-5)</td>
<td>5(3-5)</td>
<td>4(2-5)</td>
<td>4(2-5)</td>
</tr>
<tr>
<td>VIP</td>
<td>2(0-5)</td>
<td>4(1-5)</td>
<td>3(0-5)</td>
<td>3(2-5)</td>
</tr>
<tr>
<td>CGRP</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NADPH-d</td>
<td>2(0-4)</td>
<td>4(3-5)</td>
<td>2(2-3)</td>
<td>2(2-4)</td>
</tr>
</tbody>
</table>

Values given are the median score with the range in parentheses. Scoring system: 0 = absent; 1 = very sparse; 2 = sparse; 3 = moderate; 4 = dense; 5 = very dense. Tissues from 8 control patients and 5 patients with idiopathic megabowel, all of whom had marked sigmoid dilatation.
Table 15. Density of innervation in samples of rectum from patients with non-obstructive carcinoma (controls) and in patients with idiopathic megarectum.

<table>
<thead>
<tr>
<th></th>
<th>Longitudinal muscle</th>
<th>Circular muscle</th>
<th>Muscularis mucosae</th>
<th>Lamina propria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S100</td>
<td>4(2-5)</td>
<td>5(4-5)</td>
<td>3(2-5)</td>
<td>3(2-5)</td>
</tr>
<tr>
<td>PGP 9.5</td>
<td>4(2-5)</td>
<td>5(5)</td>
<td>3(3-4)</td>
<td>3(2-4)</td>
</tr>
<tr>
<td>VIP</td>
<td>3(1-5)</td>
<td>3(3-5)</td>
<td>3(1-3)</td>
<td>3(2-4)</td>
</tr>
<tr>
<td>CGRP</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NADPH-d</td>
<td>2.5(0-5)</td>
<td>5(3-5)</td>
<td>2(1-2)</td>
<td>1(0-2)</td>
</tr>
</tbody>
</table>

|                |                     |                 |                    |                |
| **Megacolon/megarectum** |           |                 |                    |                |
| S100           | 2(0-5)              | 5(4-5)          | 5(3-5)             | 5(3-5)         |
| PGP9.5         | 2(0-4)              | 5(4-5)          | 5(2-5)             | 5(3-5)         |
| VIP            | 2(0-4)              | 3(2-5)          | 4(3-5)             | 4(3-5)         |
| CGRP           | 0                   | 0               | 0                  | 0              |
| NADPH-d        | 1.5(0-3)            | 4(3-5)          | 3(2-4)             | 3(2-4)         |

Values given are the median score with the range in parentheses. Scoring system: 0 = absent; 1 = very sparse; 2 = sparse; 3 = moderate; 4 = dense; 5 = very dense. Tissues from 4 control patients and 3 patients with idiopathic megarectum.
Table 16. Levels of calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP) in the muscularis externa and mucosal regions in samples of the distal sigmoid colon obtained from five control patients and four patients with idiopathic megarectum.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Megabowel</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGRP muscle</td>
<td>11.4 ± 3.9</td>
<td>3.6 ± 2.4</td>
</tr>
<tr>
<td>CGRP mucosa</td>
<td>3.0 ± 1.0</td>
<td>7.4 ± 2.3</td>
</tr>
<tr>
<td>VIP muscle</td>
<td>21.6 ± 7.3</td>
<td>14.3 ± 4.4</td>
</tr>
<tr>
<td>VIP mucosa</td>
<td>69.5 ± 26.7</td>
<td>29.4 ± 16</td>
</tr>
</tbody>
</table>

Values are mean ± standard error of the mean, in pmol/g tissue.
Figure 7. Intramural innervation of the large intestine of patients with non-obstructive carcinoma (control) and idiopathic megarectum or megacolon. a) Section through sigmoid colon from a control patient, stained for immunoreactivity to vasoactive intestinal polypeptide (VIP-IR). The top of the field shows longitudinal muscle (taenia coli) in cross section. A ganglion in the myenteric plexus (small downward pointing arrow) lies between the longitudinal muscle and the underlying circular muscle, beneath which are three small submucosal ganglia (in Henle's plexus, upward arrows). At the lower edge of the field is the muscularis mucosae, which is lightly innervated (large downward arrow). b) Section through sigmoid colon from a patient with idiopathic megarectum, stained for immunoreactivity to VIP. The orientation is the same as in a), with myenteric ganglia (small downward arrows) lying between the longitudinal (above) and circular muscle (below) layers. In the submucosa there is a ganglion in Henle's plexus (upward arrow), and also a small ganglion in Meissner's plexus, lying close to the muscularis mucosae (chevron). The muscularis mucosae (large downward arrow) appears more densely innervated than that in a). Note also the relative hypertrophy of the circular muscle. c) Immunoreactivity for calcitonin gene-related peptide (CGRP) in a myenteric ganglion form a patient with idiopathic megarectum. The immuno-positive CGRP-containing fibres
form meshworks around immuno-negative (arrows) nerve cell bodies. d) An ectopic ganglion of the myenteric plexus, showing immunoreactivity for PGP 9.5. This ganglion lies embedded in the longitudinal muscle. The circular muscle layer would be some distance to the left. e) NADPH-diaphorase activity in the myenteric plexus of a patient with idiopathic megarectum. A myenteric ganglion, with numerous stained nerve cell bodies (upward arrows) separates the longitudinal (above) from the circular muscle (below). The circular muscle layer contains bundles of NADPH-diaphorase-positive nerves (downward arrows). f) NADPH-diaphorase activity in the mucosa and submucosa of a sample of rectum from a patient with idiopathic megarectum. A ganglion in the intermediate layer of the submucous plexus (upward arrow) contains positively stained nerve cell bodies. The muscularis mucosae (downward arrow) contains little innervation. Scale bar represents 100 \( \mu m \) in panels a) and b), and 50 \( \mu m \) in panels c), d), e) and f).
**Figure 8.** Intramural innervation of the large intestine in a patient with idiopathic megarectum. a) and b) Section through the sigmoid colon, stained for immunoreactivity to PGP 9.5. In both fields the circular muscle (cm) is to the left and has a uniform density of innervation, the longitudinal muscle (lm) is to the right and in a) is densely innervated but in b) the innervation appears to be sparse. c) and d) Section through the rectum of a patient with idiopathic megarectum stained for immunoreactivity to PGP 9.5 showing the dense innervation of the muscularis mucosae (mm) and the lamina propria (lp). Scale bar represents 100 um in panels a) and b), and 50 um in c) and 25 um in d).
CHAPTER 7

Contractile proteins, neural markers and electron microscopy in idiopathic megarectum and megacolon

Smith et al (1992) found a previously unsuspected abnormality of the contractile elements of the enteric muscle in one patient with chronic intestinal pseudo-obstruction. Similar 'hidden' biochemical or ultrastructural abnormalities of enteric nerves or muscle may be present in patients with idiopathic megarectum and megacolon.

In this chapter the results of an assessment of the enteric muscle and its innervation in idiopathic megarectum and megacolon is reported.

PATIENTS AND METHODS

TISSUE STUDIED

(i) Patients

Tissue was obtained from 4 patients with idiopathic megarectum and one with idiopathic megacolon. Three patients (1 female, ages 18, 20, and 32 years), whose symptoms of faecal impaction and overflow faecal incontinence started in childhood, had gross dilatation of the rectum and sigmoid colon. One patient (male, 25 years), who presented with adult onset alternating bowel habit, abdominal distension and pain, had total colonic
and rectal dilatation. One patient (male, 37 years) had a 5-year history of intractable constipation, associated abdominal distension and pain but no rectal faecal impaction, had a relatively normal diameter rectum with total colonic and sigmoid colon dilatation.

The diagnosis of idiopathic megarectum and megacolon was reached after other known causes of gut dilatation, such as Hirschsprung's disease or chronic idiopathic intestinal pseudo-obstruction, had been excluded by full thickness rectal biopsy, demonstration of the rectoanal inhibitory reflex, and upper gut radiology. Medical treatment failed to relieve the disabling symptoms and surgery, colectomy and ileorectal anastomosis in 2 patients, Duhamel procedure in 2 patients, and left hemicolecction in 1 patient, was performed.

Full thickness specimens were obtained from the rectum in 4 patients, the sigmoid colon in 4 patients and more proximal colon in 3 patients.

(ii) Controls
There is little information in the literature about the immunostaining pattern in normal human gut with the antibodies used (see below). The immunoreactivity in the samples from the 5 patients with idiopathic megarectum and megacolon was therefore compared with immunostaining from normal and diseased adult and child tissue in Dr V
Smith's archives at Great Ormond Street. These included rectal and colonic biopsies from 38 surgical resection specimens and 6 autopsy specimens previously reported (Smith et al 1992). The tissues from the patients with idiopathic megarectum or megacolon were run concurrently with rectal and colonic tissue from a further 16 surgical resection specimens from patients diagnosed on clinical, electrophysiological and histopathological criteria to have intestinal myopathies (7), intestinal neuropathies (7) and unknown (2). The age of these patients ranged from less than 1 year to 8 years. Those with myopathies act as controls for those with neuropathies and vice versa.

HISTOLOGICAL PREPARATION

The resected full-thickness specimens were processed as follows: one portion was fixed in 4% phosphate buffered formalin for routine histology, another in cacodylate buffered 2.5% glutaraldehyde for electron microscopy, and further blocks were snap frozen in liquid nitrogen for immunohistochemical studies.

(i) Histopathology
Sections of paraffin wax-embedded tissue were stained with haematoxylin and eosin (H&E). The presence of melanosis coli or other histological features were noted.
On these sections the diameter of the muscularis mucosae and muscularis externa were measured using a graded graticule. On frozen tissue, acetylcholinesterase activity was demonstrated and the amount of connective tissue was assessed using the Gomori trichrome and picrosirius stains. Acid Phosphatase activity was studied to detect any lysosomal activity, and accumulation of glycogen was assessed with periodic acid-Schiff (PAS) staining. The methodology used in these preparations was according to previous publications (Felipe and Lake 1990).

(ii) Immunohistochemistry

Immunohistochemical studies were based on a panel of antibodies for neural and muscle markers. Cryostat sections of fresh frozen tissue cut at 9μ were stained using the avidin-biotin-peroxidase complex (ABC) method (Hsu, Raine and Fanger 1981). Biotinylated antimouse and antirabbit antibodies and the ABC complex were obtained from Dako (High Wycombe, UK).

The muscle markers used were: myosin light chain kinase (clone K36), smooth muscle myosin (clone hSM-V), alpha smooth muscle actin (clone 1A4), beta cytoplasmic actin (clone AD-15 and AC-74), filamin (clone Fil2), and tropomyosin (clone TM311) all from Sigma (Dorset, UK). Alpha muscle actin (clone HHF35) and alpha and gamma smooth muscle actin from Universal Biologicals (London,
The neural markers used were: phosphorylated 200 kD neurofilaments (clone RT97, from Professor Anderton, Institute of Psychiatry, London, UK), phosphorylated 160 kD neurofilaments (clone BF10, from Boehringer, Mannheim, UK), phosphorylated and dephosphorylated 160kD neurofilaments (clone NN18, Sigma, Dorset, UK), dephosphorylated 200kD neurofilaments (clone SM132, Sternberger, Baltimore, Maryland, USA) and neural cell adhesion molecule (N-CAM, clone Eric1, from Professor Walsh, Guy's Hospital, London, UK).

(iii) Electronmicroscopy:
Selected blocks from the glutaraldehyde-fixed tissue were post-osmicated and processed into Araldite resin using standard methods. Ultrathin sections were cut to show the circular and longitudinal muscle of the muscularis propria and the myenteric plexus. The ultrathin sections were contrasted with uranyl acetate and lead citrate before examination.

HISTOLOGICAL ANALYSIS

Dr VV Smith (Histopathologist, Hospital for Sick Children, Great Ormond St, London) assessed all the neural and smooth muscle immunohistochemistry and electron microscopy. She provided a written report for
each histological preparation from each patient. The results below are collated from this expert assessment.

RESULTS

(i) Histopathology
Mild melanosis coli was seen in 2 patients with idiopathic megarectum. A mild 'obstructive colitis', that is a mild chronic inflammatory cell infiltrate in the lamina propria, was seen in all 5 patients.

The longitudinal muscle in the rectum of all 3 patients with idiopathic megarectum and megasigmoid had marked hypertrophy of the longitudinal muscle (900, 1150, 1330, normal range (see chapter 5) 183-643 mean 330, all in um). A lesser degree of hypertrophy of the circular muscle was also seen in these 3 patients (1412, 1270, 1180, normal range 330-1670 mean 701, all in um). This hypertrophy of the muscularis externa was associated with a thickened muscularis mucosae in one patient with idiopathic megarectum (88, normal range 21-61 mean 35, all in um) and was also seen in the patient with idiopathic megacolon. No atrophy of any of the 3 smooth muscle layers was seen in any patient.

A decrease in nerve density in the muscularis externa was found in 2 (1 female) of the 4 patients with a dilated rectum and in the patient with idiopathic megacolon on
acetyl cholinesterase staining. This was most marked in the longitudinal muscle and was associated with longitudinal muscle hypertrophy in the 2 patients with idiopathic megarectum.

In 1 patient with idiopathic megarectum and in the patient with idiopathic megacolon an increased density of acetyl cholinesterase-positive nerves was seen in the lamina propria. No excess of glycogen was seen in any of the patients.

(ii) Immunohistochemistry
Sparse innervation of the longitudinal muscle was confirmed by N-Cam immunostaining in the same 2 patients with idiopathic megarectum described above.

Abnormalities of smooth muscle contractile protein markers were seen in one female patient. In rectal tissue there was a reduction in immunostaining in the muscularis externa with both antibodies to beta actins and to myosin light chain kinase. In tissue from the sigmoid colon from the same patient, a similar reduction in immunostaining for myosin light chain kinase and beta actin (clone AC-15) in the muscularis externa, but normal levels of immunostaining for clone AC-74, was seen. The distribution of other muscle and neural markers was unremarkable. There were no other significant abnormalities in the immunoreactivity of the nerve or
muscle markers in the other patients.

(iii) Electronmicroscopy
In the patient with idiopathic megacolon mild to moderate fibrosis of the muscularis externa was seen, but the smooth muscle cells appeared to be normal. No other neural or smooth muscle abnormality was seen.

**DISCUSSION**

Atrophy of the muscularis externa was not seen despite often gross gut dilatation. The significance of the thickened muscularis mucosae and increased density of nerve fibres in the lamina propria is unknown. The apparent sparsity of nerves in the longitudinal muscle of the muscularis externa may reflect thickening of this muscle layer rather than any primary abnormality of the innervation of this muscle. Some of these changes may be secondary to a 'functional obstruction'. In the circular muscle of the muscularis externa no such decrease in density of innervation was seen despite a degree of muscle hypertrophy.

We found definite changes in the staining of contractile proteins in one patient, which may be of pathogenic significance. In smooth muscle contraction the thick and thin filaments interact. The thick filaments consist of myosin. The thin filaments contain tropomyosin, caldesmon
or filamin (Hartshorne 1987, Lehman, Sheldon and Madonia 1987), but the major component is actin which exists in a variety of isoforms. The major constituent of adult intestinal smooth muscle is gamma actin but a significant amount of alpha actin is present. The beta isoform is cytoplasmic and may not have a direct role in smooth muscle contraction (Hartshorne 1987). However, an abnormality of the distribution of the actin isoforms may be associated with abnormalities of smooth muscle function. It is also possible that any alteration in the 'ratio' of smooth muscle proteins may result in changes in the function of the muscle, even if the protein is not a major component of the contractile elements.

No abnormality in the distribution of the smooth muscle markers was seen in the other patients. They may have other subtle abnormalities, either primary or secondary, of enteric nerve or muscle that we are currently unable to demonstrate. Apart from hypertrophy, no other structural abnormality was demonstrated in the smooth muscle of any of the patients by light- or electronmicroscopy.
Figure 8: Cryostat sections of rectum immunostained for beta cytoplasmic actin. Normal distribution of immunostaining (a) compared to a reduction in immunostaining in both the longitudinal (LM) and circular muscle (CM) of the muscularis externa in a patient with idiopathic megarectum (b).
CHAPTER 8

Evaluation of DNA Viruses in

Idiopathic Megarectum and Idiopathic Megacolon

In patients with idiopathic megarectum and idiopathic megacolon the architecture of the enteric innervation appears to be intact. However, there are some subtle neuronal abnormalities (see chapters 5, 6 and 7) and in one patient with idiopathic megarectum abnormalities in the contractile proteins of the muscularis externa have been seen (chapter 7). The causes of idiopathic megarectum and idiopathic megacolon remain unknown. It is possible that there may be a viral aetiology.

PATIENTS AND METHODS

TISSUE STUDIED

(i) Patients

Tissue was obtained from the resection specimens of patients who had had an acute or adult onset of their condition; such cases were felt most likely to have a viral aetiology. All had had previous surgery for intractable symptoms and failed medical therapy. Tissue from 3 patients with idiopathic megarectum and 3 patients with idiopathic megacolon was studied (See Table 17).

The following full thickness specimens were obtained: (i) sigmoid colon from all 6 patients, all of whom had a megasigmoid (ii) rectum from 1 patient with idiopathic
megarectum and 1 patients with idiopathic megacolon. (iii) proximal colonic tissue from 5 patients (2 with idiopathic megarectum).

(ii) Controls
Positive control material consisting of DNA prepared from human foreskin fibroblast infected with CMV (strain C-81), VZV (H-551) or HSV 1 (TC-50). EBV was prepared from chronically infected B95-8 cells (obtained from ECACC, Porton Down). Apart from the EBV all were clinical isolates routinely used in the Department of Virology at St Bartholomew's Hospital. The CMV isolate was originally from an aborted fetus with congenital CMV infection. VZV was from a patient with herpes zoster (24) and the HSV 1 isolate from a patient with gingivostomatitis.

HISTOLOGICAL PREPARATION

(i) Histopathology
Longitudinally orientated blocks of the full thickness of the bowel wall were taken for processing into paraffin wax after fixation in 10% formal saline. Sections were cut at 6 um and stained with Haematoxylin and Eosin (H&E) and periodic acid Schiff (PAS).

(ii) Polymerase chain reaction (PCR)
Paraffin embedded blocks were cut at 10 um and 4 sections from each block were dewaxed with xylene, spun in a
microfuge at 13 000 rpm for 10 minutes and the xylene discarded. The resultant pellet was rinsed in 95% ethanol and spun at 13 000 rpm for a further 10 minutes. This was repeated with clean ethanol to ensure complete removal of the xylene. The pellet was dried in a heating block at 45 °C and resuspended in sterile distilled water.

This solution was incubated with 0.5 mg/ml of proteinase K at 37°C for 12 hours. Phenol chloroform was added to the samples, which were mixed by inversion and centrifuged at 13 000 rpm for 15 minutes. The phenol layer was discarded and 0.3 M sodium acetate, 3 ul of tRNA and ethanol was added to the aqueous phase. This was mixed and left to precipitate at -70°C for 20 minutes. The samples were spun for 15 minutes at 4°C at 13 000 rpm to pellet the DNA. The pellet was washed in 70% ethanol and centrifuged for 5 minutes at 13 000 rpm. The pellet was then dried and resuspended in sterile distilled water and boiled for 15 minutes.

The PCR was done as described by Saiki (Saiki et al) using recombinant DNA polymerase from Thermus aquaticus (Amplitaq; Perkin-Elmer Cetus) as per the manufacturer's protocol. All preparative work for the PCR was carried out in an ultraviolet-irradiated class II microbiological safety cabinet, using autoclaved plastic tubes and pipette tips throughout.
Amplification reactions were carried out in a total volume of 100 ul comprising 50 ul test sample and 50 ul reaction buffer in 0.6 ml microcentrifuge tubes. The reaction buffer was prepared in bulk mastermix at double strength to give final concentrations of 50 mM KCl, 10 mM Tris-HCl (pH 8.3), 2.0 mM MgCl₂, 0.01% gelatin, 0.2 mM of each deoxynucleoside triphosphate (dNTP) and 0.2 uM of each oligonucleotide primer and stored at -20°C.

The mastermix was thawed and the AmpliTaq was added to give a final concentration of 2.5 units per reaction tube. The reaction mixture was dispensed into 0.6 ml microcentrifuge tubes and the test sample was added, either neat or diluted with distilled water, using sterile 50 ul glass capillaries. The reaction mixture was overlaid with mineral oil to prevent evaporation. Reaction tubes containing positive and negative viral DNA control samples were included in each batch of tests. Nested PCR for cytomegalovirus (CMV), Epstein-Barr virus (EBV), Herpes Simplex virus type 1 (HSV 1) and varicella zoster virus (VZV) was performed in a DNA Thermal Cycler (Perkin-Elmer Cetus).

The samples were amplified through 20 cycles consisting of denaturation at 94°C for 1 minute, annealing at 60°C for 1 minute and primer extension at 72°C for 2 minutes. Aliquots of 5 ul of amplified products were added to 45 ul of sterile distilled water and transferred in a
separate room to fresh reaction tubes, containing standard mastermix with 2.5 units of Taq polymerase and 1.0 uM of each of the nested primers. The reactions were then done according to the standard protocol for 30 cycles.

**Gel electrophoresis of the PCR products:** After PCR amplification the products were transferred to a separate laboratory where they were collected with sterile 100 ul glass capillaries and 8 ul aliquots were mixed with 2 ul of loading buffer (0.25% bromophenol blue, 30 % (w/v) glycerol in water). 10 ul of each mixture was electrophoresed through a 2% agarose gel (Sigma, UK) at 100 volts. A sample of PHI X174 RF DNA digested by Hae III (Gibco, BRL) was included on each gel as a DNA size marker. After electrophoresis, the gels were stained with ethidium bromide for 15 minutes at room temperature, destained with distilled water for 15-30 minutes, and visualised under a UV transilluminator (UVP Inc, USA). The gels were photographed using a Polaroid DS camera and Polaroid T667 film (Sigma).

**Oligonucleotide primers:** The oligonucleotide primers had been custom synthesised using the 380B or 391 DNA synthesizers (Applied Biosystems). The oligonucleotides were deprotected after synthesis, precipitated with ethanol and used without further purification.

**RESULTS**

(i) Histopathology
Routine H&E staining did not show changes suggestive of viral infection. PAS staining did not demonstrate inclusion bodies.

(ii) Polymerase chain reaction

No herpes virus DNA for the 4 viruses tested was identified in tissue from patients with either idiopathic megarectum or idiopathic megacolon. Positive results were obtained with the control material.

**DISCUSSION**

There are subtle abnormalities of the enteric nervous system in patients with idiopathically dilated large bowel. The work described in this chapter was specifically looking for any evidence of a neurotropic effect of herpes viruses.

PAS staining did not demonstrate any inclusion bodies and no herpes virus DNA for EBV, HSV type 1, VZV or CMV was detected using the PCR technique described. Validation of the PCR technique with control tissue would suggest that although there may be morphological evidence of neural damage this is not attributable to these herpes viruses.
Table 17. The details of 3 patients with idiopathic megarectum and 3 with idiopathic megacolon.

<table>
<thead>
<tr>
<th></th>
<th>Idiopathic megarectum</th>
<th>Idiopathic megacolon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JM</td>
<td>BC (f)</td>
</tr>
<tr>
<td>Age at operation (years)</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Duration symptoms (years)</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>
Patients with idiopathic megarectum are often dependent on laxatives to achieve defaecation. Laxative use often starts in childhood and dependence is lifelong. Little is known of laxative toxicology. Most came into common usage well before the current stringent requirements relating to the licensing of new drugs existed.

In this chapter the adverse effects of laxatives are considered. The main focus is on predictable and unpredictable side effects at therapeutic doses or inadvertent overdose. Possible adverse effects associated with the chronic use of these drugs is considered, although there is a paucity of published work regarding this.

Laxatives can exert an effect via several different mechanisms, and for many drugs these have not been clearly defined. Some probably have an effect via more than one mechanism, and some drugs contain more than one active constituent. Mechanisms of action include:

1. Fluid retention within the colon, thereby increasing the bulk and softness of the stool and facilitating intestinal transit.

2. Decreasing the net absorption of luminal water
by actions on the colonic mucosa.

(3) Increased intestinal motility, resulting in decreased intestinal transit time and less time for absorption of salt and water.

(4) Direct softening of stool, facilitating transit and defaecation. The faecal softeners, (emollient laxatives), soften the faeces by decreasing the surface tension and increasing the penetration of intestinal fluids into the faecal mass (Martindale 1989).

Laxatives have traditionally been divided into 4 groups: dietary fibre and bulk-forming laxatives, stimulant laxatives, osmotic laxatives, and faecal softeners.

(1) BULKING AGENTS

Bulking agents, which include dietary fibre and bulk-forming laxatives, are safe and well established agents. The commonly reported side effects are flatulence and abdominal distension (Martindale 1989, Goodman and Gilman 1990, British National Formulary 1992). An excessive dose or possibly an inadequate fluid intake can cause bolus obstruction (Martindale 1989). An increased fluid intake is not mandatory with the use of bulking agents. Ziegenhagen et al (1991) demonstrated that additional fluid intake (600ml) in 11 healthy volunteers did not improve the laxative effect of bran; no adverse effects of an increased fluid intake were noted. However, an
adequate fluid intake is important in the elderly and it would seem sensible to recommend an increased fluid intake when bulking agents are prescribed. Large bowel obstruction and perforation (Souter 1965, Elliot and Glover 1983) have been reported although these complications are rare. In the three cases of bolus obstruction reported by Souter (1965) isogel was given in the immediate post-operative period following major colonic surgery. Bulking agents are contraindicated in the presence of an obstructing lesion and should be avoided in patients with intestinal strictures, such as in Crohn's disease.

Unprocessed bran and most cereal grains contain phytic acid which forms insoluble complexes with iron, calcium and zinc (Godding 1976a, Dwyer et al 1978). A high intake of fibre may lead to excessive faecal excretion of these minerals (Eastwood and Passmore 1983). This may be important in cereal based diets, but is unlikely to be clinically significant with Western diets (Jenkins and Jenkins 1984, Bennett 1986).

Wheat based bulking agents have the theoretical advantage of containing little phytic acid and do not appear to impair mineral absorption (Drug and Therapeutics Bulletin 1992). Bulk laxatives derived from wheat husk contain gluten and should therefore be avoided in patients with Coeliac disease.
Carboxymethylcellulose sodium and psyllium husk may contain significant quantities of sodium; this may be clinically relevant when treating cardiac failure or hypertension.

Bulking agents can interfere with drug absorption. Perlman (1990) reported a patient in whom ispaghula husk was thought to retain lithium within the gut, leading to low serum lithium levels. However, Nordstrom et al (1987) assessed the influence of a gel-forming wheat bran and ispaghula on the steady state concentration of digoxin in 30 geriatric in-patients, and found that neither substance had a clinically significant effect. In 5 patients with hypercholesterolaemia treated with lovastatin an increase in dietary fibre resulted in a rise in serum low-density lipoprotein cholesterol (Richter, Jacob and Schwandt 1991). Three patients were taking pectin and two patients were taking oat bran. Both these fibres may reduce the absorption of lovastatin from the gut. The effect of bulking agents on the absorption of most other drugs has not been investigated.

Psyllium can cause an IgE-mediated hypersensitivity reaction. Symptoms can include rhinoconjunctivitis, skin rashes and urticaria, asthma, gastrointestinal symptoms and even anaphylaxis (Gillespie and Rathbun 1992). Most problems arise from staff preparing the powdered form of the product and inhaling the dust. Nurses (Machado,
Zetterstrom and Fagerberg 1979, Machado and Stalenheim 1984) or pharmaceutical workers (Bardy et al 1987, McConnochie, Edwards and Fitfield 1990) are most at risk. Although rare, oral ingestion can lead to serious allergic reactions in previously sensitised individuals (Lantner et al 1990).

(2) STIMULANT LAXATIVES

Stimulant laxatives are thought to increase intestinal motility, decreasing the time available for salt and water absorption. These laxatives increase the colonic formation of histamine, serotonin and prostaglandins; of these prostaglandins appear to be the most important mediators in the development of increased mass movements, and are also involved in the increased secretion associated with these drugs (Fioramonti and Bueno 1991, Leng-Peschlow 1992).

Common side effects include flatulence and abdominal pain. The latter is presumably related to increased intestinal contractile activity, although no studies have examined this. Some anthraquinones, such as danthron, colour the urine pink, as does phenolphthalein if the urine is alkaline. Excessive ingestion can lead to diarrhoea and its sequelae, such as hypokalaemia.

Although the chronic ingestion of laxatives has been
blamed for the development of intractable constipation ("cathartic colon"), there are no prospective human or animal studies which have shown such an effect. The end result of slow colonic transit may result from a primary disorder of motility, rather than an effect of the drugs.

(i) Anthraquinones

Anthraquinones are a group of drugs which occur naturally in senna, cascara, aloe, and rhubarb, or can be synthesised. Some are glycosylated and some are not, leading to differences in pharmacokinetic profiles.

The active constituent of standardised senna is rheindanthron glycoside, also known as sennosides A and B, while the most active metabolite is rhein-9-anthrone. Danthron is 1-8 dihydroxyanthraquinone, that is a free anthraquinone without an attached glycoside molecule. The glycosides (senna) are 'protected' from small intestinal absorption by their glucose molecules. Colonic bacteria cleave the glucose molecules, releasing the active rheinanthrone and producing an action which is potentially specific for the colon. This is in contrast to danthron, which is absorbed in the small intestine and largely metabolised in the liver (Godding 1976a & b, Leng-Peschlow 1992).

Of the available commercial preparations, approximately
a fifth contain pure senna products, half are combinations with other anthraquinone drugs (aloe, frangula, cascara, rhubarb), ten percent are combinations with bulking agents (Plantago ovata seeds, husks, linseed), 5 percent are combined with a synthetic laxative (bisacodyl) and a fifth are combined with other plants (Leng-Peschlow 1992).

Beuers, Spengler and Pape (1991) reported what was thought to be a 'non-predictable' (idiosyncratic) hepatitis in a patient taking large doses of senna tea, a preparation which probably contained a variety of anthraquinones. Although senna is not absorbed from the small intestine, its derivative rhein-anthrone is absorbed from the colon and conjugated or sulphated by the liver. Abnormal liver function recurred on rechallenge, and resolved with cessation of the drug. We are not aware of any other reports of hepatotoxicity related to senna ingestion.

Tolman, Hammar and Sannella (1976) reported a single case of hepatotoxicity associated with the ingestion of doxidan (danthron and dioctyl calcium sulfosuccinate). Challenging the patient with danthron did not produce a change in liver function tests, but rechallenge with doxidan did.

Danthron is available combined with several different
compounds (see Table 18), including poloxamer ('Dorbanex' or 'Co-danthramer') and docusate sodium. In many countries danthron preparations were withdrawn or restricted in their use after reports of hepatic and intestinal tumours in laboratory animals (Mori et al 1985 & 1986). Animals were treated for 16 months with doses approximately 300 times that used in humans. Two major studies (Nakamura, Schneiderman and Klauber 1984, Kune et al 1988) did not show any association of anthranoid ingestion with cancer in humans. Patel et al (1989) reported a single case of a possible link between a danthron containing laxative and leiomyosarcoma of the small bowel. Some danthron preparations have been reintroduced for use in geriatric patients and the terminally ill.

When danthron with poloxamer ('Dorbanex') was in routine use, red-brown staining of the perianal skin occurred in incontinent patients (Barth et al 1984, Cox and Vickers 1984, Verbov 1984). The skin discolouration and excoriation resolved on cessation of 'Dorbanex'.

Stimulant laxatives are thought to cause melanosis coli, or more correctly pseudomelanosis coli. The brown pigmentation of the colonic mucosa is related to pseudomelanin (Smith 1973) or lipofuscin, a "wear and tear" pigment, (Smith 1972b, Steer and Colin-Jones 1975) in the mucosal macrophages. Its functional significance
is unknown; it does not appear to be associated with colonic malignancy (Wittoesch, Jackman and McDonald 1958). It occurs if anthraquinone type drugs are taken for an extended time and is said to disappear within 4 to 12 months if the drug is discontinued (Bockus, Willard and Band 1933, Speare 1951, Wittoesch, Jackman and McDonald 1958). In contrast, Siegers (1992) reported that chronic anthranoid laxative abuse was associated with an increased cancer risk, but reliable data on this association is lacking.

The major concern about the chronic use of stimulant laxatives relates to the possibility of permanent gut nerve or muscle damage. Studies of the resected colon from intractably constipated women have demonstrated morphological changes of neurons in the myenteric plexus, when examined using a silver stain (Smith 1973, Preston et al 1983, Krishnamurthy et al 1985). Changes include loss of neurons, replacement of ganglia by Schwann cells, and shrinkage and clubbing of remaining argyrophilic cells. Electron microscopic studies have shown oedematous distension of individual axons and loss of structural elements (Riemann and Schmidt 1982). The neurotransmitter content or functional nature of these argyrophilic neurons is unknown. It is unknown whether these changes are a primary part of the motility disorder or secondary to chronic laxative ingestion. It also not known whether they are of functional significance.
Riemann and Schmidt (1982) have also demonstrated similar ultra-structural changes in patients with diabetic autonomic neuropathy and chronic inflammatory bowel disease, suggesting that these changes may not be specific to laxative damage. Douthwaite and Goulding (1957) gave high dose standardised senna to mice for up to 4 weeks. They did not find any pathological abnormality on histological examination. Smith (1968) administered senna to mice, but it is not clear what quantity or quality of senna was used. Animals given syrup of senna showed few myenteric plexus changes after a month, but after four months axonal fragmentation and dendritic swelling were present. Non-standardised extracts containing free anthraquinones may have caused some or all of these effects.

Riemann et al (1978) found that on ultrastructural examination the colonic epithelial cells of 10 patients with "long standing laxative abuse" were damaged. This consisted of changes in the microvilli, structural defects in cytoplasmic organelles and increases in lysosomes and dense bodies. However, this study was retrospective, without a control group, and the exact nature of the laxatives taken was unknown. Verhaeren, Geboes and Lemli (1985) found that high oral doses of 1,8-dihydroxyanthraquinone (danthon) damaged the colonic epithelial surface in guinea pigs. The changes suggested an increased epithelial cell turnover. All the
pathological changes reverted to normal after stopping the drug for 3 weeks.

In a careful histological and ultrastructural animal study by Dufour and Gendre (1988) no changes were demonstrated in the myenteric plexus after 11 weeks treatment with a standardised preparation of senna containing little free anthraquinones. Myenteric plexus changes did develop, however, in danthron treated animals.

Hoyle (1991) has demonstrated that long-term ingestion of unpurified senna by rats results in changes to the function of the purinergic nerves supplying the colonic circular muscle.

There are several single case reports of hypertrophic osteoarthropathy and clubbing of the digits occurring in association with chronic senna intake (Silk, Gibson and Murray 1975, Prior and White 1978, Malmquist et al 1980, Armstrong et al 1981, Frier and Scott 1981, Levine, Goode and Wingate 1981, Fitzgerald and Redmond 1985). If the laxative abuse is stopped, both are said to regress (Levine, Goode and Wingate 1975, Silk, Gibson and Murray 1975, Armstrong et al 1982, Fitzgerald and Redmond 1985). Although the clubbing has been attributed to the induced diarrhoea, there is no evidence to support this (Prior and White 1978).
Laxatives, especially senna, have been linked to analgesic nephropathy, although prospective data about this are lacking. Wainscoat and Finn (1974) reported that regular laxative intake was increased in 8 out of 10 patients with analgesic nephropathy, in contrast to 40 patients with rheumatoid arthritis and normal renal function who were taking the same analgesics but who did not take laxatives. These findings suggest that analgesic nephropathy may be due to the combined abuse of laxatives and analgesics. This would also explain why analgesic nephropathy is rare in patients with rheumatoid arthritis despite the fact that they are chronic, heavy analgesic takers.

In a review of the literature on senna, Leng-Peschlow (1992) found no reports of adverse effects during pregnancy. Studies in rats and rabbits have not shown a tendency to induce abortion, or to produce teratogenic effects. There have been no reports of human teratogenicity. Senna laxatives are often used in pregnancy. Ten studies involving a total of 937 women who used a variety of senna preparations for 2 weeks to 9 months showed good laxative efficacy with few side effects (Scott 1965, Leng-Peschlow 1992). There were no reports of threatened miscarriage or premature labour.

There are no definitive studies of anthraquinone concentrations in maternal breast milk, although many
physicians believe that babies' stools are softer when the mother is taking such drugs. In two studies there were no apparent effects on the consistency of the babies' stools (Baldwin 1963, Shelton 1980). However, maternal ingestion of a senokot preparation containing 7mg standardised senna caused diarrhoea in 6 of 35 breast fed infants (17%) in a study by Greenhalf and Leonard (1973). In the same study, only one of 35 breast fed infants whose mother took Normax (dioctyl sodium sulphosuccinate and dihydroxyquinone) was noted to have diarrhoea.

(ii) Polyphenolic derivatives.

The primary diphenylmethane laxatives, phenolphthalein and bisacodyl, are closely structurally related and are pharmacologically similar. About 15 percent of phenolphthalein is absorbed and eliminated by the kidney; some of the drug is excreted in bile and undergoes enterohepatic recycling (Martindale 1989, Goodman and Gilman 1990). Bisacodyl is mainly excreted in the stool; about 5 percent is absorbed and excreted in the urine as a glucuronide. Both bisacodyl and phenolphthalein preparations are usually coated with pH sensitive materials to minimise their absorption.

Phenolphthalein is contained in many over-the-counter laxative preparations. It can cause allergic reactions, notably dermal sensitisation and 'fixed' drug eruptions.
Osteomalacia (Martindale 1989), protein losing gastroenteropathy (Moriarty 1987) and rarely toxic epidermal necrolysis or the scalded skin syndrome (Lowney et al 1967) have been reported. Kendall (1954) reported a case of fatal encephalitis possibly due to a hypersensitivity reaction to phenolphthalein, in a previously well infant who inadvertently took an indeterminate number of laxative tablets.

Bisacodyl can cause abdominal colic when taken orally. Bisacodyl enemas can alter the macroscopic, light and electron microscopic appearances of the rectal mucosa (Meisel et al 1977). This may cause some diagnostic confusion on examining rectal biopsies. The clinical significance is otherwise uncertain, but bisacodyl suppositories may rarely cause proctitis with sloughing of the epithelium, if used long term (Martindale 1989).

'Picolax' is a mixture of sodium picosulphate, which decreases water and electrolyte absorption and increases motility, and magnesium citrate, which is an osmotic laxative. Sodium picosulphate is a sulphated bisacodyl molecule, which is hydrolysed by colonic bacteria into its active constituent. It is extensively used in colonic preparation prior to radiological examination and surgery (Barker, Hanning and Trotter 1992). It is occasionally used in refractory constipation. Side effects include
abdominal pain, nausea and vomiting. Patients having bowel preparation prior to surgery are at risk of dehydration and may require extra intravenous fluids (Dodson 1991, Barker, Hanning and Trotter 1992, German, Chandiramani and Stephenson 1993). Its effectiveness and short-term safety are well established (Hughes et al 1983, Boulos et al 1984, Lee and Ferrando 1984, Grace and Hale 1987). It should be used with great caution if there is an obstructing lesion as there is a risk of colonic perforation (Phipps and Fraser 1987). Bowyer and Urquhart (1987) also reported a single case of rectosigmoid colon infarction following the administration of picolax in an elderly woman with altered bowel habit.

Sodium picosulphate may cause headaches, because of dehydration. In one prospective study (Kutt et al 1988) 27 percent of patients undergoing preparation for a barium enema complained of headaches, and these patients had a rise in their haemoglobin consistent with dehydration. Dehydration was not identified as a causative factor in the 38 percent of patients given sodium picosulphate, who developed a headache, in another study (Lawrance et al 1991).

There is no definitive evidence that patients with inflammatory bowel disease are at increased risk from laxative bowel preparation. McDonagh et al (1989) found no difference in the incidence or type of adverse effects
with 'Picolax' bowel preparation in patients with inflammatory bowel disease compared to patients with other colonic disorders such as irritable bowel syndrome, diverticular disease, and colonic carcinoma.

Oxyphenisatin should no longer be taken orally in the long-term because of the development of chronic active hepatitis in humans (Reynolds, Peters and Yamada 1971, Anonymous BMJ editorial 1972, Gjone et al 1972). A single case of acute hepatitis in a 56 year old female has also been reported (Pearson et al 1971). It is still available as an effective enema preparation ('Veripaque'), which should only be used prior to radiological investigation or for short term use as a 'last resort' in severely constipated patients because of the possibility of liver toxicity. There are little data about systemic absorption of the enema preparation.

(iii) Miscellaneous stimulant laxatives.

Castor oil is a triglyceride which is hydrolysed in the small intestine to release glycerol and the active component ricinoleic acid. Ricinoleic acid causes cyclic AMP-mediated intestinal fluid secretion (Binder, Dobbins and Whiting 1977) and alters colonic motor activity in dogs (Karaus et al 1987). It has also been shown to damage the gut epithelium (Gaginella et al 1977, Bernier, Hirondel and Bretagne 1979).
Steingrub et al (1988) reported a single case of amniotic fluid embolism associated temporally with ingestion of 30ml of castor oil, which was taken in an effort to induce labour. Ludever, Demers and Nanides (1980) documented a significant increase in portal venous prostaglandin E concentration after oral administration of castor oil in rats. Some prostaglandins are uterotonic, stimulating or augmenting uterine contractions and are used clinically to induce labour. Steingrub et al (1988) suggested that the ingested castor oil may have stimulated prostaglandin production causing irregularly strong uterine contractions, which caused entry of amniotic fluid into the circulation.

Castor oil is now rarely used as a laxative because of its unpleasant side-effects of cramping and fluid bowel actions. Thompson (1980) stated that 'Castor oil was used to lubricate aircraft in World War I, but many consider it too violent for peacetime use.'!

Glycerin is used in suppository form only. It may act as a mild stimulant and lubricant. There are no reports of adverse effects.

Docusate sodium (dioctyl sodium sulphosuccinate) is a stool softener as well as a stimulant laxative. It is discussed below.
OSMOTIC LAXATIVES

The common side effects of the osmotic laxatives are flatulence, abdominal pain and colic. These symptoms often settle after a few days of use.

Lactulose is a synthetic disaccharide [galactose and fructose], although preparations contain small amounts of galactose and lactose. Up to 20% of patients on lactulose experience troublesome flatulence, abdominal cramps and pain; these probably relate to colonic fermentation with gas release. These side effects may be transient (Watson and Ebert 1969). Some patients find the taste unpalatable and it can cause nausea and vomiting in high doses. It is usually well tolerated and long term administration appears to have no adverse effects (Elkington 1970).

Hypernatraemia has been reported when lactulose was used in high dosage for the management of hepatic encephalopathy (Kaupke, Sprague and Gitnick 1977), and was thought to be due to the lactulose rather than the encephalopathy. Lactulose and its acidic metabolic products exert an osmotic effect, causing water retention in the gut lumen. It has been postulated that because the ileum and the colon can absorb sodium against a large concentration gradient, hypernatraemia results. The dose of lactulose used in hepatic encephalopathy is usually far higher than that used in constipation, although doses
of only 40 - 60ml per day were used in some cases (Bateman and Smith 1989), suggesting that an additional disturbance of sodium regulation in encephalopathy is contributory.

Pneumatosis coli has been reported when lactulose was used to treat hepatic encephalopathy in a single patient (Zimmerman, Gupta and Ingegno 1979). Wright (1988) reported 5 cases of 'non-toxic' megacolon in elderly patients on regular lactulose. They were successfully treated by discontinuation of the lactulose and antibiotics.

Sorbitol is a nonabsorbable sugar with an osmotic laxative effect. It is considerably cheaper than lactulose. There would appear to be no difference in laxative efficacy nor adverse effects when compared to lactulose (Lederle et al 1990).

Lactitol is a disaccharide derivative of galactose and sorbitol. It is not hydrolysed in the small intestine and reaches the colon unchanged. In the colon it is broken down to short chain organic acids by enteric bacteria. Side effects are similar to those of lactulose and we are not aware of any other serious adverse events.

Magnesium containing salt laxatives are not only osmotic laxatives, but are also thought to act by releasing
cholecystokinin, which stimulates intestinal secretion and motility (Harvey and Read 1973, Binder and Donowitz 1975, Thompson 1980).

Administration of hypertonic salt laxatives can cause significant dehydration unless adequate oral hydration is maintained. There is some absorption of the cations with the osmotic salt laxatives (magnesium salts, rectal phosphates, sodium citrate). The sodium salts must be used with care in patients with congestive heart failure or renal disease and magnesium salts used with care in patients with impaired renal function (Martindale 1989, Goodman and Gilman 1990) or previous gastric surgery (Aucamp, van Achtebergh and Theron 1981).

Infants are susceptible to magnesium poisoning and great caution is needed in paediatric prescribing (Alison and Bulugahaptiya 1990). There are no reports of maternal consumption of magnesium sulphate causing congenital defects. Maternal consumption of magnesium sulphate does not appear to change the stool frequency in nursing infants (Wynne and Edwards 1992).

Overdose of magnesium sulphate ('Epsom salts') can lead to hypermagnesaemia, hypophosphataemia and secondary hypocalcaemia (Garcia-Webb et al 1984). Magnesium salt enemas can cause severe hypermagnesaemia and should be used with care. Children are at risk from these metabolic

Phosphate enemas ('Fleet enema') are a mixture of sodium biphosphate (NaH$_2$PO$_4$) and sodium monophosphate (Na$_2$HPO$_4$). Some of the anion is absorbed, but if kidney function is normal no toxic accumulation occurs (Honig and Holtzapple 1975).

Phosphate enemas can cause traumatic injury to the rectosigmoid colon (Hool, Bokey and Pheils 1980, Bell 1990). The main problem is the risk of mechanical trauma to the rectal wall, but this is extremely rare. Should it happen, then the hypertonic phosphate solution can potentially exacerbate the mucosal necrosis.

There have been a number of reports in the literature documenting severe and even lethal episodes of hyperphosphatemic hypocalcaemia caused by phosphate enemas. Rohack, Mehta and Subramanyam (1985) reported a case in an adult. Davies et al (1977) reported hypocalcaemia, hyperphosphatemia and dehydration after a single hypertonic phosphate enema in two normal but
acutely constipated infants. Reedy and Zwiren (1983) reported one case of phosphate enema induced hypocalcaemia and hyperphosphatemia said to have caused cardiac arrest during induction of anaesthesia in a 17 month boy. Hirschsprung's disease had not been excluded. Most adverse events have occurred in children with renal failure or Hirschsprung's disease (Oxnard, O'Ball and Gruppe 1974, Spinrad et al 1989). Sotos et al (1977) reported hyperphosphatemia and hypocalcaemic coma in a 2 year old girl, with a previously repaired thoracolumbar meningomyelocele and shunted hydrocephalus. Honig and Holtzapple (1975) reported a single case of hypocalcaemic tetany following multiple phosphate enemas. These enemas were inserted into the distal loop of a double barrelled colostomy in a 5 month baby undergoing bowel preparation for definitive surgery for an imperforate anus. Kidney function was normal, but prolonged retention of the 'Fleet enema' because of the imperforate anus resulted in significant absorption of the phosphate ion, depressing the serum calcium and causing tetany.

Two other case reports of hypocalcaemia and hyperphosphatemia were associated with accidental overdosage of oral sodium biphosphate/phosphate (Levitt, Gessart and Finberg 1973, Smith, Fieldman and Furukawa 1973). It should be noted that these complications are rare but caution is appropriate in susceptible patients. Prolonged enema retention or excessive use are probably
the most important causative factors in children with normal renal function.

Soap enemas are rarely used now. Hyperkalaemia has been reported with potassium based soaps (Godding 1976a).

Polyethylene glycol 4000 is the principle ingredient in 'Golytely', 'Klean Prep' and other 'osmotic' bowel preparation solutions. They are used prior to colonoscopy, radiological investigation or surgery. They are rarely used in constipation. Adverse effects include nausea, bloating, abdominal cramps, vomiting and anal irritation. Urticaria and other allergic reactions occur rarely. There are no reports of long term use of this agent.

(4) STOOL SOFTENERS

Liquid paraffin, also known as 'mineral oil', is derived from petroleum. Mineral oil is actually a generic term that covers a wide range of petroleum products. The carcinogenicity of mineral oils was recognised in the early 1900's in cotton-spinning workers (Bingham 1988). There are no such reports of carcinogenic risk with liquid paraffin when used as a laxative. Croton oil and arachis oil are seed oils. They are indigestible and are absorbed to a limited extent. It is believed that they exert their laxative action by softening the stool and
decreasing water absorption. Side effects are said to include (Sarner 1976):

(i) Interference with the absorption of fat soluble substances, including the fat soluble vitamins \([A,D,E,K]\). There is little in the literature to support this.
(ii) Foreign body reactions in the intestinal mucosa
(iii) Anal leakage
(iv) Lipoid pneumonia if aspirated

Fatal lipid pneumonia occurred in one patient following asymptomatic inhalation of liquid paraffin prior to prostatectomy under epidural anaesthesia (Paraskevaides 1990).

The side effects of this substance, and the existence of equally effective safer drugs, suggest that the use of liquid paraffin and paraffin based drugs should be discouraged (Godding 1976a, Thompson 1980).

Dioctyl sodium sulphonate succinate (docusate sodium, DSS) is a surface-active agent with emulsifying and detergent properties which softens the stool by enabling water to penetrate the faecal mass. It is also thought to have some stimulant activity (Lish 1961, Saunders, Sillery and Rachmilewitz 1975). In vitro studies by Donowitz and Binder (1974) showed that DSS stimulated colonic electrolyte secretion, probably mediated by mucosal cyclic-AMP. The most important potential adverse effect
is the potentiation of hepatotoxicity produced by other drugs (Tolman, Hammar and Sannella 1976, Abromowiez 1977). DSS is excreted in the bile and may enhance the gastrointestinal or hepatic uptake of other drugs and thus increase their potential toxicity; the mechanism for this increased uptake has not been well defined.

There is a single case report of neonatal hypomagnesaemia associated with maternal overuse of oral docusate sodium (Schied 1984).

Docusate produces morphological changes in gut mucosa at the light and electron microscope level (Saunders, Sillery and Rachmilewitz 1975, Phillips 1976), although the physiopathological importance of this is not known.

(5) PROKINETIC DRUGS

(i) Cisapride

Cisapride is a prokinetic drug which has been used in the management of chronic constipation. Muller-Lissner (1987) reported that cisapride increased stool frequency and reduced laxative consumption in patients with idiopathic constipation. There were no significant side effects. Cisapride is well tolerated with few adverse effects; headaches and urinary frequency are occasional
complaints. The evidence for its efficacy in constipation is contradictory.

CLINICAL OVERVIEW AND CONCLUSIONS

Most laxatives, if used intermittently in the absence of contraindications, are safe. It is important that the clinician becomes familiar with a limited number of laxative preparations and uses them appropriately. The majority of patients with mild and chronic constipation need only an increase in dietary fibre or a bulking agent. The latter are well established and safe agents. Bulking agents may diminish absorption of some minerals and drugs, but this is not usually clinically significant. Psyllium can cause serious allergic reactions. Bulking agents are not useful in patients with idiopathic megarectum. In pregnant women bulking agents are safe, but not as effective as stimulant laxatives and low doses of senna would appear to be the drug of choice.

In patients with more severe constipation, oral or rectal preparations, or a combination, are used. Glycerol or the stronger bisacodyl suppositories should be used initially. Serious adverse effects are rare. Phosphate enemas are usually effective, with little risk of significant adverse events if administered correctly and
prescribed appropriately. There do not appear to be long term effects from the regular use of bisacodyl suppositories or phosphate enemas.

'Veripaque' (oxyphenisatin) enemas should only be used for radiological investigation preparation or for patients with intractable severe constipation as there is a theoretical risk of hepatotoxicity. The oral preparation should no longer be used.

There is a great reluctance amongst many physicians to prescribe senna. However, standardised senna preparations would not appear to be as toxic as was once thought. Their is little evidence that standardised senna preparations cause myenteric nerve damage and other serious side effects are rare. Long term use of senna is probably not advisable, but short courses are usually effective.

Phenolphthalein causes a significant incidence of allergic skin reactions and oral bisacodyl is therefore the polyphenolic derivative of choice. The adverse effects of chronic, regular use of oral bisacodyl are unknown. 'Picolax' can be used occasionally, but not on a regular basis; its use as a safe bowel cleansing agent prior to radiological investigation or surgery is well established but there is no information regarding more frequent use.
Docusate (dioctyl) may potentiate the hepatotoxicity of other drugs, but reports of this are rare. The role of cisapride in constipation has not been established.

'Epsom salts' (magnesium sulphate) is the laxative of choice in patients with idiopathic megarectum and is useful in some patients with severe idiopathic constipation. It is unpalatable and patient compliance may be poor. Serious adverse effects in adults, even with long term regular use, are rare.
Table 18. **DRUGS USED IN THE MANAGEMENT OF CONSTIPATION**

(Generic names in bold, trade names follow)

**I Bulking agents**

- bulk agents: 'Fybranta', 'Proctofibe'
- methylcellulose: 'Celevac'
- psyllium (ispaghula): 'Fybogel', 'Isogel', 'Metamucil', 'Regulan'
- sterculia: 'Normacol', 'Normacol plus' [plus frangula]
- wheat husk: 'Trifyba'

**II Stimulant laxatives**

- POLYPHENOLIC (diphenylmethane derivatives)
  - phenolphthalein
  - bisacodyl
  - sodium picosulphate (bisacodyl disulphate): 'Picolax'
  - oxyphenisatin: 'Veripaque'

- ANTHRAQUINONES (anthraquinoid derivatives)
  - danthron (1,8-dihydroxyanthraquinone, free anthraquinone): 'Codanthramer' [plus poloxamer 188], 'Codanthrasate' [plus docusate sodium], 'Dorbanex' [plus poloxamer]
  - senna (sennosides, glycosides of rhein dianthrone): 'Senokot'

- MISCELLANEOUS
  - castor oil
  - glycerol: glycerol suppositories
  - docusate sodium: 'Dioctyl', 'Fletchers' enemette', 'Norgalax micro-enema'

**III Osmotic laxatives**

- alcohols: mannitol, sorbitol
- lactitol
- lactulose
- magnesium sulphate: Epsom salts
- magnesium citrate: 'Citrimag'
- magnesium hydroxide\carbonate
- rectal phosphates: 'Carbalax', 'Fletchers' phosphate enema'
- rectal sodium citrates: 'Micolette micro-enema' (plus sodium laurylsulphoacetate and glycerol), 'Micralax micro-enema' (plus sodium alkylsulphoacetate and glycerol), 'Relaxit microenema' (sodium laurylsulphate and sorbic acid).

**PTO for IV**

192
IV Stool softeners

**arachis oil**: 'Fletchers' Arachis Oil retention enema'

**dioctyl sodium sulphosuccinate (docusate)**: 'Dioctyl', 'Fletchers' Enemette', 'Norgalax' [plus glycerol].

**liquid paraffin**: 'Petrolagar', 'Agarol' [with phenolphthalein]
Chapter 10

Colostomy irrigation

A colostomy is managed by one of the following: (i) natural spontaneous evacuation (ii) control of the colostomy output by drugs (iii) colostomy irrigation (Griffiths et al 1976). The first two regimens lack good continence control, may require the use of a bulky appliance, and may produce a faecal odour. Colostomy irrigation is gaining in popularity as the safety of modern methods and the ability of even elderly patients to cope with the technique is recognised (Laucks et al 1988, MacLeod 1972, Venturini et al 1990).

A major disadvantage is the time needed to perform irrigation, usually up to one hour every one to two days. There is also very little information regarding the ideal volume to be infused (Meyhoff, Andersen and Nielsen 1990), and there is no information about the effect of the rate of inflow on the outcome of irrigation. These factors may be critical in obtaining the maximum benefit from irrigation.

The aims of this study were: (i) to determine whether a large volume of fluid infusion produces a better result than a small volume infusion, (ii) to determine if the infusion rate of the fluid is important in achieving a good result, (iii) to determine whether a pump is
necessary to achieve rapid infusion, and whether this is beneficial and safe, (iv) to measure the intracolonic pressures during different volumes and rates of infusion, and (v) to determine the relationship between the intracolonic pressures during colostomy irrigation with the outcome and the occurrence of side effects such as pain.

**PATIENTS AND METHODS**

Five patients (2 female, mean age 63 years, range 59-66 years) were studied. One patient (KC) had long standing constipation (bowel action every 4-5 days) pre-operatively, the rest had a pre-stoma bowel frequency of once per day. The patients had no other gastrointestinal problems. All had undergone abdominoperineal resection with formation of an end colostomy for rectal adenocarcinoma and were using irrigation as their preferred method of colostomy management. The patients' details are shown in Table 19. The time spent performing colostomy irrigation was variable, but usually took up to 1 hour, including 'cleaning up'. Three patients had difficulties with excessive flatus and four had occasional minor soiling, both occurring during the few hours prior to irrigation. Four patients graded the effectiveness of their usual irrigation technique as good or excellent, and one patient (ES) as fair to good. No patient was taking any laxatives or other medication that
significantly affects gastrointestinal function.

Patients were studied when they would normally irrigate; in two patients this was 24 hours and in 3 patients this was 48 hours after their last irrigation. Patients had a light breakfast 4 hours before the study, but there were no other dietary exclusions and no bowel preparation was used.

Colonoscopy was undertaken at 10 am on each study day on unprepared bowel, without sedation. A guide wire was passed under direct colonoscopic vision into the proximal colon via the stoma. An ambulatory recording catheter (Gaeltec Ambulatory Recording System, Gaeltec Ltd, Dunvegan, Isle of Skye, Scotland), with 3 pressure transducers 10 cm apart, was passed over the guide wire to lie 30 to 40 cm proximal to the stoma. The position of the catheter was confirmed by x-ray screening after catheter placement and at the end of each individual study.

Recording of colonic pressures started once correct siting of the pressure transducers had been confirmed. Recording was undertaken for: (i) 30 minutes 'at rest', (ii) during a study meal of a sandwich and coffee, which was consumed within 20 minutes, (iii) for 30 minutes after the meal (iv) during the infusion of the irrigation water, and (v) for 60 minutes after the infusion.
After the post meal period, a standard colostomy irrigation cone of the Laird type (Dansac, Dansac A/S, Fredensborg, Denmark) was inserted and bags and tubing connected. Tap water at 37°C was run in either under gravity, at the patients head height, or using the pump.

Baseline pressures were measured during each component of the study. High pressure contractile activity was also assessed, with high pressure propagated waves being defined as a pressure rise above the baseline of more than 50 cm H₂O, involving two or more sensors, and progressing distally.

The post-infusion period was 'divided' into six 10-minute periods. The output from the stoma was collected and measured during each 10-minute period.

The study was designed to investigate each subject on 6 separate study days. These involved: (i) 500 ml - infusion by gravity alone (ii) 500 ml - infused over 5 minutes by pump (Masterflex Pump Controller, model 7518-00, Barnant Company, Barrington, Illinois USA) (iii) 500 ml - infused over 2.5 minutes by pump (iv) 1500 ml - gravity alone (v) 1500 ml - infused over 5 minutes by pump (vi) 1500 ml - infused over 2.5 minutes by pump. If a particular volume of fluid entered the bowel in less than 5 minutes under gravity alone, then the 5 minute pump infusion was not performed for that volume.
Similarly for the 2.5 minute infusions.

After each study the patients returned home, but were asked to record any "breakthrough" discharge of colonic contents prior to the next usually timed irrigation, in order to provide some guide as to the clinical effectiveness of each speed and volume of irrigation.

The study was approved by the Barts NHS Group Ethics Committee and all patients gave informed consent for each individual session.

RESULTS

Colonoscopy and sitting of recording catheter

All 5 patients completed the protocol, resulting in a total of 18 studies. At colonoscopy the colon contained formed stool in all patients. Colonoscopy was achieved without complication. The catheter was sited as proximally as possible, usually with the proximal tip in the transverse colon or splenic flexure and the distal pressure transducer at least 15 cm from the stoma. No significant catheter movement occurred in 14 studies as assessed radiographically. In four studies the distal transducer was extruded during the study, although the proximal two sensors remained in the colon.

Infusion of irrigate
Difficulty was experienced in initiating flow of the irrigate into the colon in some studies due to the anatomy of the stoma rather than colonic contraction. Once the infusion started the rate of flow was always rapid. Times of infusion were recorded from when the flow started.

Using gravity alone 500 ml was infused in a median 2 minutes (range 2-6 minutes) and 1500 ml in a median 5 minutes (range 3-8 minutes).

All patients had an infusion of 500 ml and 1500 ml under gravity alone. Those patients who had a slow infusion for a particular volume using gravity alone then had studies performed for that volume using the pump.

**Pressure activity in the colon**

Figure 9 illustrates a typical manometric recording obtained during the studies. In all patients in all studies the baseline pressures did not change between the first three phases of the study, that is at rest, during and after the meal. The median baseline pressure of the 5 patients was 17 cm H\(_2\)O (range 3-50 cm H\(_2\)O).

In 4 of the 18 studies high pressure propagated waves occurred during the pre-infusion phases (Figure 10).
After commencing the infusions the baseline colonic pressures increased, as shown in Figures 11 and 12. The increase in baseline pressure was not linearly related to either the volume infused or the rate of infusion. The median baseline pressure immediately prior to infusion was 14 cm H$_2$O (range 0-34) and rose to a median peak of 45 cm H$_2$O (range 14-101) with the 500 ml infusions and 59 cm H$_2$O (range 18-126) with the 1500 ml infusions.

The median change in baseline pressure after a 500 ml infusion under gravity was 11 cm H$_2$O (range 8-64) and after a 1500 ml infusion under gravity 33 cm H$_2$O (range 11-102). The pump was used to infuse 500 ml in 5 minutes in two patients, with pressure rises of 21 and 69 cm H$_2$O respectively. In the same two patients the pump was used to infuse 500 ml in 2.5 minutes with pressure rises of 12 and 63 cm H$_2$O respectively. The pump was used to infuse 1500 ml in 5 minutes in two patients, with pressure rises of 42 and 139 cm H$_2$O. In two patients pressure rises of 37 and 68 cm H$_2$O occurred with a 2.5 minute pump infusion. One 1500 ml pump infusion was terminated after 1300 ml due to abdominal discomfort. In this patient the peak pressure in the proximal transducer was 87 cm H$_2$O, an increase of 68 cm H$_2$O.

At the end of the infusion the cone was removed. There was usually an immediate discharge of liquid followed by a number of effluent boluses containing solid and semi-
formed faeces. These boluses occurred in association with recorded high pressure propagated waves as shown in Figure 13. These high pressure propagated waves often reached peaks of more than 200 cm H$_2$O. Occasional recorded high pressure waves were not associated with any stoma output. Table 20 shows the number of high pressure propagated waves in each patient before and after infusion. The figures for 'pre-infusion' include a minimum of 1.5 hours of recording, the post-infusion figures are per 10 minute period. The 1500 ml infusions were associated with a marginally significantly greater number of high pressure propagated waves (median 4.5 (range 3-8) v 2 (range 1-9) 1500 ml v 500 ml, p = 0.0650).

The baseline colonic pressure returned to preinfusion levels after the infusion was completed. This usually occurred within the first 10 minutes, and in all cases after one hour.

**Clinical effectiveness**

No patient had any complications from the study. Subjectively patients felt that the 500 ml volume was not as successful as their usual volume or the 1500 ml infusion, although it was not practical to measure the actual amount of stool produced by irrigation. The output of irrigation fluid was measured, however, and was found to be almost always complete with either volume.
DISCUSSION

Irrigation is a safe and effective method of colostomy management (Seargent 1966, MacLeod 1972, Mazier et al 1976, Terranova et al 1979, Williams and Johnston 1980, Laucks et al 1988, Venturini et al 1990). Perforation (Hoffman and Macht 1954, Grillo and Nardi 1958, Green and Blank 1965, Spiro and Hertz 1966, Marino and Marino 1967, Isa and Quan 1978) is now rare as the irrigating cone (Laird 1969) is widely used and complications such as burns (Jackson, Ott and Gelfand 1981 and Giunchi, Cacciaguerra and Drudi 1985) and subsequent stricture formation are avoidable.

The baseline colonic intralumenal pressures obtained in this study were similar to those reported elsewhere (Noveroske 1964, Kozarek et al 1980). The light study meal did not induce any significant change in colonic pressures, reflecting the low calorific value of the meal (Snape, Matarazzo and Cohen 1978). The high amplitude propagated waves have also been documented previously, both in anatomically normal colon (Narducci et al 1987 and Bassotti et al 1988) and in patients with a colostomy (Hardcastle and Mann 1970) where the introduction of the stimulant bisacodyl into the stoma produced progressive peristaltic activity similar to that observed with the introduction of water. These high pressure events appear to be the manometric equivalent of radiographically
observed mass movements. In the normal colon they occur approximately four to six times in 24 hours (Narducci et al 1987, Bassotti et al 1988). After irrigation these were induced almost immediately, were most frequent in the first 10 to 20 minutes, and were associated with the effective evacuation of colonic contents.

Water infusion increased the basal colonic pressure. The pressure rise was greater with larger volumes, but was not greatly increased with a faster speed of infusion. Since the range of variables studied is likely to embrace the range of volumes and infusion speeds of everyday life, it is concluded that these speeds of infusion and volumes are safe.

This study has demonstrated that 1500 ml tends to result in a subjectively more effective 'irrigation' than 500 ml. In a study comparing the effectiveness of 250 ml, 500 ml and 1000 ml irrigation volumes, 500 ml was preferred by the majority of patients. Objective parameters were similar, except for an increased incidence of faecal break through with 250 ml (Meyhoff, Anderesen and Nielsen 1990).

The rate of infusion is usually easily adjustable with gravity alone and this study suggests that there is no benefit from the use of a pump.
There are occasions when even well established irrigators fail to obtain a satisfactory result from their usual irrigation technique. These data show that colostomy irrigation appears to work by the induction of high pressure propagated waves. Further studies involving the addition of a stimulant to the irrigation fluid to achieve this may be useful (Doran and Hardcastle 1981, Christensen, Kjaergaard and Stadil 1982, Kjaergaard et al 1984). Colostomy irrigation using 500 to 1500 ml can usually be easily achieved without the need for a pump.
Table 19. Patient details.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Usual volume (ml)</th>
<th>Interval between irrigations</th>
<th>Breakthrough</th>
</tr>
</thead>
<tbody>
<tr>
<td>KC</td>
<td>65</td>
<td>F</td>
<td>750-1500</td>
<td>48 hours</td>
<td>none</td>
</tr>
<tr>
<td>ES</td>
<td>64</td>
<td>M</td>
<td>1500</td>
<td>48 hours</td>
<td>x1/week</td>
</tr>
<tr>
<td>BD</td>
<td>62</td>
<td>M</td>
<td>650</td>
<td>24 hours</td>
<td>occasional</td>
</tr>
<tr>
<td>LR</td>
<td>66</td>
<td>M</td>
<td>1500</td>
<td>48 hours</td>
<td>occasional</td>
</tr>
<tr>
<td>CE</td>
<td>59</td>
<td>F</td>
<td>800</td>
<td>24 hours</td>
<td>yes-minor</td>
</tr>
</tbody>
</table>

Breakthrough was defined as any faecal discharge from the stoma between usual irrigations.
Table 20. The median number of high pressure propagated waves before and after infusion of 500 ml and 1500 ml of tap water in 18 studies performed in 5 individuals.

<table>
<thead>
<tr>
<th></th>
<th>KC</th>
<th>ES</th>
<th>BD</th>
<th>LR</th>
<th>CE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRE-INFUSION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(90 minutes)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>POST-INFUSION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 ml / 1500 ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-10 min</td>
<td>1  \ 3</td>
<td>&gt;1* 0</td>
<td>0 \ 2</td>
<td>2 \ 3</td>
<td>1 \ 3</td>
</tr>
<tr>
<td>11-20 min</td>
<td>0 \ 1</td>
<td>&gt;1* 0</td>
<td>1 \ 3</td>
<td>1 \ 0</td>
<td>2 \ 1</td>
</tr>
<tr>
<td>21-30 min</td>
<td>0 \ 1</td>
<td>&gt;1* 0</td>
<td>1 \ 2</td>
<td>2 \ 0</td>
<td>0 \ 1</td>
</tr>
<tr>
<td>31-40 min</td>
<td>0</td>
<td>0 \ 2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>41-50 min</td>
<td>0</td>
<td>0 \ 2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>51-60 min</td>
<td>0</td>
<td>0</td>
<td>0 \ 1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* = due to equipment failure, limited data only available for 2 studies in this patient.
Figure 9. Typical baseline pressure recording over a 30 minute period. Only a small amount of non-propagated segmenting activity is seen.

Figure 10. One of the few pre-infusion high pressure propagated waves.
Figure 11. Example of the effect of the infusion on baseline colonic pressures. 1500 ml was infused in 5 minutes using gravity. High pressure waves had not yet been induced.

100 cmH2O

Proximal sensor

Distal sensor

2 mins

START OF INFUSION
Figure 12. Changes in intralumenal pressure produced by infusion of 500 and 1500 ml.
Figure 13. Example of a high pressure propagated wave in the post-infusion phase, induced by irrigation.
CHAPTER 11
Discussion

Dilatation of the rectum and/or colon, in the absence of demonstrable organic disease, is an uncommon and poorly characterised condition. The work reported in this thesis was to characterise idiopathic megarectum and megacolon clinically and to investigate the pathophysiology of this condition.

Clinical features:

Goodhart (1902) in his paper on constipation emphasised the importance of obtaining an accurate diagnosis to ensure optimum management; 'one man's constipation is another's diarrhoea'. The 'diagnostic dump heap of idiopathic megacolon' remains unacceptable (Goligher 1961).

The two conditions of idiopathic large bowel enlargement have been characterised and shown to be clearly distinguishable. I have used radiological criteria to separate the patient groups into those with idiopathic megarectum (with or without more proximal colonic dilatation) and those with idiopathic megacolon (and a normal diameter rectum). This correlated well with the clinical presentation. Those with a megarectum tended to have onset of their symptoms in childhood or adolescence.
and experience impaction and soiling. A frequent misconception is that impaired intellect is a common feature in these patients. Although it was marked in a few, the majority appeared to be within the normal range. Those with idiopathic megacolon often presented at an older age and rarely experienced faecal impaction. Both conditions can be distinguished from chronic idiopathic intestinal pseudo-obstruction as there was no upper gut dilatation. Clear distinction of these conditions will prevent confusion in the assessment of histological and other data from these patients in the search for the underlying aetiology, as well as ensuring optimum management.

The rest of the work presented in this thesis differentiates between those patients with idiopathic megarectum and idiopathic megacolon as defined in chapter 2.

**The anal sphincter:**

In patients with idiopathic megacolon the internal and external anal sphincters were functionally and structurally intact. In contrast, many patients with idiopathic megarectum were found to have disrupted anal sphincters, however this was always in association with a history of previous manual disimpaction under general anaesthetic. The endosonographic changes were
characteristic of those identified previously in patients following anal dilatation (Speakman et al 1991).

Manual disimpaction under general anaesthetic appears to be associated with iatrogenic structural injury to the anal sphincters. This may contribute to the incontinence experienced by patients with idiopathic megarectum, especially when the patient is not impacted. Faecal impaction also occurs in other age groups, especially the paediatric and geriatric populations. They are often the subject of manual disimpaction and care should be taken to avoid iatrogenic injury to the anal sphincters.

The aim of both medical and surgical treatment of megarectum is the production of a liquid or semi-liquid stool to prevent further impaction (Kamm and Stabile 1991). If impaction does occur, it is possible to perform repeated manual disimpactions under general anaesthetic without traumatising the anal sphincters. Three patients had had more than 4 disimpactions each, without sustaining any endosonographic evidence of sphincter disruption.

In patients with idiopathic megarectum a low resting anal pressure, indicative of internal anal sphincter dysfunction (Read and Sun 1992, Delechenaut et al 1992, Engel et al 1995), was found in a substantial proportion of patients with either an endosonographically intact or
disrupted internal anal sphincter. This lack of correlation between the structural and functional integrity may be related to the wide normal range of resting pressure, or the possibility of sphincter damage not detected endosonographically. The voluntary contraction increment, a reflection of external sphincter function (Read and Sun 1992, Delechanaut et al 1992, Engel et al 1995), was normal in all patients.

Patients with a disrupted internal anal sphincter and low resting anal canal pressures are at risk of passive faecal incontinence if the stool is rendered liquid or semi-formed either medically or surgically. The 2 patients reported in chapter 3, both with disrupted sphincters and poor manometric function, one continent after colectomy and ileorectal anastomosis and one incontinent, illustrate how continence is multifactorial (Bennett and Duthie 1964, McHugh and Diamant 1987, Delechenaut et al 1992). Incontinence after surgery remains difficult to predict in these patients.

There is no evidence to suggest that there is any intrinsic abnormality of the anal sphincters in patients with idiopathic megarectum or idiopathic megacolon. Iatrogenic damage to the anal sphincters can contribute to persistent incontinence even when rectal faecal impaction is prevented.
Gastrointestinal transit:

I have demonstrated abnormalities of late gastric emptying in patients with idiopathic megarectum and idiopathic megacolon. The functional significance of this is unknown. Preston et al (1985) demonstrated that patients with slow transit constipation and idiopathic megacolon had impaired motilin and gastrin release in response to drinking water. However, this may be a secondary result rather than of primary aetiological significance.

In patients with idiopathic megarectum both the radioisotope scans and radio-opaque marker studies showed abnormal colonic transit. The regions of delay corresponded with the region of dilated bowel. Symptoms of abdominal distension and bloating did not correspond to abnormalities of gastric emptying, but rather with the effectiveness of rectal evacuation. Patients with idiopathic megarectum had abnormal colonic transit, delay occurring predominantly in dilated gut. Marker studies are less sensitive than isotope studies, but provide adequate information for clinical purposes. Although motility abnormalities of the upper gut are common symptoms correlate with large bowel abnormalities.

In patients with idiopathic megacolon the colonic isotope scans detected colonic motility abnormalities missed by
marker studies. If surgery is contemplated in these patients formal radio-isotope colonic motility studies should be considered as part of a pre-operative work-up. Ryan (1982) reported 6 cases of sigmoid volvulus in patients with acquired megacolon. He concluded that total colectomy rather than sigmoid colectomy was the operation of choice in these patients. Motility studies may support this view.

The key to choosing the operation likely to offer most benefit to the patient remains in meticulous preoperative assessment to obtain an accurate diagnosis with particular attention to colonic and anorectal function (Todd 1971). On the basis of published results in patients with idiopathic megarectum, colectomy and ileorectal anastomosis would appear to be the operation of choice (Kamm and Stabile 1991) as it is in patients with idiopathic slow transit constipation (Preston et al 1984, Wexner, Daniel and Jagelman 1991, Piccirillo, Reissman and Wexner 1995). This surgically produces a liquid or semi-formed stool preventing impaction of the dilated rectum. In patients with a functionally intact anal sphincter resection of dilated bowel and coloanal anastomosis (Stabile 1992b) or colectomy and formation of an ileo-anal pouch (Hosie, Kmiot and Keighley 1990, Ecker, Kreissler-Haag and Lindemann 1994, MacSweeney, Stewart, Kumar and Keighley 1994, Shankar and Theodorou 1995) may be more appropriate.
**Histopathology:**

Patients with idiopathic megarectum were found to have significant thickening of the muscularis mucosae, circular muscle and longitudinal muscle. Despite marked gut dilatation smooth muscle atrophy was not seen. This thickening was relatively greater in the longitudinal compared to the circular muscle. Fibrosis of the longitudinal muscle was seen but the relationship between muscle thickening and fibrosis was variable.

The architecture of the enteric innervation appeared to be normal in patients with idiopathic megarectum and idiopathic megacolon. However, the density of neural tissue, using a variety of neural markers, appeared to be reduced in the longitudinal muscle of patients with idiopathic megarectum. The apparent sparsity of nerve fibres in the longitudinal muscle and hypertrophy of this muscle layer in patients with idiopathic megarectum may reflect an abnormal neural inhibitory system in the muscularis externa.

There was no significant thickening of enteric muscle or alteration in the density of innervation in patients with idiopathic megacolon.

There was an increase in VIP and nitric oxide containing nerve fibres in the muscularis mucosae and
lamina propria and a decrease in the longitudinal muscle in rectal tissue of patients with idiopathic megarectum. Both are NANC (nonadrenergic noncholinergic) inhibitory transmitters in the gut. It is unknown whether these abnormalities are primary or secondary, but abnormalities in the VIP or nitric oxide inhibitory systems may contribute to abnormal gut function and subsequent gut dilatation.

The disparate mean ages of the patients and controls may have a bearing on the interpretation of these results. It has been reported that the patterns of neuropeptide distribution and coexistence appear to be established from 26-week gestational age in human foetuses and although a lower nerve fibre frequency may be seen in older patients (more than 60 years) selective variation in immunoreactive fibre types does not occur with increasing age (Wattchow, Furness and Costa 1988). Thus, the decreased innervation in the longitudinal muscle in the younger megabowel patients should have more weight than the apparent greater innervation in the muscularis mucosae and lamina propria, which have a greater probability of being so because of the relative ages.

Biochemical or ultrastructural abnormalities of enteric smooth muscle have been observed in patients with chronic idiopathic intestinal pseudo-obstruction
Normal gut motility is dependent on functional enteric smooth muscle, and an alteration in the contractile elements is likely to result in abnormal propulsion.

In one patient with idiopathic megarectum abnormalities of constituents of both the thick and thin filaments were observed which may have explained her abnormal gut motility. No abnormality in the distribution of the smooth muscle markers was seen in the other patients studied. They may have other subtle abnormalities, either primary or secondary, of enteric nerve or muscle that have not been demonstrated by the techniques used. Investigation for other specific contractile protein or neural abnormalities is warranted.

The subtle abnormalities of the enteric innervation in patients with idiopathic megarectum and idiopathic megacolon do not appear to be attributable to the neurotropic effects of herpes viruses. Evaluation for other viruses may be warranted.

**Laxatives:**

Many patients with idiopathic megarectum can be managed with drugs. The rectum must be disimpacted at the start of treatment, and this may require manual evacuation.
under general anaesthetic. The aim of laxative treatment is to achieve a liquid stool, to prevent re-impaction and ease defaecation. Magnesium sulphate (Epsom salts) is the osmotic laxative of choice. The required dose is very variable and has to be titrated to achieve a semi-liquid stool in each patient. Significant side effects are unusual, but excessive doses can cause biochemical abnormalities even in adults.

Patients with idiopathic megarectum are often poorly compliant with oral laxatives. Phosphate enemas are a useful alternative, especially if liquid stool results in faecal incontinence secondary to poor anal sphincter function.

**Colostomy irrigation:**

Some patients with idiopathic megarectum will have a colostomy formed, either as a first surgical procedure or after failed or complicated surgery. Colostomy irrigation can restore faecal continence, but is both time consuming and not always successful. In an effort to improve the technique of colostomy irrigation I investigated different infusion volumes, rates of infusion and whether an infusion pump would be useful.

Larger infusion volumes produced the best results, but
there is no role for an infusion pump. Infusion volumes probably need to be determined on an individual basis, the smallest effective volume should be used as there is anecdotal evidence that progressively larger volumes are needed over a period of years. The role of motility stimulants in the infusate needs to be investigated.

**Conclusion:**

Idiopathic megarectum and idiopathic megacolon are discrete conditions. The aetiology remains unknown. There is no primary abnormality of the anal sphincter. Abnormalities of enteric nerve and muscle have been demonstrated, but it remains likely that a number of different aetiologies underlie a common clinical picture. Bentley’s words (1964) remain pertinent:

> 'When simple histologic examination reveals no abnormality in the wall of the bowel, subtle intrinsic factors might still exist to impair the reflex of defaecation. As knowledge of neurochemistry and smooth muscle activity increases, more sophisticated techniques may develop to study the tissue excised from the rectum'.

221
Personal Over-View

Idiopathic megacolon remains an ill-defined condition. The clinical features of such patients often have more in common with patients who have idiopathic slow transit constipation rather than those with idiopathic megarectum. In the prospective study few patients were classified as having idiopathic megacolon, especially when compared to the retrospective series. This may suggest that some patients with 'long redundant colon' have been misclassified as true megacolon, when it is more likely that the bowel is not truly dilated at all.

In contrast idiopathic megarectum is a well defined, discrete condition. A dilated rectum, with a variable extent of proximal colonic dilatation, is likely to be a common endpoint of a number of different conditions. I have demonstrated abnormalities of the enteric innervation in these patients and in one patient abnormalities of the constituents of the smooth muscle proteins of the muscularis externa.

If sufficient patients are studied it is likely that the following groups will be defined:
1. those with a primary abnormality of enteric innervation
2. those with a primary abnormality of enteric muscle
3. a group with no intrinsic neuromuscular abnormality, in whom secondary changes may be seen.

Children who have severe constipation often develop a megarectum. Their original symptoms may originate from the development of an anal fissure or the more complicated issues of a dysfunctional family or even child sexual abuse. Medical intervention will fail some of these children who will become adolescents and young adults with a megarectum. At this stage there may be secondary neuropathic or myopathic changes.

Future developments

Larger groups of well-defined patients need to be studied to usefully extend this evaluation of patients with idiopathic megarectum. This will entail maintaining continuity of clinical care of patients progressing from paediatric to adult medical departments. Many patients would appear to 'disappear' into the community at this stage. Due to the socially disabling nature of this condition and their own denial of any problem, many patients refrain from seeking further medical assistance and this attitude is often gratefully accepted by the doctors involved.

Idiopathic megarectum is a rare condition and most centres will only see a few cases. It may be appropriate for such patients to attend designated tertiary referral centres. Relatively few patients are treated surgically and any one unit will only have limited tissue to study either histologically or physiologically (ie muscle bath work). As in a number of other rare conditions there would appear to a role for a central national tissue storage bank. If an appropriate databank included relevant clinical information, investigation results etc, then adequate amounts of tissue from a carefully defined patient group could be usefully studied. I feel that it is only in this way that the aetiology of this condition(s) will be definitively elucidated.
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Amendment to References

Journal Titles: In full and standard abbreviations

Acta Chirurgica Scandinavica : Acta Chir Scand
Acta Hepatology-Gastroenterology : Acta Hepato-Gastroenterol
Acta Histochemica : Acta Histochem
Advances Prostaglandin Thromboxane Leukotriene Research : Adv Prostaglandin Thromboxane Leukot Res
Advances Nutritional Research : Adv Nutr Res
Allergy : Allergy
American Journal Digestive Diseases : Am J Dig Dis
American Journal Medicine : Am J Med
American Journal Physiology : Am J Physiol
American Journal Roentgenology : Am J Roentgenology
American Journal Surgery : Am J Surg
American Review Respiratory Diseases : Am Rev Respir Dis
Anesthesiology : Anesthesiology
Annals Internal Medicine : Ann Int Med
Archives Dermatology : Arch Dermatol
Archives Disease Childhood : Arch Dis Child
Archives Internal Medicine : Arch Int Med
Biochemica et Biophysica Acta : Biochim Biophys Acta
Brain : Brain
British Journal Anaesthesia : Br J Anaesth
British Journal Cancer : Br J Cancer
British Journal Clinical Practice : Br J Clin Pract
British Journal Dermatology : Br J Dermatol
British Journal Experimental Pathology : Br J Exp Path
British Journal Surgery: Br J Surg
British Medical Journal: BMJ (Br Med J)
Canadian Journal Physiology Pharmacology: Can J Physiol Pharmacol
Canadian Journal Surgery: Can J Surg
Canadian Medical Association Journal: Can Med Assoc J
Cancer: Cancer
Clinical Experimental Allergy: Clin Exp Allergy
Clinical Experimental Dermatology: Clin Exp Dermatol
Clinical Medicine: Clin Med
Clinical Pediatrics: Clin Pediatr
Clinical Radiology: Clin Radiol
Coloproctology: Coloproctology
Current Opinion Gastroenterology: Curr Opin Gastroenterology
Digestive Disease Sciences: Dig Dis Sci
Diseases Colon Rectum: Dis Colon Rectum
Drugs: Drugs
Drug Nutrient Interactions: Drug Nutr Interactions
Drug Safety: Drug Saf
Drug and Therapeutics Bulletin: Drug Ther Bull
European Journal Nuclear Medicine: Eur J Nucl Med
European Society Gastrointestinal Radiologists: Eur Soc Gastrointest Radiol
Gastroenterology: Gastroenterology
Gastroenterology International: Gastroenterol Int
Gastroenterology In Practice: Gastroenterol In Pract
Gastrointestinal Endoscopy: Gastrointest Endosc
Gastrointestinal Radiology: Gastrointest Radiol
Gut: Gut
Hepato-gastroenterology: Hepatogastroenterology