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206

THE CHRONIC CONSTIPATION OF YOUNG WOMEN

A thesis submitted by

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for the degree of

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THE CHRONIC CONSTIPATION OF YOUNG WOMEN

DAVID MICHAEL PRESTON

ABSTRACT

A group of patients with severe constipation without known primary cause has been identified. These patients have been described previously as suffering from idiopathic slow transit constipation. All were women and comparison by questionnaire with a control group suggested a disturbance of many bodily systems. The sex ratio, barium enema, and rectal elasticity findings differentiate this group from other constipated patients with idiopathic megacolon. Studies designed to investigate possible causes for this condition showed a disorder of defaecation with innapropriate spasm of the pelvic floor and external sphincter muscles on attempted defaecation. A new radiological technique, the balloon proctogram was developed allowing observation of the rectum and pelvic floor during defaecation. Colonic pressure wave activity was reduced and in some patients there was no colonic response to a powerful surface acting laxative. An attempt was made to correlate these findings with neuropathological changes in colons subsequently resected. Hormonal disturbances were demonstrated, including hyperprolactinaemia and decreased pancreatic polypeptide, motilin and gastrin release following an oral stimulus. The psychological state of some patients as assessed by questionnaire was normal, but this did not correlate with the opinion of an experienced psychiatrist. The results of medical and surgical treatment were analysed, and suggest that most patients respond to saline laxatives. However those worst affected responded only to sub-total colectomy. Operations on the anal sphincters were not helpful. It is proposed that this disorder represents an identifiable syndrome, but the primary cause and reason for the abnormalities of structure and function so far recorded is not clear.

DEDICATION

This work is dedicated to the memory of two great Guy's men:

Sir William Arbuthnot Lane
(1856-1943)

and

Sir Alan Guyatt Parks
(1920-1982)

Both of whom in their time were outstanding surgical innovators with a particular interest in patients with constipation. Lane was probably the first to describe the condition studied in this thesis and to carry out successful colectomies for chronic constipation. Many recent advances in our understanding of ano-rectal physiology are the result of work stimulated by Parks and some of the techniques used in the present study would not have been developed without this knowledge.

(Proverbs 1. 7)

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CONTENTS

		Page
CHAPTER 1	Historical Introduction	12
CHAPTER 2	Selection of Patients	31
CHAPTER 3	Results of Questionnaire	40
CHAPTER 4	Dietary Assessment	66
CHAPTER 5	Barium Enema Study	72
CHAPTER 6	Studies of Defaecation	89
CHAPTER 7	The Proctometrogram	125
CHAPTER 8	Colonic Motility Studies	140
CHAPTER 9	A Study of the Myenteric Plexus	159
CHAPTER 10	Gut Hormone Localisation in the Colon	172
CHAPTER 11	A Study of Gut Hormone Release	182
CHAPTER 12	A Study of Sex Hormones	201
CHAPTER 13	Psychiatric Investigation	218
CHAPTER 14	Results of Treatment	231
CHAPTER 15	Final Discussion	262
REFERENCES		270
APPENDICES		291

ILLUSTRATIONS

Fig		Page
2a	Polythene pellets for transit studies.	39
2b	Bowel transit study.	39
5a	Barium enema: Normal lateral pelvic view.	85
5b	Barium enema: Pelvic view - Idiopathic megacolon.	85
5c	Barium enema: Pelvic view - Slow transit constipation.	86
5d	Barium enema: Abdominal view - Slow transit constipation.	86
5e	Barium enema: Pelvic view showing rectal bend - Idiopathic megacolon.	87
5f	Gastrograffin enema - Idiopathic megacolon.	87
5g	Bowel widths at the pelvic brim in normal and constipated subjects.	88
6a	Ano-rectal distension reflex - method.	97
6b	Normal ano-rectal distension reflex.	97
6c	Balloon used for defaecation studies.	99
6d	Position adopted for balloon expulsion studies.	99
6e	Weight needed to expel a balloon from the rectum in constipated patients and controls.	101
6f	Normal electromyography.	101
6g	Electromyography in constipated patient 1.	107
6h	Electromyography in constipated patient 2.	107
6i	Electromyography on maximal rectal distension 1.	108
6j	Electromyography on maximal rectal distension 2.	108
6k	Balloon used for defaecating balloon proctogram.	114
6l	Radioluscent lavatory seat.	114
6m	Measurement of ano-rectal angle.	115
6n	Balloon proctogram: Normal subject at rest.	115

6o	Balloon proctogram: Normal subject during defaecation.	116
6p	Balloon proctogram: Slow transit constipation 1.	117
6q	Balloon proctogram: Slow transit constipation 2.	117
6r	Balloon proctogram: Patient with faecal incontinence before and after post anal repair.	118
6s	Trace of proctograms before and after post anal repair.	118
6t	Trace of resting and straining proctograms in rectal prolapse.	119
6u	Trace of resting and straining proctograms in the descending perineum syndrome.	119
7a	Bench tests on balloons.	132
7b	Proctometrogram apparatus.	132
7c	Normal proctometrogram.	133
7d	Proctometrogram: Slow transit constipation.	133
7e	Proctometrogram: Idiopathic megacolon.	134
7f	Proctometrogram: Irritable bowel syndrome.	134
7g	Proctometrogram: Repeated study.	135
7h	Proctometrogram: Mean results in controls and 3 groups of constipated patients.	135
8a	Fasting colonic activity for all patients studied.	146
8b	Effect of age on colonic activity.	146
8c	Normal colonic motility.	147
8d	Colonic motility in irritable bowel syndrome with constipation.	147
8e	Colonic motility in slow transit constipation.	148
8f	Colonic motility in irritable bowel syndrome with diarrhoea.	148
8g	Normal response to bisacodyl.	149
8h	Response to bisacodyl in slow transit constipation 1.	150

8i	Response to bisacodyl in slow transit constipation 2.	150
8j	Response to bisacodyl in slow transit constipation (motility indices).	151
9a	Colectomy specimen 1.	164
9b	Colectomy specimen 2.	164
9c	Normal myenteric plexus.	165
9d	Myenteric plexus in patients with slow transit constipation.	165
11a	Response of circulating Pancreatic polypeptide, Motilin and Gastrin to an oral water load in patients with constipation or diarrhoea.	192
11b	Response of circulating Pancreatic polypeptide to an oral water load in patients with megacolon or irritable bowel syndrome and constipation.	193
11c	Response of circulatin Gastrin to an oral water load in patients with megacolon or irritable bowel syndrome and constipation.	193
11d	Pilot study: Neurotensin levels in slow transit constipation.	194
11e	Pilot study: Vasoactive polypeptide levels in patients with slow transit constipation.	194
12a	Prolactin levels in patients with constipation.	207
12b	Prolactin cycle.	207
12c	Growth hormone levels in patients with constipation.	208
12d	Testosterone levels in patients with constipation.	208
12e	Oestradiol and 24 hour urinary oestrogen levels in patients with constipation.	209
12f	Met-enkephalin levels in patients with slow transit constipation.	210
12g	B-endorphin levels in patients with constipation.	211
13a	Crown-Crisp index scores 1.	224
13b	Crown-Crisp index scores 2.	224
13c	HDHQ: Psychiatric patient scores.	225
13d	HDHQ: Results for patients with constipation or Crohn's disease 1.	226

13e	HDHQ: Results for patients with constipation or Crohn's disease 2.	227
14a	Rectal impaction after colectomy.	241
14b	Abdominal Ptosis: Before colectomy	242
14c	Abdominal ptosis: After colectomy.	243
14d	Abdominal ptosis: Elecromyography.	244
14e	Gastrograffin enema after caeco-rectal anastomosis.	245

TABLES

		Page
2a	Primary causes of constipation.	33
2b	Patients referred for investigation of chronic constipation 1969-1982.	35
3a	Ages of patients presenting with slow transit constipation.	44
4a	Diet study: Recording of food quantities.	68
4b	Results of diet study.	69
5a	Colonic and rectal widths in control subjects and constipated patients.	80
6a	Anal canal pressures in slow transit constipation.	103
6b	Results of electromyography.	106
7a	Rectal sensation results	136
9a	Comparison between motilty studies before, and neuropathological findings after, colectomy.	167
9b	Differences between neuropathological findings in cathartic colon and slow transit constipation.	168
10a	Results of immunocytochemical staining in colectomy specimens from constipated patients.	179
11a	Motilin levels after an oral stimulus in patients with constipation or diarrhoea.	189

11b	Pancreatic polypeptide levels after an oral stimulus in constipation or diarrhoea.	190
11c	Gastrin levels after an oral stimulus in patients with constipation or diarrhoea.	191
13a	Quality of life questionnaire results.	228
14a	Patients undergoing colectomy for constipation from 1969-1982.	232
14b	Results of sub-total colectomy for slow transit constipation.	236
14c	Results of partial colectomy for slow transit constipation.	238
14d	Patients assessment of the results of colectomy.	239
14e	Conversion of Gamma linoleic acid to prostaglandins E1 and E2.	254

APPENDICES

		Page
1	Resected colons	291
2	Silver staining method	294
3	Tissue peptide biopsy study	296
4	Antisera for histochemical studies	299
5	Naloxone study	300
6	Psychiatric questionnaires	303
7	Prostaglandin E2 study	311

CHAPTER 1

HISTORICAL INTRODUCTION

Early records

Constipation is sometimes described as a disease of modern civilisation, and attributed to dietary changes. Support for this idea comes from a study of some primitive races. For example, the eskimos had no word in their language for the condition which was apparently unknown to them. This may be explained however by the recent discovery that a food they prepare from moss found in dead reindeer stomachs has laxative properties. Study of other civilisations has shown records of constipation and its medical treatment going back about 6000 years.

Clay tablets from Mesopotamia (c.4000 BC) record prescriptions for enemas using colocynth and liquorice, and similar prescriptions have been found on Assyrian and Babylonian tablets. The Ebers papyrus (c.1500 BC) lists prescriptions for enemas and recommends dates, olive oil and castor oil to assist bowel movements. The Chester-Beatty papyrus VI in the British museum (c.1400 BC) is devoted almost entirely to ano-rectal disorders. It lists 41 prescriptions including figs, myrrh, fat, honey, milk and beer for rectal administration (Banov 1965). Early Chinese records describe herbs with laxative properties and mention the use of rhubarb. Arabian records refer to the use of purgatives and they were probably the first to use senna.

In later writings laxative and enema use was

distorted by religious practices. This may perhaps help to explain the widespread belief in the middle ages that faeces were somehow evil or harmful - a subconscious element of which seems to have percolated through to the beginning of this century. Hindu religious writings of about 800 BC advised purgation at regular intervals and Hippocrates (c.460-380 BC) gave prescriptions for cathartics suggesting that if the bowels were not moved a man became posessed by impurities which defiled him in the eyes of the gods (Talalay 1964).

Herodotus (484-425 BC) in his histories reported the ritual purgation of the Egyptians for 3 days each month. He recorded their belief that all illness came from the food they had eaten. The use of enemas by the Egyptians may have led to the craze for their use in Europe hundreds of years later. The ibis was sacred to the Egyptians - possibly for the eminently practical reason that it destroyed poisonous snakes and insects on the river banks. The Roman writer Pliny (23-79 AD), who was a poor naturalist, thought that the ibis was injecting itself with water when collecting oil from a preen gland near the anus. He suggested that the Egyptians had copied the bird and his writings were disseminated widely throughout Europe before and after the reformation. He was often quoted in French literature as a justification for the medicinal use of the enema.

Other Roman and Greek records show that laxatives and enemas were widely used. The Romans were the first to introduce abdominal massage as a treatment for constipation and developed an effective clyster syringe. Galen writing in

the second century gave a list of prescriptions for use in enemas. They also encouraged the use of spas, the waters of which had a mild laxative action. Following the collapse of the Roman empire records are very scanty. Paulus Aegineta (c.600 AD) advised the use of sour milk to avoid constipation. The Egyptian Judaeus writing in the 9th century, gave the first surviving prescription for senna.

Enemas

The Arab physician Avicenna described an enema syringe in the 10th century and the English surgeon Arderne (1306-90) wrote an essay on their use. De Graaf published a major work in 1668 (De Clysteribus) in which he resurrected the fable of the ibis and first suggested the use of saline enemas. Ambrose Pare, the great French surgeon, was partially responsible for spreading the craze for enemas. In 17th century France they achieved their greatest popularity and Louis XIII is reported to have had 213 lavages in one year. His successor Louis XIV had over 2000 during his reign and even received foreign ambassadors whilst seated on the commode. He gave enemas to his pet dogs and the female attendants at court were required to have up to 3 enemas daily. Apart from producing general well being, this was to improve their complexions. Royal enema fluids were frequently coloured or perfumed and the enema or clyster stool became a feature of every fashionable home.

The Liverpool surgeon Higginson invented his syringe in 1852 encouraging wider use of the enema in England. Colonic irrigation also became popular in the 19th

century, the fashion again started by the French in the old Roman baths at Plombieres. Further modifications allowed the patients to receive irrigation whilst in the bath or sitting upright in a chair and clinics sprang up in all the spa towns of Europe.

Purgatives

In the 17th and 18th centuries a wider range of purgatives became available. Senna was introduced to western Europe where it was mixed with sweets because of its bitter taste. Popular mixtures were Co. Mix of senna (Black draught) and Co. powder of rhubarb (Gregory's powder). It was, and still is, a constituent of syrup of figs. Castor oil which was known to the Greeks and Romans, was forgotten until the late 18th century when it was rediscovered in the West Indies. Cascara (dried bark of buckthorn) was used by North American indians for hundreds of years before its introduction to Europe. Aloes had been used by Arabs, Greeks and Romans and may have been used in England as early as the 10th century. Popular in herbal remedies, it is still a constituent of 18 such preparations today.

Mineral salts were ingested unknowingly for centuries in mild doses at hot springs. The aperient properties of mineral water were first recognised in Hungary and Germany in the 14th century. Paracelcus recommended Potassium sulphate in the 16th century; Glauber, Sodium sulphate in 1658; and Grew, Magnesium sulphate (Epsom salts) in 1695. The last of these became especially popular in Victorian England.

Mercury, despite its toxicity, was used by Hippocrates and became a popular laxative in the 19th century as calomel pills. These seem to have been available until recently in America (Wands et al. 1974). Another surprising drug was strychnine, given in combination with vegetable laxatives. The purgative action of Phenolpthalein was discovered in 1900 by accident when it was being tested for addition to wines. Liquid paraffin was introduced in 1908 by Lane and is still in use as a constituent of Milpar. Frangula bark, with properties similar to cascara, has been reintroduced as a constituent of Normacol. Many other traditional remedies are now obsolete but occasionally are used in herbal medicines. They include jalap, colocynth, podophyllum, croton oil, sulphur, cassia, euonymus, ipomoea, kaladona and tamarind.

Intestinal autointoxication

To the Frenchman Bouchard (1887) goes the dubious distinction of being the first to coin the word autointoxication, though Von Haller in 1765 expressed the belief that in constipation foul water is absorbed from the faeces and "filling the blood with rancid parts, produces fever, haemorrhages, consumption and insanity". It is difficult to discern exactly how this theory arose, but similar views were widespread in America and Europe around the turn of the century. Two books seem to have had a strong impact on contemporary thought.

The first by Elie Metchnikoff, the Russian bacteriologist and Nobel prizewinner, was called "The nature

of man" (1903). In this he suggested that the colon was a vestigial organ that could perhaps be dispensed with. Later he suggested that toxins absorbed from the colon might be responsible for the ageing process and advocated the use of sour milk to alter intestinal flora (Metchnikoff 1908).

The second influential book was L'Auto-intoxication Intestinale by Combe (1907). Largely incomprehensible to the modern reader it purports to give biochemical and bacteriological evidence for the disorder suggesting treatment with diet, purges and lavage. An example of the tests used was a disparity in the ratio of Gram +ve baccilli (known as the Bulgaria group) to other faecal flora giving the so called "Bulgar index" (Bryce 1920). Another test for intoxication was measurement of urinary indicans, until recently used for diagnosis of bacterial overgrowth in the small bowel.

Early surgical treatment of constipation

Following the devopment of safer abdominal surgery it became possible to carry out the dream of Metchnikoff and to remove the "vestigial" colon. One of the strongest advocates of surgery for constipation was the British surgeon Arbuthnot Lane. In the years after meeting Metchnikoff he operated on a large number of patients with chronic constipation, initially by ileo-simoidostomy, but later performing total colectomy (Lane 1908, 1913, Chapple 1911). His early reports are of particular interest with regard to the present work as he described a condition of chronic intestinal stasis in young women. Associated

symptoms included peripheral cyanosis, abdominal ptosis, gynaecological symptoms with amenorrhoea and loss of the secondary sexual characteristics. He also claimed a high incidence of ovarian cysts and breast disease (Lane 1909, 1912). Some patients he treated medically, advocating prostatic extract and later liquid paraffin.

His enthusiasm became excessive towards the end of his career, and his belief that autointoxication caused most of the ills of mankind led to a diminution in his reputation as a surgeon. Later he performed colectomy for Still's disease, tuberculosis and thyrotoxicosis and this has diverted attention from the undoubted success of his earlier surgery. He had a profound influence on his contemporaries with surgeons in Paris, South America and the United States as well as others in Britain all reporting colectomy as a treatment for constipation (Barling 1914, Mothersole 1914, Draper 1922, Flint 1922, Pauchet 1922, Lockhart-Mummery 1922, Coffey 1923).

Dietary treatment of constipation

Gallant (1912) was the first doctor to suggest that a daily dose of bran would prevent constipation. Von Noorden (1916) was later quoted by Hurst as reporting that constipation was very uncommon in the German army during the first world war, because of the coarse bread they ate. Kellog in the United States disagreed with the ideas of Lane and Metchnikoff about the need for colectomy, and suggested that autointoxication was entirely the result of a poor diet. He set up a special clinic where in addition to

dietary therapy patients could enjoy treatment with massage, hydrotherapy, electricity and vibration. He also conducted a survey amongst missionary doctors to discover the bowel habits of primitive peoples. Almost without exception the missionaries had noticed that a largely vegetable diet resulted in frequent soft stools. The laxative action of fruits and sour milk was appreciated by many, and some reported that the natives used home made enemas. The squatting position for defaecation was also noted. (Kellog 1923). From this Kellog suggested that the "normal" bowel frequency should be three times daily and he advocated laxative foods, regular bran or agar-agar, alteration of colonic bacteria with sour milk and adoption of the squatting position for defaecation.

Similar conclusions had been reached by McCarrison (1921) from a study of different diets in India. In addition he noticed the importance of vitamins, and suggested that the vitamin B in grain might be partly responsible for its laxative action. His work had a profound influence on thinking in Britain so that Arbuthnot Lane changed his views and advocated a change in diet rather than surgery (Lane 1932). Cowgill and Anderson were the first to study the laxative action of bran and showed that men on a low roughage diet became constipated. They then went on to demonstrate a direct relationship between the amount of fibre in the diet and stool frequency and also that constipated patients could be treated successfully with bran (Cowgill et al. 1932, 1933). Their views were later endorsed by Dimock (1936). Despite these studies and the efforts of

Lane and McCarrison in founding the New Health Society to inform the public about the importance of diet, it was another 30 years before the message was widely appreciated.

Early Monographs on Constipation

Hamilton in 1805 wrote a treatise on "The utility of purgative medicines" in which he claimed a number of different symptoms were due to constipation. One chapter was devoted to chlorosis in young girls which he thought was caused by constipation and he advocated purgation for this and a variety of other disorders.

The first book on constipation is that of Reece (1826). He points out the dangers of over purgation and gives a recipe for wholemeal bread. Particular mention is made of constipation in the sedentary, elderly, hysterical or nervous types. It was also noted in pregnacy, in epileptics, and secondary to anal problems. One chapter is devoted to constipation associated with amenorrhoea in young women and he notes that "it is not uncommon for girls in boarding schools to open their bowels once a week". O'Beirne (1833) in a discussion of the mechanism of defaecation, suggested that obstruction of the bowel at the recto-sigmoid junction was a common cause of constipation. Burne (1840) suggested that habitual constipation was largely due to sedentary habits and "inattention to the calls of nature". He suggested constipation might be common in women because they were reluctant to retire to the closet out of "a misplaced sense of delicacy".

Birch (1868) attributed constipation to abuse of

laxatives, indolence, failure to answer the call to stool, neuraesthenia, intestinal atony or obstruction. Treatments suggested were mainly laxatives or enemata as well as exercise. Herschell in 1898 published a small book in which he classified the causes of constipation as: defective peristalsis, increased resistance (including a deficiency of cellulose in the diet), neurological disease, abdominal ptosis and anal spasm. He stated that bran, oats, spinach and other vegetables had a laxative action.

Blake (1900) quoted Fleiner (1893) as dividing constipation into spastic and atonic types. Atonic constipation was held to be common in the young and very old, wheras spastic constipation was found in hypochondriacs, neurasthenics and women with uterine disease. In the latter cases, small scybala accompanied by catarrh were a feature. He proposed that the sigmoid flexure acted as a dam, holding back the stool propelled foreward by peristalsis. He also gave the first description of the "ball-valve" rectum and recorded constipation as common in young girls in boarding school or factories.

Improvements in abdominal surgery and the introduction of radiology led to a number of publications over the next few years. The most important was Constipation and allied intestinal disorders by Hertz, later Hurst, which remained a standard work of reference for 50 years. In America Gant (1909) and Illoway (1912) published large textbooks both of which summarized previous work and outlined treatment by hydrotherapy, massage, galvanism or diet in great detail. Lane (1909) published a summary of his

ideas on the aetiology of chronic constipation and suggested that adoption of the erect posture had resulted in a number of mesenteric bands to support the bowel. He thought ptosis of the bowel caused kinking across the bands with obstruction of faecal flow. These ideas were reproduced by others who described eponymous bands all along the gut. The best summary of contemporary thought and surgical practice on both sides of the atlantic was given by Coffey in his book "Gastroenteroptosis" (1923).

Publications by Arthur Hurst

The second edition of Hurst's monograph (1919) is an important milestone in the history of the study of constipation. Before him there was much fancy, some empiricism and little logic. Afterwards all ideas had to be matched against his inspired research and common sense. The book contains details of his published papers on the sensation of the gut, anal achalasia and megacolon, with radiographs from his studies of gut motility (Hurst et al. 1907, 1911, 1934). In addition he gave an excellent review of previous work. He elaborated on the classification of causes proposed by Herschell and gave a new group of causes which he placed under the heading "dyschezia" (or difficulty in defaecation). Towards the end of his life he seems to have changed his mind, suggesting that dyschezia is an important factor in all cases of constipation (Hurst 1943). He recognised cases of short segment Hirschsprung's disease as being due to a failure of anal relaxation and coined the term "anal achalasia". It is astonishing that although Hurst

postulated that Hirschsprung's disease might be caused by a deficiency of the intramural plexus, similar to that described in achalasia of the cardia by Rake, it was another 20 years before this was confirmed.

The major contribution by Hurst was his studies of gut transit. Though the bismuth mixture he used was unphysiological, it did show that transit to the colon was rapid. Residue was then seen to pass slowly along the colon and to be evacuated 1 to 3 days later. He was able to disprove the then current theories about intestinal stasis and to show that "kinks" in the small intestine did not impede movement of bowel contents. In his review of previous work he seemed to accept uncritically some bizarre ideas such as the theory that ptosis of the kidney could cause constipation. His spastic constipation may have included cases that we would now regard as having an irritable colon, but both he and his contemporaries suffered from their inability to distinguish this from ulcerative colitis.

Le Dolichocolon

In his monograph Hurst clearly differentiated megacolon from an elongated colon or dolichocolon. He stated that elongation of the bowel was an almost universal accompaniment of megacolon, but those cases where the colon was congenitally elongated but of normal width were quite different. He also noted that an elongated sigmoid colon alone was not associated with constipation.

In 1931 a French monograph devoted entirely to "Le Dolichocolon" was published (Chiray et al.). However they

did not make the same distinction as Hurst and regarded all cases of elongated colon as the same. The result is rather confused to the modern reader, and no clear clinical picture emerges. Case histories are given which suggest some of the patients would have been regarded as having idiopathic megacolon or megarectum today. Some others probably had Hirschsprung's disease, but others had an elongated colon of normal diameter. The association of an elongated colon with constipation had been earlier confirmed by radiological study of normal subjects (Kantor 1924). Much later it was postulated that a long colon caused constipation (Brummer et al. 1962), though in all studies it was noted that asymptomatic subjects could also have a long colon.

Definition of Hirschsprung's disease

Probably first described by Parry in 1825, the clinical picture of severe constipation and megacolon in children was given by Hirschsprung in 1888. No further progress was made and there was considerable confusion between this condition and idiopathic megacolon until the neuropathology was defined. It was shown that the narrowed distal part of bowel is aganglionic and therefore unable to relax. The dilated part is normally innervated, but enlarges with considerable muscle hypertrophy in an attempt to overcome the obstruction (Swenson et al. 1948, Bodian et al. 1949). Later the original observations by Gowers (1877) and Denny-Brown et al. (1935) enabled the ano-rectal distension reflex to be used as a diagnostic test. Because the intramural plexus is deficient in Hirschsprung's disease no

reflex can be elicited (Lawson et al. 1967). Cases can present in adult life and treatment is always surgical (Nixon 1964, Todd 1977).

Idiopathic megacolon

Definition of the neuropathology of Hirschsprung's disease still left a group of patients with constipation and megacolon without a diagnosis. A primary cause for megacolon was discovered in some, such as Chagas' disease, ano-rectal malformation, endocrine disorder or drug induced nerve damage. Where no cause was found the condition was referred to as "idiopathic" megacolon (Todd 1961). Some authors attempted to subdivide these patients depending on the site of maximum distension (Kune 1966). This may have theraputic implications but there is no evidence that the aetiology differs. Those with sigmoid dilatation alone are cured by sigmoid colectomy and it is possible that this is a separate disorder (Gardiner 1953, Ryan 1982).

Tobon and Shuster (1974) in a review of patients with idiopathic megacolon presenting to the Johns Hopkins Hospital found that the majority developed symptoms in the first year of life, and almost all before the age of 10. Encopresis and personality disorders were common, and a number of their patients were mentally subnormal. Anal sphincter tone was reduced and faecal soiling common, features which helped to differentiate this condition clinically fron Hirschsprung's disease. Lane and Todd (1977) in a review of 42 adults presenting with the same condition found that half had presented to their doctor in the first

decade. Some of their patients had an abnormal ano-rectal reflex, with absence of the normal progressive fall in anal canal pressure on stepwise distension of the rectum. This was regarded as evidence of a disorder of the internal anal sphincter (Lane 1979). Porter (1961) had shown that complete inhibition of the external sphincter could not be obtained in patients with megacolon until very high volumes of air had been instilled into the rectum. It is not clear whether these abnormalities are primary or secondary events. Investigation of patients with idiopathic megacolon has shown that colonic pressure wave activity is reduced (Connell 1961b), but this almost certainly reflects the difficulty of recording pressure in a dilated bowel.

Children with constipation and megarectum can be successfully treated by rectal disimpaction and laxatives, though some may also need anal stretch or internal sphincterotomy. Psychological factors seem to be important in younger patients (Clayden 1976). It is not known whether adults with the same condition are some of these children who were inadequately treated or whether they have a separate disorder.

Constipation without megacolon

Classification of the causes of constipation has been greatly modified since the work of Hurst (Hinton 1972). Endocrine, metabolic, mechanical and neurological causes are recognised as well as the effects of drugs, though the pathophysiology is not always clear. Three main groups of patients without megacolon remain in whom no anatomical or

metabolic disturbance can be found. The first disorder, known as simple constipation, is caused by a faulty diet. Enviromental factors and lack of exercise may contribute (Avery-Jones 1972). Pioneer studies such as those of Dimock (1936) have been "rediscovered". Clear proof now exists of the reduction in gut transit time resulting from a increase in dietary fibre (Burkitt et al. 1972) and that simple constipation can thus be relieved (Graham et al. 1982).

Patients whose symptoms are not improved by an increase in dietary fibre have been regarded as having a functional disorder of colonic motility. Two groups have been distinguished by studying gut transit rate using radiopaque polythene pellets. Some have a normal whole gut transit time whilst in others it is delayed (Hinton et al. 1968,1969). The first group were included in the large number of patients suffering from the irritable bowel syndrome whilst the others were described as having idiopathic slow transit constipation.

Idiopathic constipation

This term has been used to describe cases of severe constipation in the presence of a normal sized colon and when all primary causes have been exluded. However many researchers see no difference between this disorder and idiopathic megacolon, and the literature is consequantly confused. In one study (Devroede et al. 1973) a group of 9 patients, 6 of whom had a megabowel, were shown to have increased absorption of water and sodium. This was however probably directly related to slow colonic transit. Later the

same authors defined the rate of transit of polythene markers in a normal population on a high residue diet (Martelli et al. 1978a). Using this data they next assessed the effect of ano-rectal myectomy on bowel frequency and transit rate in patients with constipation (Martelli et al. 1978b). Again patients with megacolon, 14 of whom had Hirschsprung's disease, were included as well as 12 patients whose reported bowel frequency was normal. A high success rate was claimed, but it is difficult to interpret the results. Those with short segment Hirschsprung's disease might have been expected to do well as this operation had previously been successful in this group (Bentley 1966). The reason why patients with normal bowel frequency underwent operation is not made clear, and those with slow "colonic transit" apparently did not respond.

Ano-rectal studies in idiopathic constipation

Apart from studies of megacolon there have been few investigations of anal function in constipation. Martelli et al. (1978b) studied only 13 of the 62 patients on whom they performed ano-rectal myectomy. They described 4 different abnormalities but did not say whether these patients had aganglionosis or not. Lane (1979) studied 9 patients with severe constipation, but without megacolon. Transit studies were not performed, and therefore some may not have had idiopathic slow transit constipation. He claimed that rectal sensation was normal in this group, and found that 2 of the 9 patients had a disturbance of progressive internal sphincter inhibition similar to that he recorded in patients

with idiopathic megacolon. Baldi et al. (1982), measuring delayed transit by means of a radioisotope capsule, studied 6 constipated patients and compared them with 7 others in whom transit was normal and controls. They found that the recto-anal inhibitory reflex in both constipated groups was normal. They also claimed rectal sensation was abnormal in the group with delayed transit, but some of their patients may have had a megacolon which could account for this finding.

Colonic motility in idiopathic constipation

No studies have previously been reported in patients with idiopathic slow transit constipation. The published work refers to patients with a complaint of constipation, many of whom were regarded as having a form of the irritable bowel syndrome. Connell (1962) reported paradoxical motility of the sigmoid colon in patients complaining of constipation or diarrhoea. Those with constipation having excess segmenting activity. His findings were confirmed by others but have recently been questioned. Meunier et al. (1979) used a prolonged fast before making pressure recordings and found no difference between constipated patients and controls at rest. After a meal there was a wide variation in response in the constipated group, some showing less and some more activity than normals. Though they stated that their patients had no evidence of laxative abuse on barium enema, it is not made clear whether any had megabowel. No transit studies were done, and no trial of a high residue diet given to exclude

patients with simple constipation.

Electromyography of the colon has been introduced as a research procedure, but the significance of the recorded activity and its relationship to colonic movement is still not clear. One study has suggested that there is an increase in the number of short bursts of electrical activity in patients complaining of constipation (Bueno et al. 1980). A corresponding decrease was shown in those with diarrhoea, findings which correlate with the original pressure studies by Connell (1962). Bowel transit studies were not done and these patients may have suffered from an irritable bowel.

CHAPTER 2

SELECTION OF PATIENTS

Introduction

The purpose of this thesis was to study patients who had been diagnosed as suffering from idiopathic slow transit constipation. The only previous description of this disorder was given in the monograph by Avery-Jones and Godding (1972). They claimed that this was the commonest motility disorder giving rise to constipation. The cause was alleged to be a failure of normal colonic propulsion of faeces, although no evidence was given for this apart from the observed delay in colonic transit measured by using polythene pellets. Motility studies were reported as showing localised increase in segmenting pressures though this data was never published. The suggested treatment was mild doses of stimulant laxatives such as senna.

In their book a clear distinction was drawn between such patients and those with idiopathic megacolon, though the size at which the bowel was regarded as being a megacolon was not defined. Patients with the irritable bowel syndrome and constipation were also regarded as having a separate disorder. The distinction given in the latter case was partly clinical, as severe pain was said to be a marked feature in the irritable bowel syndrome. Transit studies provided an objective method of separating this group as such studies were said to be normal in patients with an irritable bowel.

Definition of Slow Transit Constipation

Constipation is a symptom that may mean different things to the patient and physician. Some patients use the term to describe difficulty in evacuation of stool that may be small or hard. In others the complaint may be of infrequent defaecation, a sensation of incomplete evacuation or just abdominal fulness and "wind". A definition of this complaint can therefore be based on the patients complaint (i.e. straining at stool), or attempt an objective measurement such as stool frequency.

A purely clinical definition is impossible for slow transit constipation since such a definition must involve measurement of whole gut transit rate. For the purposes of the present study in which a retrospective analysis of the patients notes was made, clinical details were inadequate. The patients reported bowel frequency was in any case likely to be unreliable (Manning et al. 1976).

There was previously no strict definition of megacolon so that cases with an enlarged bowel could be excuded and not all the radiographs had been preserved. For the purposes of the present study therefore the radiologists report at the time of initial presentation was accepted. If the colon had been reported as unusually wide or described as a megacolon the patient was excluded from the follow up study. All other cases in whom primary causes of constipation had been excluded and in whom the gut transit time was prolonged were regarded as suffering from idiopathic slow transit constipation. The transit study gave

objective evidence to support the patients claim of constipation but by itself was not diagnostic, other primary causes having first to be ruled out. A modified classification of the primary causes of constipation as defined by Avery-Jones and Godding (1972) is given in Table 2a to indicate the disorders thus excluded.

Table 2a

PRIMARY CAUSES OF CONSTIPATION

SIMPLE
- Low food intake
- Lack of adequate dietary fibre
- Ignoring call to stool etc.

ANO-RECTAL DISORDERS
- Painful anal lesion (eg Fissure)
- Anal stricture
- Congenital disorder (eg Ectopic anus)
- Rectal prolapse
- Descending perineum syndrome

COLONIC DISORDERS
- Carcinoma
- Stricture
- Diverticular disease
- Recurrant volvulus
- Myopathy (eg Systemic sclerosis)

NEUROLOGICAL DISORDERS
- Hirschsprung's disease
- Chagas' disease
- Cathartic colon
- Autonomic neuropathy
- Spinal cord lesion
- Damage to sacral outflow
- Multiple sclerosis
- Cerebrovascular accident

METABOLOIC OR ENDOCRINE DISORDER
- Diabetes mellitus
- Hypothyroidism
- Hypopituitarism
- Hypercalcaemia
- Porphyria
- Heavy metal poisoning (eg Lead)
- Phaeochromocytoma
- Amyloidosis

Dehydration
Obstetric bowel

PSYCHIATRIC DISORDER
Anorexia nervosa
Denied bowel action
Chronic psychosis
Depression
Purgative addiction

SECONDARY TO DRUG INGESTION
Ganglion blockers
Iron
Opiate analgesics
Anticonvulsants
Tricyclic antidepressants
MAO Inhibitors
Phenothiazines
Anticholinergics
Muscle relaxants
Antacids
Diuretics
Vinca alkaloids

How common is Slow transit constipation?

Because of the unusual referral pattern at St Mark's Hospital (which is a specialist postgraduate teaching centre) an unfair picture is given of the frequency of many disorders. Examination of the hospital records was hampered by the fact that there was no central register of referrals. Inpatients were classified separately, and many patients were admitted for investigation directly without an outpatient visit. The records of the outpatient department could be examined and these showed 267 patients referred by another specialist or family doctor for the investigation of "constipation" alone from 1969-1979. Unfortunately this excluded those in whom the referring doctor had already made a diagnosis such as irritable bowel or Hirschsprung's disease. Table 2b shows the final diagnosis reached in the 267 patients.

Table 2b

FINAL DIAGNOSIS IN PATIENTS REFERRED FOR INVESTIGATION OF CONSTIPATION (St Mark's Hospital 1969-1979)

Simple/Dietary	126
Ano-rectal disorder	41
Irritable colon	26
Slow transit constipation	26
Senile/Rectal impaction	18
Idiopathic megabowel	16
Primary medical disorder	11
Colonic disorder	3

These results suggested that cases of slow transit constipation provided only about 10% of those referred for specialist investigation of constipation. The relative frequency compared to idiopathic megabowel and irritable colon cannot be assessed as not all these cases were included in the outpatient records.

How common is constipation in the general population?

Connell et al. (1965) studied patients attending a general practitioner for other reasons and a group of normal subjects working in a sausage factory. They found the normal range of reported bowel frequency varied from 3 per day to 3 per week (mean ± 2 standard deviations). 0.7% of all the subjects opened their bowels twice weekly or less and all of these were women. If this study were representative of the

general population it would mean that there were 350,000 women in England and Wales with constipation defined in terms of reported bowel frequency. The majority of these would presumably respond to an increase in dietary fibre, but an unknown number of this group might have slow transit constipation.

A National Opinion Poll survey carried out in 1975 to investigate laxative use in Great Britain found that 11% of the population regarded themselves as constipated. 16% of the women and 6% of the men had used laxatives in the preceding 6 months and 27% of those had taken senna. The sucess of the pharmaceutical industry is thus illustrated by the fact that 1.4 million people in the country would have taken senna at some time in the preceeding 6 months if the sample studied were representative! Whether many of these would be regarded as constipated by any objective criteria is doubtful.

It is possible that much laxative use is cultural rather than theraputic. Reid (1956) found that 22% of girls and 13% of boys attending a primary school were being given laxatives at least weekly by their mothers. Half of these were being given anthracenes. The relevance of this observation to the present studies is that the children of that generation will now be in their early thirties and may belong to the group of adults who seek help or continue to take purgatives for "constipation".

Selection of patients for present studies.

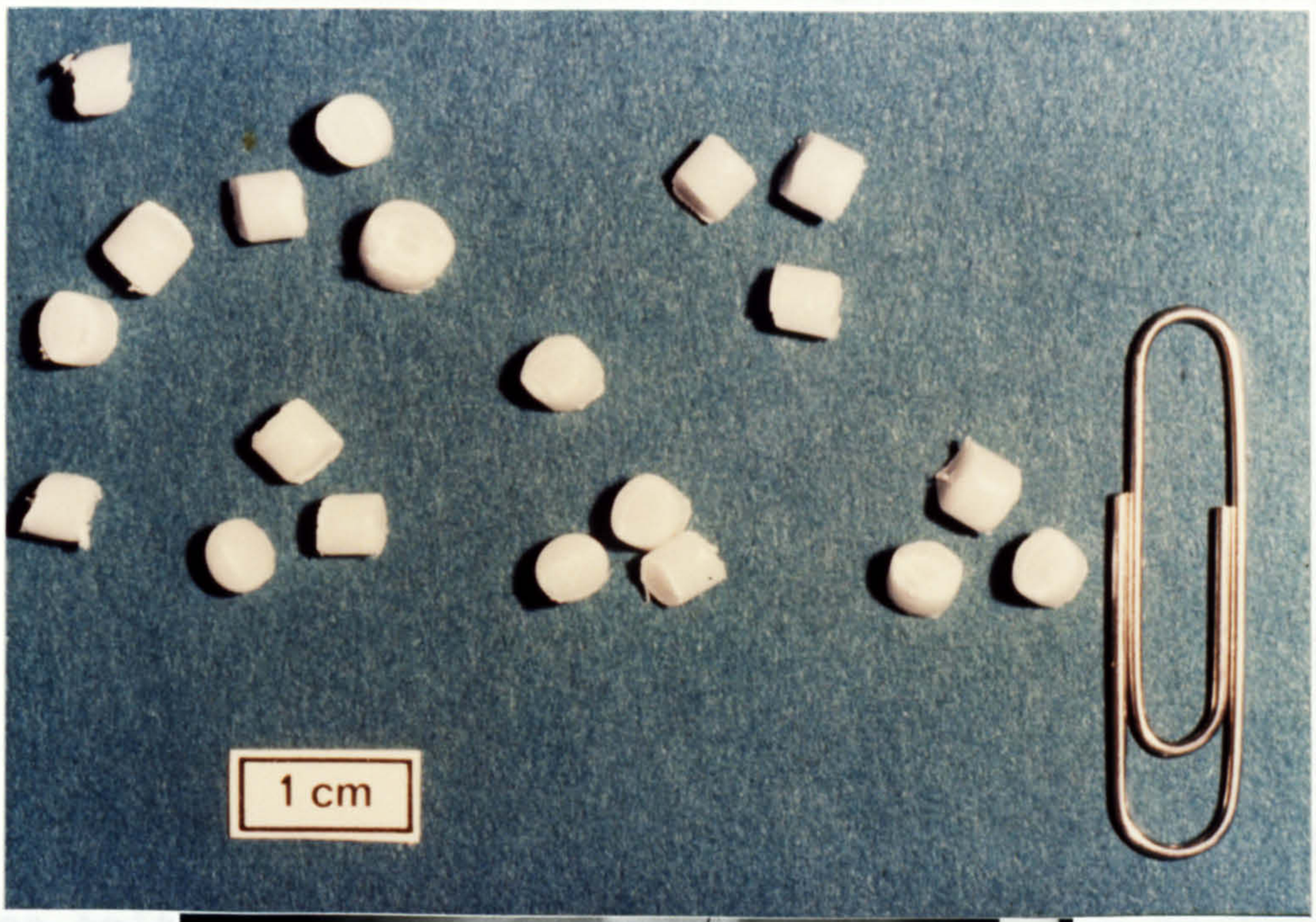
Measurement of transit time using polythene pellets had been introduced to clinical practice at St Mark's Hospital in 1969 and this therefore restricted the study to patients who had presented since that date. The normal range of whole gut transit time with this method was defined by Hinton et al. (1969) and the barium impregnated pellets used are illustrated in Figure 2a. Normal subjects pass 80% of such pellets administered by mouth within 5 days. Stools can be collected and X-rayed to identify the passage of markers, but it is easier to carry out a plain abdominal radiograph (Figure 2b).

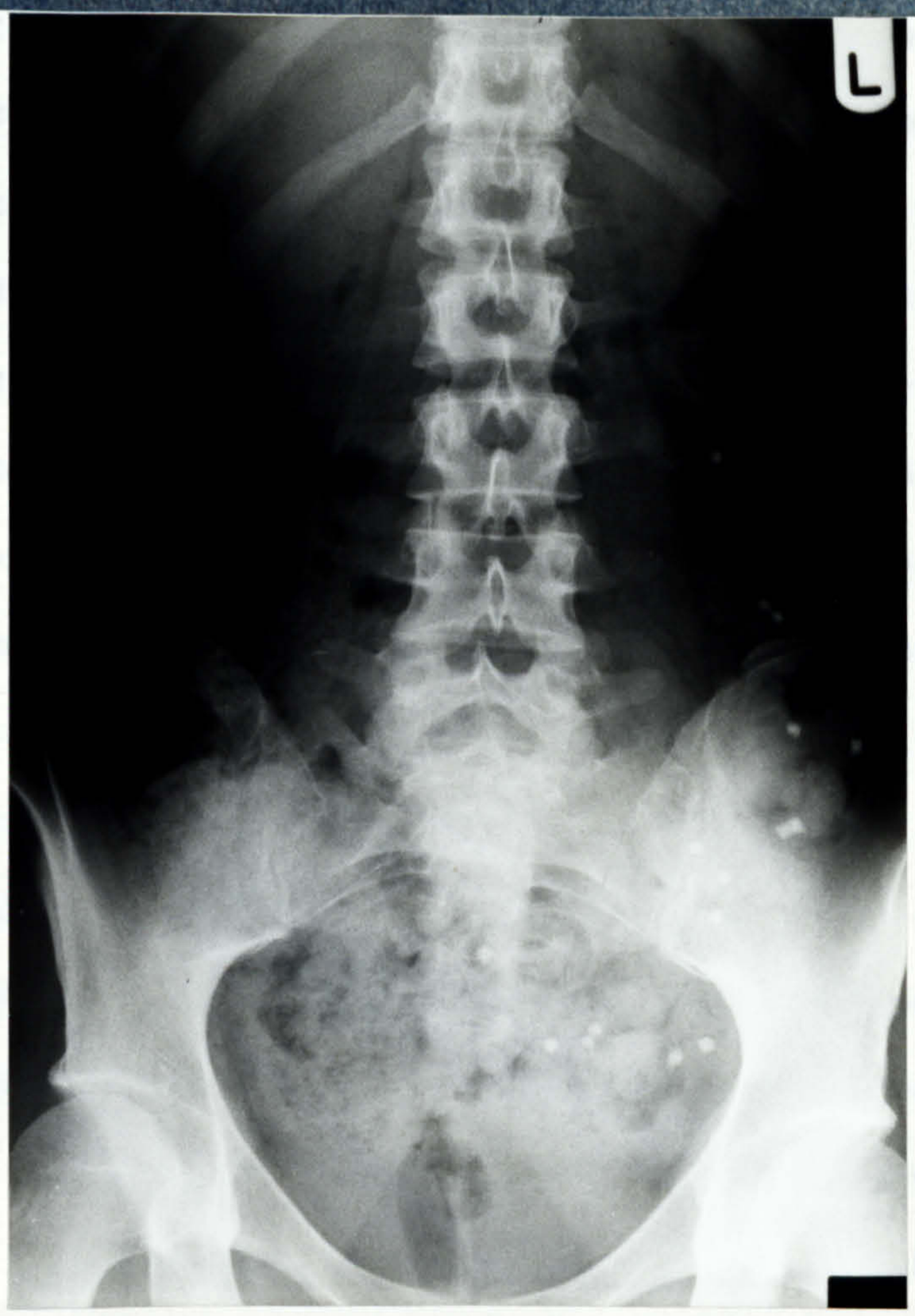
When all the case records of both in and outpatients at St Mark's Hospital since 1969 were examined, a total of 46 cases were found who had been diagnosed as suffering from idiopathic slow transit constipation. In all cases primary causes of constipation as outlined above had been excluded and the barium enemas were reported as "normal". To this number were added 39 patients who presented during the 3 years these studies were performed. The increased frequency of diagnosis since 1979 probably resulted from an increased referral rate rather than a rise in the incidence of the disorder.

An immediate observation was that all the patients were women. This had not been reported before though clinicians seemed aware that the problem was mainly seen in young women. Examination of the case notes showed that routine physical examination was always normal, and in particular no patient appeared to have had faecal mases felt

per abdomen nor to have evidence of faecal soiling. Records of previous medical and family history were scanty and as the histories had been taken by many different doctors no coherent picture emerged. Gynaecological problems seemed however to be common. An adequate clinical description of the disorder could not be obtained fron the case notes and it was therefore decided to perform a detailed survey of past and present patients by postal questionnaire. The results of this are presented in Chapters 3 and 4.

The remainder of the studies presented here were carried out on some of the patients who were diagnosed for the first time between 1979 and 1982. Most of the 39 patients in this group took part in one or more of the studies. No conscious attempt was made to discriminate between the patients, but those agreeing to help with the more difficult studies were self selecting. It is possible that they were therefore those with more severe symptoms who were more anxious to find a cure.





FIGURES 2a and 2b. BOWEL TRANSIT STUDY.
The first figure shows the barium impregnated polythene pellets used for the study. These have the same specific gravity as faeces and therefore mix well. Below is an example of a plain abdominal radiograph taken at the conclusion of the study showing that the markers have not been passed.

CHAPTER 3

RESULTS OF QUESTIONNAIRE

INTRODUCTION

In order to find out more about the natural history of slow transit constipation it was decided to send a detailed questionnaire to all the patients who had presented to St Mark's hospital since the bowel transit studies had been initiated in 1969. The selection of these patients has been discussed in Chapter 3. The majority were young women and questions about gynaecological problems were asked as initial clinical impressions had suggested an association. A matched control group was therefore necessary as there is no clear data on the incidence of such problems in the general population. In addition it was hoped to obtain information about bowel function in a group of normal women.

PATIENTS AND METHODS

a) Constipated group.

This group comprised all patients seen at St. Mark's hospital from 1969 - 1982 who had presented with a complaint of severe constipation for which no cause could be found. All had a barium enema of normal width. All had apparently failed to respond to an increase in dietary fibre and other primary causes of constipation such as hypothyroidism had been excluded. In all 46 cases were found from the records who were no longer attending. Ten of these could not be used: four did not reply to repeated letters,

four could not be traced, one had subsequently been found to have abdominal tuberculosis and one patient refused to help. Another 39 patients were still attending the outpatients department and were seen between 1980 and 1982. The total number of patients available for the study was therefore 75 of whom 64 completed a satisfactory questionnaire.

b) Control group

Age and sex matched controls were sought by approaching healthy women through a third party. The selection was random and each person approached was asked if she was suffering from any bowel disorder or attending a doctor for any bowel complaint (including piles). Any person answering "yes" was excluded from the study. No other questions were asked about bowel history or gynaecological problems and no help was given in completing the questionnaire. Of the 64 controls, 20 were recruited from residents of council flats in North-East London. A further 20 were approached via toddler groups and similar organisations in South-East London. 10 students from London and Edinburgh took part. Finally to complete the age matching 14 women of appropriate age were found from hospital staff, their friends or relatives.

c) Comparison of the groups

All 128 subjects in this study were women and all caucasoid. Age matching was done so that there were equal numbers in the decades 16-25, 26-35, 36-45, and 46-55. The mean age in the patient group was 30.4 ± 1.1 years and of

the control group 30.9 ± 1.1 years. Data was not available from the control population to match the groups for social class, occupation or marital status. The controls had taken part only on the understanding that their replies (some of which contained intimate personal details) would remain strictly anonymous.

d) Structure of the questionnaire.

The constipated subjects alone were asked 30 questions about the history of their disorder. These were designed to find the age of onset and the progression of symptoms with details of bowel frequency in childhood and adolescence. Patients were asked about laxative use, the effects of treatment and the effects of the illness on their home life and work.

All subjects were asked a further 70 questions which were designed to find details of their dietary habits, any attempts to lose weight and the effect of a high residue diet on bowel symptoms. Details of bodily functions were requested with particular reference to defaecation, urination and gynaecological problems. The effects of menstruation and pregnacy on bowel function were noted. Subjects were then asked for details of all previous medical problems including surgical proceedures and whether there was a family history of constipation or any other disorder. Finally an attempt was made to determine whether there was any abnormal illness behaviour in either group by asking for details of drug use and the frequency of consultations with the family doctor for minor ailments.

RESULTS

a) QUESTIONS PUT TO PATIENTS WITH SLOW TRANSIT CONSTIPATION.

An attempt was made to obtain some idea of the natural history of the disorder by asking the age and mode of onset of symptoms.

1) Mean age at first symptoms — 13.5 ± 1.1 years

2) Mean age at first medical consultation — 17.5 ± 1.0 years

3) Mean age at first hospital attendance — 23.3 ± 1.1 years

Table 3a gives a breakdown of the responses to the first 3 questions by 5 year groups which suggests there may in fact be a bimodal onset of the disorder.

4) First reported symptom:

Patients were asked if they could recall the first time they had realised something was wrong. This question was poorly understood and the majority recalled their first symptom as "constipation" without defining what was abnormal.

"Constipation"	50%
Abdominal pain	35%
Bloating	10%
Rectal bleeding	3%
Anal pain	1pt

5) Mode of onset:

Gradual	84%	
Sudden	16%	Hysterectomy in 4 pts. Appendicectomy 4 Fall (vulval injury) 1 Unknown 1

Table 3a

Age (years)	0-5	6-10	11-15	16-20	21-25	26-30	31-40	40-50
Onset of Symptoms	15	6	16	16	8	1	2	0
Consulted Doctor	6	4	11	22	14	5	2	0
Seen at Hospital	0	3	7	16	21	5	7	5

Ages at which the patients first experienced symptoms, attended their general practitioner or were referred to hospital for specialist advice. The figures in each column represent the number of patients responding for each 5 year period.

6) Childhood laxative use.

Patients were asked if they could recall being given laxatives before the age of 10 and responded as follows:

Yes	51%
No	49%

7) Reported bowel frequency.

The patients gave what they recalled as their "normal" bowel frequency in childhood and early adult life. The earlier values were thought likely to be unreliable but the mean values for the mid-teens and early twenties were as follows:

As a teenager	2.7 ± 0.1	weekly
After 20	0.9 ± 0.1	weekly

8) Present method of achieving defaecation.

This question was answered by all patients including those who had already undergone colectomy.

Spontaneous defaecation	19%
Only with laxatives	60%
Usually with laxatives	10%
Only with enemas	5%
Only with suppositories	3%
Only with digital evacuation	1pt

44% had used suppositories in the past 6/12
38% had used enemas in the past 6/12

9) Patients were next asked what effect the illness had on their work and social life and gave the following responses:

Time lost from work	73%
Job lost (direct result)	19%
Leisure time spoilt	80%

The reasons given for this restricted life style were:

Pain	86%
Abdominal swelling	88%
Nausea	58%
Effect of laxatives	46%
General malaise	92%

10) Did hospital treatment help?

The patients were asked if they felt the advice and treatment (including surgical treatment) given at St Mark's Hospital had been helpful and replied as follows:

Yes	48%
No	52%

12) Prognosis.

Finally they were asked if they thought their condition was spontaneously improving or not:

Gradually getting worse	55%
Staying about the same	28%
Getting better/cured	15%

b) QUESTIONS PUT TO ALL SUBJECTS.

All the remaining questions allow a direct comparison to be made between the patients with constipation and their controls. Statistical differences were assessed by using a Chi-squared test or Fishers exact test on the actual numbers of patients responding to each question rather than on the percentages. Where actual figures were given by individual subjects (for example in question 1) the Students t-test has been applied.

Bowel function

1) Present weekly bowel frequency (mean + sem)

Controls	6.8 ± 0.4	p<0.001
Patients	1.0 ± 0.2	

2) Sensation indicating need to defaecate.

Many patients with constipation claim that they have no urge to defaecate. Some may only realise that the bowel is distended because of abdominal pain. All subjects were therefore asked how they knew when they needed to empty their bowels:

	Controls	Patients	
Abdominal sensation	12%	43%	
Rectal sensation	76%	25%	p<0.001
Both	10%	31%	

3) Number with pain in relation to bowel movements:

Controls	6%	p<0.001
Patients	76%	

4) Reported stool consistency.

This question proved to have been badly phrased as many of the constipated patients had been using laxatives

which might have softened the stool.

	Controls	Patients	
Hard	26%	59%	
Medium	12%	9%	p<0.001
Soft	61%	21%	

5) Straining at stool.

Subjects were asked if they needed to strain repeatedly to pass a motion and responded as follows:

Controls	23%	p<0.001
Patients	74%	

The time spent straining varied enormously amongst the constipated patients from 1 minute to over an hour. The few normal subjects who reported straining did so for an average of 4 minutes each time.

6) Digital evacuation.

The subjects were asked if they ever found it necessary to assist the passage of a motion using a finger:

Controls	14%	p<0.01
Patients	40%	

7) Rectal bleeding.

No specific question about piles or fissure were asked but all subjects were asked if they had ever noticed blood in their motions:

Controls	16%	p<0.01
Patients	51%	

8) Prolapse.

The presence of a protrusion from the back passage after defaecation was reported in the following numbers:

Controls	18%	
		p<0.01
Patients	43%	

9) Passage of flatus.

A number of patients had claimed never to pass flatus. All subjects were asked if they passed flatus spontaneously and the following denied ever doing so:

Controls	3%	
		p<0.01
Patients	19%	

Gynaecological history

1) Menstrual cycle:

	Controls	Patients
Hysterectomy (or none)	3%	20%
On contraceptive pill	34%	17%
No contraception:		
Regular periods	50%	34%
Irregular periods	12%	28%

2) Dysmenorrhoea (in those menstruating).

	Controls	Patients	
Yes	72%	76%	
Activities limited	23%	59%	(p<0.001)
Taking pain killers	37%	66%	(p<0.01)
Have consulted G.P.	10%	36%	(p<0.005)

3) Effect of menstruation on bowel habit:

	Controls	Patients	
Constipated/Worse	15%	29%	
No effect	50%	41%	N.S.
Diarrhoea/Easier	34	29%	

Questions 4-11 refer to only some of the respondants as about a quarter of each group were not, or had not been, sexually active. Dyspareunia was defined as painful intercourse from any cause and anorgasmia as failure ever to achieve a climax from intercourse. The reason for difficulty in becoming pregnant was not asked and could therefore refer to physical or to hormonal problems.

4) Effect of contraceptive pill on bowel habit:

	Controls	Patients	
Pill used	57%	66%	N.S
Effect on bowels:			
Constipated/Worse	9%	0	
No effect	91%	95%	N.S.
Looser/Better	0	5%	

5) Dyspareunia:

Controls	23%	
		N.S.
Patients	32%	

6) Anorgasmia:

Controls	19%	
		N.S.
Patients	34%	

7) Difficulty getting pregnant:

Controls	9%	
		p<0.05
Patients	27%	

8) Successful pregnancy:

Controls	57%	
		N.S.
Patients	50%	

9) Effect of pregnacy on bowel habit:

	Controls	Patients	
Constipated/Worse	53%	27%	
No effect	41%	48%	p<0.01
Diarrhoea/Better	6%	24%	

7 of the 32 constipated patients who achieved pregnacy thought that their symptoms were better afterwards.

10) Problems at delivery:

	Controls	Patients	
Caesarian section	9%	6%	
Perineal tear	12%	6%	N.S.
Forceps used	18%	18%	

11) Any miscarriage:

Controls	31%	
		N.S.
Patients	27%	

12) Breast problems.

	Controls	Patients	
Breast lump: Benign	3%	9%	N.S.
Malignant	1pt	1pt	N.S.
Painful lumpy breasts	16%	31%	N.S.
Worse > menses	14%	28%	N.S.
Discharge (not related to pregnacy)	1pt	11%	p<0.05

13) Gynaecological surgery:

i) Number having any operation.

Controls	30%	
		p<0.05
Patients	48%	

ii) Any operation excluding minor procedures such as D&C, TOP, Sterilisation and Ceasarian section.

Controls	10%	
		p<0.001
Patients	39%	

iii) Specific procedures.

	Controls	Patients.	
Hysterectomy	3%	19%	p<0.01
Ovarian cystectomy	3%	22%	p<0.01

Nutrition

1) Mean body weight (in Kg. as % ideal)

Controls	108 ± 2	p<0.01
Patients	101 ± 2	

2) Maximum known weight (Kg.):

Controls	116 ± 4	p<0.05
Patients	111 ± 3	

3) Minimum known weight (Kg.):

Controls	95 ± 1	p<0.05
Patients	90 ± 1	

4) Numbers who tried weight reduction:

Controls	32%	N.S.
Patients	30%	

(Average length of diet in both groups: 5.8 + 1.3 v 6.7 + 1.9 months. N.S.)

5) Numbers who have tried a high residue diet:

Controls	36%	p>0.001
Patients	91%	

6) Effect of high residue diet on bowels (those who replied yes to question 5):

No Change	5pts	36pts	
More frequent	16pts	9pts	p<0.01
Worse	0	13pts	

7) Food sensetivities:

Huge list of different claimed food sensetivities in both groups. The only significant differences were as follows:

	Controls	Patients	
Fried/Fatty food	3%	15%	p<0.05
Onions	0	11%	
White bread	0	8%	

Other Symptoms

1) Urinary frequency:

Controls	6.8 ± 0.4 Daily	N.S.
Patients	6.9 ± 0.4 Daily	

2) Nocturia:

Controls	21%	p>0.02
Patients	42%	

3) Hesitancy:

Controls	2%	p<0.001
Patients	25%	

4) Urgency of micturition:

Controls	25%	N.S.
Patients	36%	

5) Abdominal bloating:

Controls	51%	p<0.01
Patients	84%	

6) Bloating present all the time:

Controls	10%	p<0.05
Patients	25%	

7) Bowel actions difficult when bloated:

Controls	34%	p<0.01
Patients	64%	

8) Number reporting "blackouts":

Controls	1pt	p<0.001
Patients	22%	

(11% of patients have a definite diagnosis of epilepsy)

9) Raynaud's phenomonem (Digital vasospasm)

Controls	18%	p<0.001
Patients	58%	

10) Frequent attacks of colds/flu:

Controls	9%	N.S.
Patients	22%	

11) Reported annual visits to family doctor over past 5 years for colds, flu and sinus trouble: (mean ± s.e.m.)

Controls	3.0 + 0.7	N.S.
Patients	3.4 + 0.4	

12) Number of different types of tablet taken over the past 6 months: (mean ± s.e.m.)

Controls	3.8 + 0.4	p<0.001
Patients	5.3 + 0.5	

<u>Family history</u>

1) Reported family history of constipation:

	Controls	Patients	
Parents	24%	37%	N.S.
Grandparents	9%	17%	N.S.
Any relative	36%	54%	N.S.

2) Other illnesses:

	Controls	Patients	
Breast disease	7%	16%	N.S.
Asthma	16%	22%	N.S.
Migraine	34%	25%	N.S.
Arthritis	28%	23%	N.S.
Epilepsy	5%	11%	N.S.

Operations

1) Total number of surgical procedures: (mean + sem)

Controls	1.7 ± 0.3	p<0.001
Patients	3.8 ± 0.5	

2) Operations on the gut: (mean + sem)

Controls	0.2 ± 0.05	p<0.001
Patients	2.1 ± 0.4	

3) Number having had appendicectomy:

Controls	19%	p<0.005
Patients	45%	

4) Gynaecological operations: (mean + sem)

Controls	0.6 ± 0.2	p<0.05
Patients	1.2 ± 0.2	

5) Number having had operations above the waist:

Controls	44%	N.S.
Patients	37%	

DISCUSSION

This study involved 64 out of 75 patients available. Examination of the case notes suggests that there was no significant bias in this selection; for example, two of the patients who failed to cooperate have had ovarian cystectomy. The sample can therefore be regarded as representative of the patients who have presented with this problem over the past 12 years. St Mark's Hospital is a specialist unit attracting patients from a wide area and a disproportionately high number present unusual problems in diagnosis and management. Patients with this degree of disability from constipation are likely to present infrequently to the general physician and very rarely to their general practitioner. The questionnaire gives useful information about the nature of the disorder but cannot answer the question of whether these patients represent the severe form of a more common ailment, or how common this problem is in the general population.

The control population was not matched for social class or marital status as this was difficult to arrange without breaking confidentiality. The control group were all volunteers and this makes it possible that the group is biased in favour of those who have been ill before or have a particular interest in medical matters. This however would tend to make the results less significant and is unlikely to affect the overall picture.

The most important finding, which was apparent before the questionnaire was sent out, is that all the patients in this series are female. They have mostly had a

long history of constipation which could begin in childhood, but more often began in the teenage years. Medical advice was usually sought towards the end of the teens or in the early twenties resulting in the clinical impression that this is a disorder principally of young women. Table 3a shows a detailed analysis of the ages of presentation. From this it will be seen that there may be a bimodal onset with some developing symptoms berore the age of 5 and it is possible that these are two separate disorders. Also a significant number of patients did not present to hospital till they were over 30. These findings are in distinction to the usual presentation of Hirschsprung's disease, which starts at birth; and also to idiopathic megarectum, which often presents in the first 2 years of life with faecal soiling.

The first symptom was usually non-specific. Patients generally are unable to explain what they mean by the term constipation, and many of these girls described a general feeling of abdominal discomfort or bloating. All noticed a gradual decrease in the frequency of their bowel actions until by the age of 20 most were passing only one spontaneous bowel action weekly. Some were unaware that this was abnormal until they discovered through conversations with friends at work that their pattern of bowel activity was unusual. In 4 older patients the symptoms came on suddenly after hysterectomy and in one girl they followed a fall at the age of 13 with injury to the perineum. It is posible that these cases represent a different form of the disorder in which there has been traumatic damage to the

nerves controlling the pelvic floor muscles.

It is interesting to note the frequency with which laxatives were given before the age of 10. In an older generation this would have been unremarkable but is probably less common now. However Reid (1956) whilst performing routine school medical examinations found that 17% of children were receiving laxatives with girls twice as likely as boys to be getting regular doses. That study was carried out about 30 years ago but may be relevant as he was questioning the mothers of school entrants aged 5-6 and the mean age of the study group is about 30. Many of the patients would therfore have been at school about the same time as Reid was doing his survey. It is unfortunate in retrospect that details of laxative use in childhood was not sought from the control group in this study.

At the time of the survey 8 (13%) of the patients had already undergone colectomy, and some had not been seen at the hospital for 10 years. The failure of hospital treatment to affect their symptoms is best illustrated by the fact that only 19% reported spontaneous bowel actions. By far the majority were using regular laxatives supplemented in many cases by enemas and suppositories. The advice given at St Mark's Hospital was considered unhelpful by over half and 55% thought that their symptoms were gradually getting worse. The 15% who were better corresponds exactly with the 15% who found bran helpful and it is possible that these are cases of dietary or simple constipation who were wrongly classified in the first few years covered by the survey. However it is also possible

that a few patients spontaneously improve.

An illness which many would consider trivial has had a devastating effect on the lives of the patients. A high proportion reported feelings of general malaise and abdominal pain or swelling. The majority had lost time from work and 1/5 had even lost their job as a direct result of time taken off sick. In this respect this disorder compares with other conditions such as ulcerative colitis (Mallett et al. 1978) in its effect on the patients work and social life.

The general picture resulting from questions put to the constipated patients alone is of a progressive disorder which is unlikely to be congenital. Onset is often around the age of puberty but does not usually seem to be related to any particular event. It is also apparent that the treatment so far offered to these girls is singularly ineffective.

Comparison of their bowel habit with a matched control group shows that the folk lore of one bowel action daily being the norm is true. Despite the fact that 1/5 of the patients were better at the time of the survey, their mean bowel frequency was once weekly. In fact many who had recently presented gave a spontaneous bowel frequency of once every 10-14 days. All subjects found it difficult to describe the sensation indicating a need to defaecate. It is interesting in this regard that patients with the irritable bowel syndrome frequently struggle to find terms to describe the bizarre visceral sensations that accompany their disorder. However a significantly greater number of control

subjects experienced a sensation referred to the sacrum or perineum as the sole urge to defaecate whereas more of the constipated group felt abdominal pain. In view of the severity of the constipation; associated symptoms such as bleeding, prolapse, repeated straining and a complaint of hard stool were not surprisingly commoner in the disease group. One totally unexpected finding however was that 14% of normal women admitted to occasionally using digital evacuation of faeces. This was also much commoner in the constipated group. Evacuation in this way was achieved by inserting a finger into the vagina, or by butressing the perineum with one finger on either side of the anus during straining. These findings suggested the possibility of a disorder of defaecation in some of the constipated patients, but the need for digital evacuation in some normal women is unexplained. It is possible that they had damaged the pelvic floor in childbirth.

The clinical records had suggested an association between this form of constipation and gynaecological problems. This was amply borne out by the results of the questionnaire. In the clinical records many women had claimed to pass no bowel action all month until the start of their menstrual period, when they would then pass several normal motions only to seize up again after the period had ended. This was thought to be strong evidence of a hormonal cause for the constipation. However this survey showed no significant difference between the groups in this regard. It is true that a significant proportion of the constipated patients find their symptoms relieved during menstruation,

but some are made worse and the varied effect of menstruation on bowel habit may be due to other factors such as the release of prostaglandins from the uterus (McCance et al. 1960, Rees et al. 1976).

Slow transit constipation seems to be associated with a higher risk of undergoing gynaecological surgery. This may be because many patients have irregular periods and abdominal pain which leads to them seeking gynaecological advice rather than presenting to a gastroenterologist. It is difficult to explain why so many should have undergone ovarian cystectomy. Some had galactorrhoea and many found difficulty in getting pregnant, though an equal number eventually did so in both groups. These findings suggest the possibility of a hormonal disturbance and this aspect has been further investigated in Chapter 12. These findings parallel observations made in the early part of this century (Lane 1909).

Pregnancy had a paradoxical effect. Some constipated patients developing diarrhoea, whilst rather more control subjects became constipated. This also suggests that hormonal influences could be important in the genesis of the constipation. Another interesting finding was that although the incidence of dysmenorrhoea was the same in both groups, the constipated patients were more likely to limit their activities, take pain killers or consult with their family doctor. This might represent abnormal learnt illness behaviour, but it seems also possible that with a degree of pelvic discomfort from a loaded bowel, patients would be less tolerant of any further pelvic pain. Hurst (1919) had

also noticed that dysmenorrhoea was aggravated by constipation and that some constipated women found their symptoms improved during menstruation.

It was possible that this type of constipation represented a form of anorexia nervosa and that the marked reduction in bowel frequency was a result of an inadequate diet. This objection has been partly answered in Chapter 4. Assessment of body weight was made as a percentage of ideal by finding each subjects height and weight. The weight was then compared with known standards for their height, age and sex derived from the Metropolitan Life Assurance Companies tables. There was a significant difference between the groups - but the study showed that the constipated patients were normal wheras the control subjects were a little overweight. To find if the constipation might have developed as a result of a prolonged diet for weight reduction each subject was asked for their lowest ever adult weight, and for the duration of any serious diet. There was no difference between the groups in both these regards.

The effect of a high residue diet was difficult to compare. It was interesting that 36% of normal women had tried such a diet, perhaps reflecting the current interest in these matters amongst the lay public and the success of health propaganda. A few of the constipated patients denied having tried such a diet. As a failure to respond to such a diet had been one of the criteria for carrying out bowel transit studies in the investigation of severe constipation it is possible that they did not understand the question. The majority of controls who had tried the diet found their

bowel actions easier or more frequent, wheras most of the patients found no effect and a significant number were made worse. This suggests a fundamental difference between the groups and it is possible that the constipated patients cannot defaecate the extra bulk or that they are in some way able to digest fibre more thoroughly than normals. Early writers described a "greedy colon" as a cause of constipation (Goodhart 1902, Campbell et al. 1930, Kellog 1923) but this possibility has not been investigated.

The higher incidence of urinary symptoms, particularly hesitancy, gives further support to the idea of a pelvic floor problem. This possibility is further investigated in Chapter 6. Bloating of the abdomen was very common, but this is an imprecise term and over half the controls had also experienced these symptoms. A significant number of both groups, but more commonly the patients, said that defaecation was difficult whilst they were bloated. The increased incidence of epilepsy is unexplained as is the high incidence of Raynaud's phenomenon. This latter association with constipation was recorded in the early part of this century (Lane 1909) and it may be that the constipation is part of a more widespread autonomic disturbance.

Previous studies have suggested that patients with functional bowel disturbances may have abnormal learned illness behaviour (Whitehead et al. 1982a). This survey finds no evidence of this in a comparison between the groups for their rate of self-referral to a family doctor for minor illness. The constipated patients had used a wider variety

of medication in the previous 6 months but this was accounted for by their use of laxatives. There was no greater family history of constipation in the constipated group despite the fact that their families would have been more aware of bowel problems. To divert interest from this question the survey also asked for specific details about the family history of a variety of other complaints and as expected there were no differences here either.

Surgical treatment had been undertaken much more commonly in the constipated group. Interestingly, this applied only to operations in the abdomen. At one time it was thought that constipation lead to appendicitis and also that adhesions after an attack obstructed the ileum. This survey confirms an association between constipation and appendicectomy. The reason is not clear but one possible explanation is that young patients with abdominal pain from constipation may undergo appendicectomy before details of their bowel habit are discovered. Where details are available many of the patients had had a normal appendix removed which tends to confirm this suggestion. In 4 patients symptoms apparently started after the appendicectomy. It is likely that they had in fact been developing constipation before, but that the bed rest after surgery exacerbated the problem.

This survey has demonstrated a significant difference between the two groups on a wide variety of symptoms and provided some interesting data on bodily functions in normal young women against which future studies can be compared. Some of the points raised have been

investigated futher in other parts of this thesis. The overall impression given is that patients with slow transit constipation have a genuine disorder affecting many systems of the body.

CHAPTER 4

DIETARY ASSESSMENT

INTRODUCTION

Stool weight and gut transit time are known to be dependant on the amount of dietary fibre ingested. It has also been shown that many patients with constipation can be helped by a supplement of bran (Williams et al. 1936, Burkitt et al. 1972, Harvey et al. 1973, Kirwan et al. 1974, Walker at al. 1975, Payler et al. 1975, Graham et al. 1982). However, there has been no assessement of the effect of a bran supplement in patients with idiopathic slow transit constipation. Previous clinical experience suggested that many patients with this form of constipation were not helped by an increase in dietary fibre and that some were made worse. It was decided to investigate the dietary habits of a group of these patients and to compare them with age and sex matched controls.

PATIENTS AND METHODS

The same patients who completed the questionnaire described in chapter 3 were invited to keep a record of everything they ate or drank for a week. Forty agreed to do so and were matched to 40 controls. A further 8 patients who had already undergone colectomy also agreed to take part.

All food and drink consumed was recorded on special tables for 7 consecutive days. This has been shown to be a more reliable method of assessing dietary intake than taking

a dietary history (Young et al. 1952). Food was not weighed because of the impossibility of achieving compliance. A rough estimate of quantity was obtained by use of simple instructions (Table 4a) and each subject was given advice on the use of the tables. All subjects were asked to remain on their normal diet.

At the end of the study a senior hospital dietician estimated the average daily intake for each subject using the tables of McCance and Widdowson (Paul et al. 1978). Computer analysis is possible for tables prepared in this manner, but it was felt that as the amounts of food recorded by the subjects were only approximate, the values obtained for trace elements and minerals would be meaningless. Statistical analysis was carried out using the students t test.

RESULTS

The mean daily intake of the main dietary constituents for the three groups is illustrated in table 4b. The important finding of this study is that there is little difference between the diets taken by healthy controls and women with severe constipation. In particular there is no difference between the groups in the amount of dietary fibre ingested. There was a reduced carbohydrate consumption in the constipated group ($p<0.01$) which resulted in a slightly lower mean calorie intake ($p<0.02$). The patients who had undergone colectomy had a more marked reduction in carbohydrate consumption ($p<0.01$) and were also drinking more fluid ($p<0.01$).

Table 4a

Instructions given to all subjects indicating the method of recording the quantities of food and drink consumed during the 7 days.

RECORDING OF FOOD QUANTITY

Please record foods in the following measures

FLUIDS	cup / glass / mug
CEREALS, RICE, VEGETABLE and FRUIT STEWS, GRAVIES, SAUCES, PUDDINGS, CUSTARD etc.	can all be measured as tablespoons
SUGAR, SALT, JAMS and PRESERVES, SALAD CREAM etc.	can all be measured as teaspoons
CHEESE	matchbox size pieces
MEAT	number of thin hand sized pieces
POTATOES	number the size of an egg
BREAD	state whether slices thick or thin

Give as accurate a description as possible - e.g. when describing a cup of coffee: 1 mug all milk + 2 teaspoons sugar or 1 slice white bread 1/4" thick with 1 level teaspoon of butter

Remember to include all snacks and drinks

Table 4b

Results of the dieticians assessment of the main dietary constituents for the control subjects and patients with slow transit constipation. (Mean daily intake over 7 consecutive days)

	Controls	Constipation	Colectomy
CALORIES (Kcal)	1728 (±56)	1613** (±72)	1531** (±158)
FAT	91 (±3)	89 (±3)	88 (±9)
CHO (Total)	172 (±8)	156** (±10)	137** (±18)
CHO (Sugar)	33 (±3)	33 (±3)	36 (±6)
PROTEIN (g)	50 (±1)	49 (±2)	47 (±3)
FIBRE (g)	15 (±0.6)	14.7 (±0.7)	12.5 (±1.2)
FLUID (ml)	1208 (±60)	1234 (±77)	1699** (±174)

** p<0.01
* p<0.02

DISCUSSION

Dietary surveys such as this can be subject to error. The blind nature of the assessment makes it unlikely that there was any consistent bias and it is probable that any errors would be spread evenly between the groups. A low intake of dietary fibre does not appear to be causing the symptoms of this group of women with severe constipation. This finding is important in that it confirms the clinical story and makes it important for physicians to consider other causes for their symptoms. Treatment with bran or a high fibre diet may therefore be ineffective and a clinical trial of bran in this group of patients would seem appropriate. If bran does not affect their symptoms, as the patients frequently assert, then it is important for physicians to know of this possibility and to realise that bran is not a universal panacea for patients who complain of constipation.

The relevance of the reduced total calorie and carbohydrate intake is difficult to assess. In the questionnaire two thirds of the patients said that they ate less than they used to. This reduced intake was often attributed to nausea or anorexia. Whilst they are bloated food intake may be reduced to avoid abdominal distension and pain. From the dietary figures it appears that this reduction is accounted for by non-sugar carbohydrate such as bread or potatoes.

Those patients who had undergone colectomy for constipation were also eating much less carbohydrate and

were drinking more than the control subjects or the other patients with constipation. These changes may be due to the fact that some of them had loose stools and had possibly reduced their food intake to avoid precipitating a bowel movement. Some had more than 5 bowel actions a day and the extra fluid intake was presumably needed to balance increased faecal losses.

CHAPTER 5

BARIUM ENEMA STUDY

INTRODUCTION

An immediate problem encountered in attempting to define slow transit constipation arises from confusion about the definition of idiopathic megacolon. Clinicians seem to recognise the latter as a clinical disorder (Tobon et al. 1974, Lane et al. 1977) but the condition has never been accurately defined. Consequently there has been confusion in reports of research in this field. Some authors do not recognise a distinction between those groups of patients with idiopathic constipation whose colons are enlarged, and those whose colons are of normal width (Patriquin et al. 1978). An attempt was therefore made to define idiopathic megacolon in radiological terms by a retrospective study of barium enemas carried out on patients with idiopathic constipation.

PATIENTS AND METHODS

Barium enemas performed at one hospital (St Mark's) by two radiologists over a ten year period from 1972-1982 were examined. Not all constipated patients seen during this time were included as the majority were referred from other institutions where radiological studies had already been performed.

a) Control population.

As a normal control group, measurements were made of radiographs from 50 barium enemas reported as normal performed on patients referred for the investigation of rectal bleeding. All these patients had been investigated by ano-rectal examination and sigmoidoscopy without detection of any abnormality. No patient had diverticular disease, carcinoma or inflammatory bowel disease. Some patients had the barium enema as part of a follow up study after removal of an adenomatous polyp at colonoscopy some years previously. Equal numbers of examinations from men and women were selected to give a representative sample from each age group from 20-60+ years.

b) Constipated group

A consecutive series of 38 patients who had been investigated for chronic constipation were studied. In all cases a primary cause for the constipation had been excluded. None had responded to a high fibre diet, none had Hirschsprung's disease (excluded by a normal ano-rectal distension reflex), and none had any structural abnormality or metabolic disorder. Twenty patients, 11 men and 9 women (mean age 36 years), had been diagnosed as suffering from idiopathic megacolon on the basis of the radiological appearences. Eighteen patients, all women (mean age 25 years), had been diagnosed as suffering from idiopathic slow transit constipation. In this group the barium enema had been reported as normal, but they all had a prolonged whole gut transit time with at least 16 out of 20 radiopaque

markers remaining in the colon 5 days after ingestion.

c) Methods.

Measurements were made on radiographs obtained during a standard double-contrast barium enema in which, after coating the bowel wall with barium, air was introduced into the rectum using a Higginson's syringe until satisfactory distension of the colon was obtained on screening. Anti-spasmodic drugs were not given. Radiographs were taken using an over-couch tube with a tube-film distance of 110 cm.

The rectal width was measured from true lateral pelvic radiographs along a line drawn perpendicular to the body of S2. The bowel width was also measured perpendicular to the lumen at the pelvic brim, on a line between the upper border of S1 and the pubis. In some patients this measurement was at the level of the recto-sigmoid junction whilst in others in the sigmoid colon (Figures 5a-c). The greatest width taken from any of the available films was recorded for each segment of the colon, excluding the caecum, the hepatic and splenic flexures. Rectal area was assessed from lateral films using a simple transparent 1 cm. grid to the line drawn from the mid portion of S2 and to the level of the pelvic brim (Farthing et al. 1978).

RESULTS

a) Control population.

In the normal control group, two-way analysis of variance showed no significant change with age or sex for any variable exept for the width of the ascending colon. This was significantly wider in males. The control group has therefore been regarded as homogeneous. The results are tabulated below to show the variability for each measurement with age and sex:

ASCENDING COLON WIDTH (cm)

	20-29	30-39	40-49	50-59	60-69
Female	6.3	7.3	6.3	6.5	5.6
	5.5	6.2	6.0	6.5	7.5
	6.5	6.5	6.2	7.5	5.0
	5.8	5.0	6.2	5.5	7.5
	7.4	6.5	6.8	6.0	6.2
Mean	6.3	6.3	6.3	6.4	6.4
Male	7.2	6.9	9.1	5.7	7.5
	7.1	6.8	7.5	7.5	5.3
	5.9	7.0	5.5	9.3	6.0
	6.8	6.5	7.0	8.0	8.0
	6.7	8.5	6.5	8.0	6.3
Mean	6.7	7.1	7.1	7.7	6.6
MEAN M/F	6.5	6.7	6.7	7.0	6.5

TOTAL MEAN 6.7 ± 1.0

2 way analysis of variance shows a significant difference between the sexes: Female mean width 6.3 ± 0.7 (SD), Male mean width 7.0 ± 1.0 ($p<0.05$).

TRANSVERSE COLON WIDTH (cm)

	20-29	30-39	40-49	50-59	60-69
Female	6.7	6.8	6.3	4.8	5.5
	4.6	5.9	6.3	7.0	4.5
	5.0	5.0	5.2	6.7	6.5
	5.8	6.0	5.2	7.3	6.2
	6.5	4.8	6.2	6.7	6.3
Mean	5.7	5.8	5.7	6.5	5.8
Male	5.5	7.0	7.0	6.3	7.6
	6.5	8.3	6.0	7.0	6.8
	7.5	5.6	7.2	8.3	5.0
	6.9	6.0	7.2	6.0	5.6
	5.3	5.7	5.7	7.0	6.5
Mean	6.3	6.5	6.6	6.9	6.7
MEAN M/F	6.0	6.1	6.2	6.7	6.0

TOTAL MEAN 6.2 ± 0.9

DESCENDING COLON WIDTH (cm)

	20-29	30-39	40-49	50-59	60-69
Female	5.0	4.0	4.5	4.1	5.0
	3.8	5.2	4.3	4.2	3.8
	4.5	4.5	4.8	5.2	5.3
	4.6	4.5	4.5	4.8	4.0
	5.3	4.5	4.4	5.0	4.8
Mean	4.6	4.5	4.5	4.7	4.6
Male	5.2	4.2	7.1	4.6	6.5
	4.5	6.3	4.5	5.3	4.3
	6.4	5.5	4.5	4.7	4.2
	5.1	3.7	5.0	4.7	4.5
	4.2	4.5	4.2	3.8	4.2
Mean	5.1	4.8	5.0	4.6	4.7
MEAN M/F	4.9	4.7	4.8	4.6	4.6

TOTAL MEAN 4.8 ± 0.4

SIGMOID COLON WIDTH (cm)

	20-29	30-39	40-49	50-59	60-69
Female	5.1	4.5	4.7	3.8	4.0
	3.8	3.7	4.2	4.7	3.0
	4.0	4.8	5.0	5.3	4.2
	3.5	3.3	4.7	4.6	3.4
	4.4	3.7	4.9	4.3	4.0
Mean	4.2	4.0	4.7	4.5	3.8
Male	5.0	5.5	6.3	4.2	5.0
	3.7	4.7	4.5	4.0	5.0
	5.6	4.7	4.2	4.2	3.2
	4.3	3.8	5.0	3.5	5.0
	4.6	4.7	4.7	4.0	4.0
Mean	4.6	4.7	4.9	4.0	4.4
MEAN M/F	4.4	4.3	4.8	4.3	4.1

TOTAL MEAN 4.4 ± 0.8

AREA TO PELVIC BRIM (cm^2)

	20-29	30-39	40-49	50-59	60-69
Female	82	79	85	73	101
	54	82	105	97	89
	81	82	103	118	78
	67	74	83	81	83
	108	99	93	92	86
Mean	78	83	94	92	87
Male	87	89	95	82	91
	76	77	89	80	72
	105	112	110	91	80
	88	83	89	105	108
	108	67	83	76	108
Mean	93	85	93	87	92
MEAM M/F	85	84	93	89	90

TOTAL MEAN 88 ± 13

RECTAL WIDTH TO BRIM (cm)

	20-29	30-39	40-49	50-59	60-69
Female	4.9	3.7	4.9	3.2	3.2
	3.2	3.0	4.5	3.5	3.5
	3.7	5.1	4.0	3.8	2.7
	3.7	3.7	4.2	4.6	3.2
	3.8	5.0	4.9	3.0	3.8
Mean	3.9	4.1	4.5	3.6	3.3
Male	4.4	4.2	5.7	4.3	5.5
	4.1	5.0	4.0	4.0	4.1
	6.2	4.3	4.5	5.3	4.6
	3.6	3.5	4.2	2.8	3.2
	5.7	4.1	4.0	4.0	4.6
Mean	4.8	4.2	4.5	4.0	4.4
MEAN M/F	4.3	4.2	4.5	3.9	3.8

TOTAL MEAN 4.2 ± 0.9

RECTAL AREA TO S2 (cm^2)

	20-29	30-39	40-49	50-59	60-69
Female	65	54	61	70	72
	40	55	83	88	71
	61	56	85	61	59
	47	77	56	74	60
	79	72	58	63	64
Mean	58	63	68	65	65
Male	77	65	74	63	75
	68	48	64	71	66
	73	63	83	73	65
	67	48	64	71	66
	67	47	70	54	59
Mean	70	54	71	66	66
MEAN M/F	64	58	70	66	66

TOTAL MEAN 65 ± 12

RECTAL WIDTH AT S2 (cm)

	20-29	30-39	40-49	50-59	60-69
Female	5.2	3.2	4.3	3.6	5.1
	2.6	2.7	4.3	3.6	5.1
	3.3	4.2	5.2	4.6	4.0
	3.2	3.5	4.6	3.4	4.0
	4.7	4.2	4.6	2.2	4.8
Mean	3.8	3.6	4.6	3.5	4.6
Male	5.2	4.6	5.5	3.2	4.8
	4.2	5.7	5.0	4.7	4.8
	5.9	4.5	6.0	5.5	5.0
	3.8	3.8	6.5	4.5	3.5
	4.8	4.9	5.2	5.5	3.9
Mean	4.8	4.7	5.6	4.7	4.4
MEAN M/F	4.3	4.1	5.1	4.1	4.5

TOTAL MEAN 4.4 ± 0.9

b) Constipated patients.

The measurements for all the 18 patients with slow transit constipation fell within the normal range as defined in section (a) above. Among the 20 patients diagnosed as having idiopathic megacolon, at least three measurements in each patient fell outside the normal range. The mean, standard deviation and range for each measurement in the two groups are given in table 5a and compared with the normal range.

Many of the patients with idiopathic megacolon had an enlarged rectum and sigmoid colon but the rest of the bowel was normal in calibre. In addition two patients had an enlarged rectum alone with a sigmoid colon width within the normal range. This meant that a separation between the two groups of patients with constipation was only possible by

Table 5a

	RECTAL AREA (cm^2)		RECTAL WIDTH (cm)		COLONIC WIDTH (cm)			
	To S2	To Brim	To S2	To Brim	SIGMOID	DESCENDING	TRANSVERSE	ASCENDING
CONTROLS								
Mean	65.2 ± 11.6	88.5 ± 13.4	4.4 ± 0.9	4.2 ± 0.9	4.4 ± 0.8	4.8 ± 0.4	6.2 ± 0.9	6.7 ± 1.0
Range	(40-88)	(54-118)	(2.2-6.5)	(2.7-6.2)	(3.3-6.3)	(3.7-7.1)	(4.5-8.3)	(5.0-9.3)
SLOW TRANSIT CONSTIPATION								
Mean	59.4 ± 9.5	83.0 + 13.0	4.5 ± 0.9	4.3 ± 1.0	4.7 ± 0.7	5.0 ± 0.7	6.6 ± 1.2	6.8 ± 1.4
Range	(42-75)	(61-109)	(3.2-6.0)	(2.7-6.2)	(3.8-6.2)	(4.0-7.0)	(5.0-9.2)	(5.0-9.5)
IDIOPATHIC MEGACOLON								
Mean	74.4 ± 9.0	130.0 ± 38.2	10.0 ± 3.0	9.5 ± 2.4	10.0 ± 3.5	7.2 ± 2.1	7.8 ± 1.4	8.2 ± 1.6
Range	(54-103)	(93-212)	(5.7-15.5)	(6.9-14.7)	(6.2-17.8)	(4.0-10.3)	(4.7-9.3)	(6.1-10.6)

The mean values (± standard deviation) and range for all measurements in the three patient groups

examining rectal size. An acute bend in the rectum at the level of S2 was a frequent finding in all patient groups and gave a falsely low measurement of rectal width in some patients with megacolon (Figure 5e). Complete separation was therefore only achieved at the level of the pelvic brim where the highest value recorded in the controls and the patients with slow transit constipation was 6.2 cm. The lowest value recorded here in those with megacolon was 6.9 cm. (Figure 5g).

An additional observation was that 17 of the 18 patients with slow transit constipation had an apparently elongated colon. The transverse segment was ptosed (Figure 5d) and the sigmoid usually tortuous (Figure 5c). These appearences were in marked contrast to those seen in patients with idiopathic megacolon (Figures 5b and 5f). However, it proved impractical to measure the length of the colon with the films available. Some resected specimens were later measured, but did not appear to be unusually long (see Appendix 1).

DISCUSSION

This study has defined the normal range of large bowel width and rectal area in adults. It is now possible to define in quantitative terms what radiologists have been calling a megacolon. A group of patients with idiopathic constipation can then be recognised who do not have an enlarged colon or rectum. This retrospective study suggests there may be two distinct clinical entities as all the patients with a bowel of normal calibre were women, wheras

the sexes were equally represented in the group with an enlarged colon. This finding is confirmed by analysis of all the patients who have presented to St Mark's Hospital in recent years. There were no men in the 75 patients with Slow transit constipation who are the subject of this thesis wheras the sex incidence is equal in over 120 patients seen in the last 20 years with idiopathic megacolon.

Barium enema is therefore a useful way of distinguishing between the two groups and the present study shows that the bowel width at the level of the pelvic brim is the most reliable measurement. At this point two standard deviations on either side of the mean for the control population give a normal range of 2.4-6.0 cm. One patient in the control group had a width of 6.2 cm and a slightly increased value of 6.5 cm would provide a clinically useful upper limit of normal. All the patients studied with idiopathic megacolon had values greater than this.

A reply can now be offered to the question posed by the title of the paper by Patriquin et al. (1978). A critical assesment of their paper shows that constipation was initially defined in terms of symptoms rather than intestinal transit time. Only 17 x-rays were selected from a group of 62 patients being treated for constipation, and of the 17 patients; 7 were children and 4 had Hirschsprung's disease. The authors based their conclusion that a barium enema was of no value in the assessment of patients with constipation on the fact that there was no change in the subjective appearence of the colon after constipation had been relieved by ano-rectal myectomy. From the information

given it appears that the 10 adults may have been suffering from either the irritable bowel syndrome, slow transit constipation or idiopathic megacolon. The radiologists were asked to diagnose whether patients were constipated or not on the basis of a barium enema - and not surprisingly could not agree amongst themselves. An attempt was then made to define constipation (which is a symptom) on the basis of bowel width and their failure to show a distinction between patients with constipation and controls presumably resulted from the mixing of patients from the two groups described in this present study.

It is doubtful whether the distinction drawn between megarectum and megacolon is valid. Such terms probably refer to different degrees of the same condition in which the lower rectum is always abnormal and the enlargement extends for a variable distance proximally. In previous publications these terms have not been clearly defined and the present study will allow them to be used with greater precision in future research.

The finding of an apparently elongated colon in patients with chronic constipation has been recognised for many years. Originally this was referred to as visceroptosis or a dolichocolon (Chiray et al. 1931), though again no distinction was drawn between those patients who had a dilated rectosigmoid and those whose bowel diameter was normal. The association between an elongated or redundant colon and constipation was studied by Brummer et al. (1962) who found this anomaly to be present in 30% of constipated subjects compared to only 2% of controls. It is not made

clear in their paper whether the constipated patients had a megacolon or not. A more comprehensive study of normal colons in the early part of this century (Kantor 1924) showed that a redundant colon was present in 9.2% of the normal population. As an apparently elongated colon can occur in asymptomatic subjects it cannot cause constipation per se. In addition not all patients with slow transit constipation have a redundant colon so it cannot be the sole cause of their symptoms. Whether the colon is in fact anatomically enlarged in patients with delayed transit remains to be determined. It is interesting to speculate why elongation develops in some groups with constipation and dilatation occurs in others. An elongated colon may prolong intestinal transit time and enhance dehydration of colonic content but as has been indicated above this cannot be the only cause of these patients symptoms.

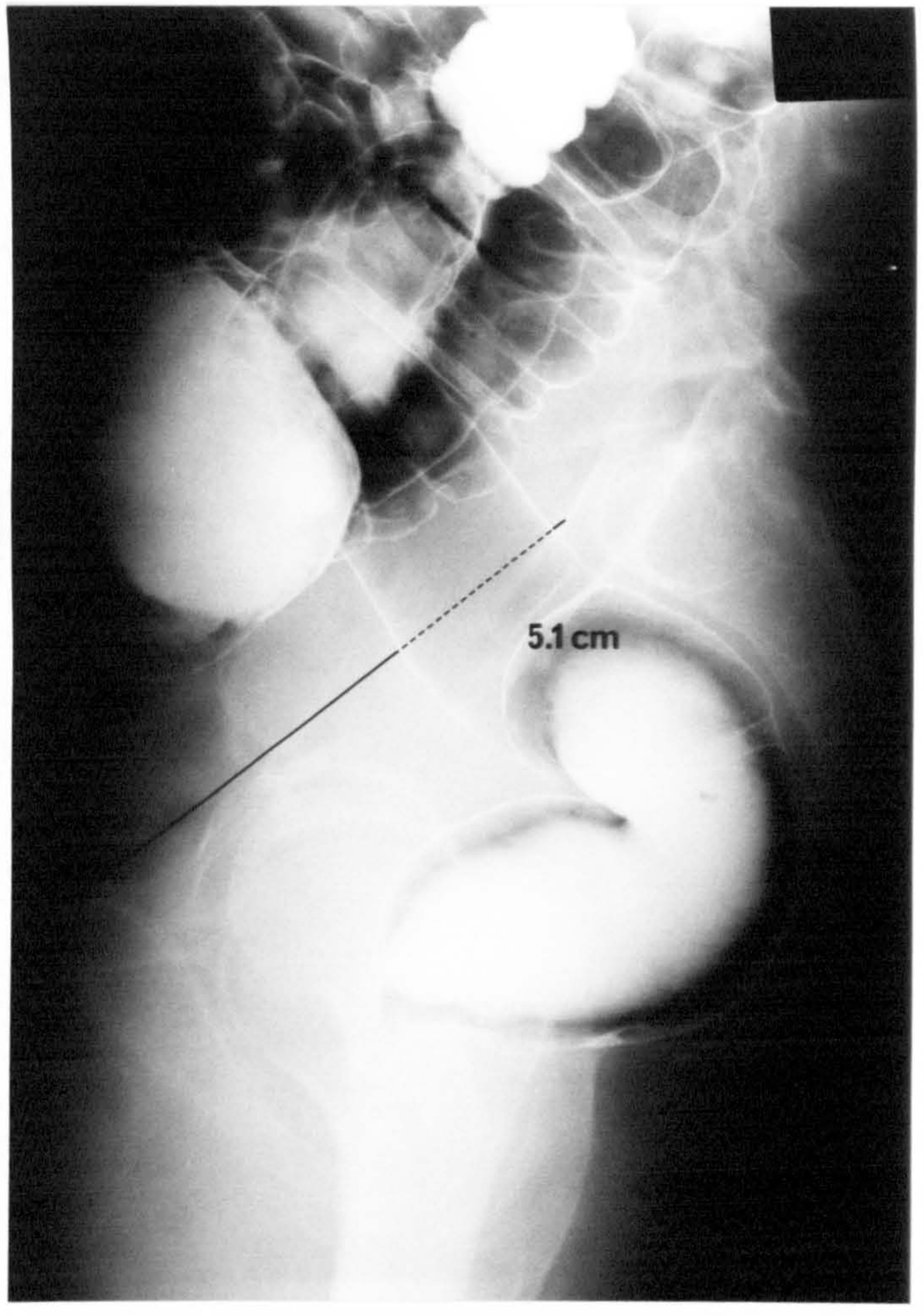


Figure 5a. LATERAL PELVIC RADIOGRAPH TAKEN FROM A NORMAL SUBJECT. The level of the pelvic brim is indicated by a line joining the top of the pubis and the upper border of the body of the second sacral vertebra

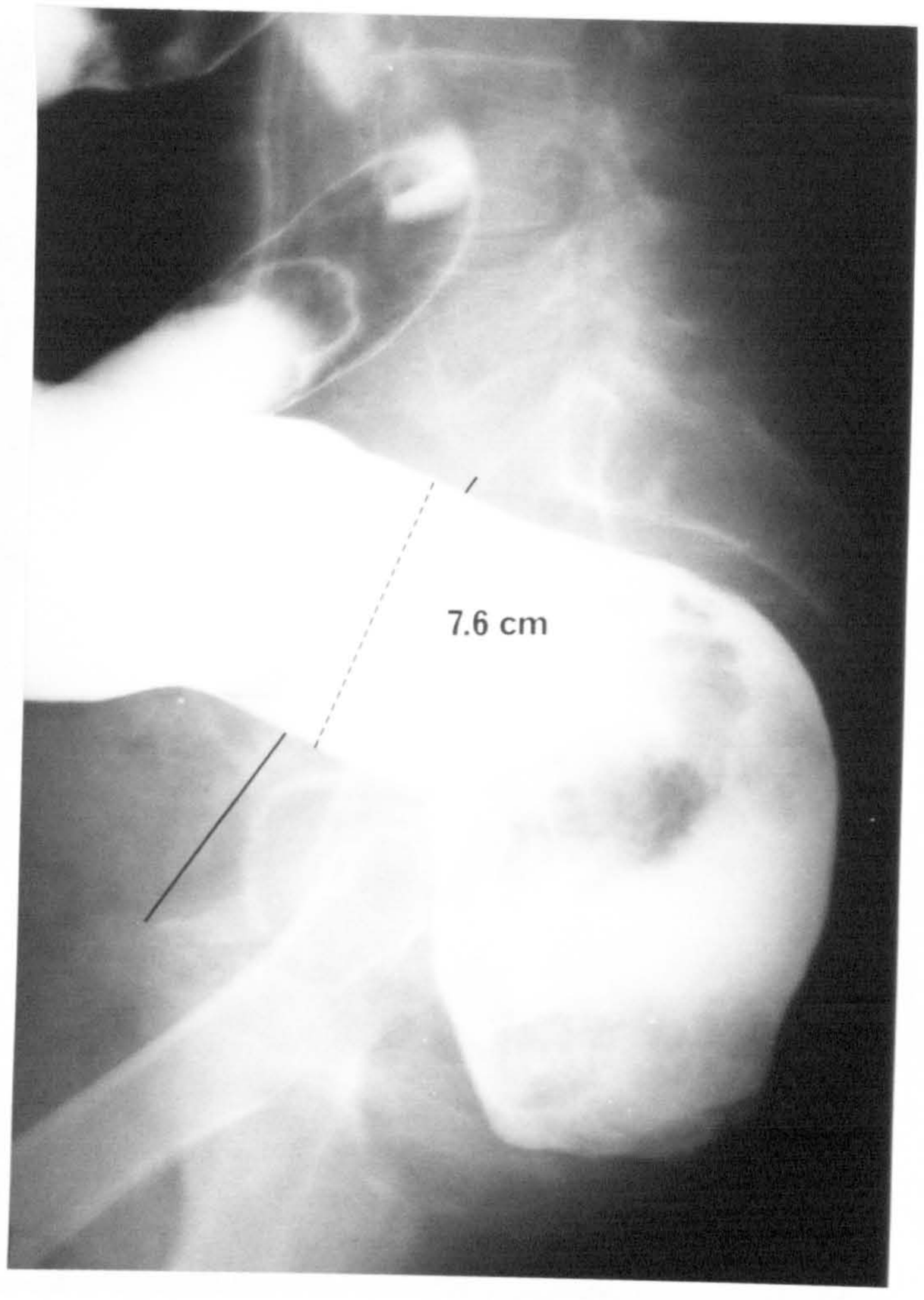


Figure 5b. LATERAL PELVIC RADIOGRAPH TAKEN FROM A PATIENT WITH IDIOPATHIC MEGACOLON

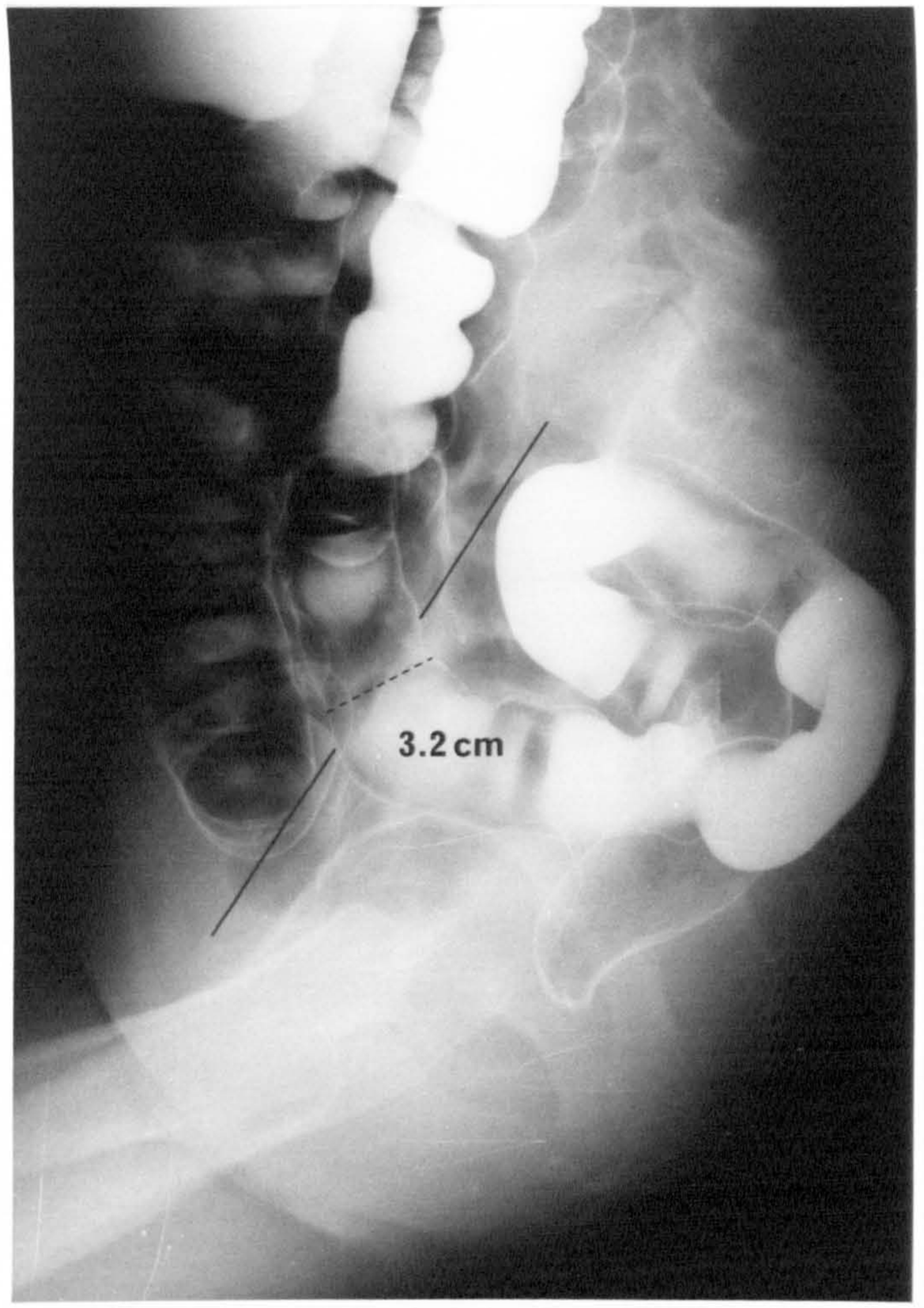


Figure 5c.



Figure 5d.

SLOW TRANSIT CONSTIPATION. These radiographs from the same patient show firstly the normal sized rectum and convoluted sigmoid colon with a distal pelvic loop. The measurement of bowel width at the level of the pelvic brim is therefore of the sigmoid colon. The abdominal view demonstrates a redundant transverse colon giving the impression that the bowel is elongated.

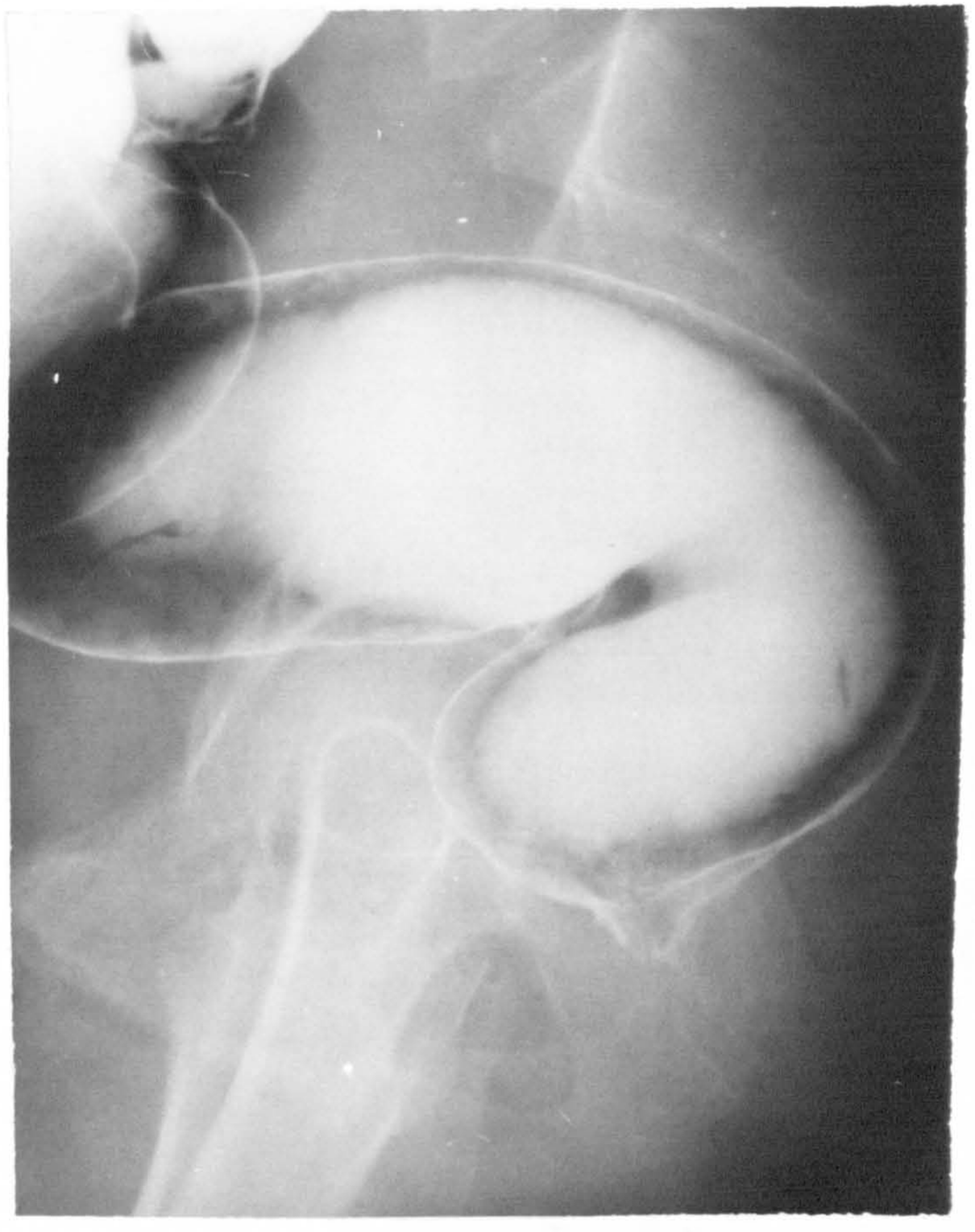


Figure 5e. IDIOPATHIC MEGACOLON
This lateral pelvic view demonstrates a bend in the rectum at the level of the second sacral vertebra making measurement difficult.



Figure 5f. IDIOPATHIC MEGACOLON
A gastrograffin enema in a severe case of megacolon showing the gross rectal enlargement.

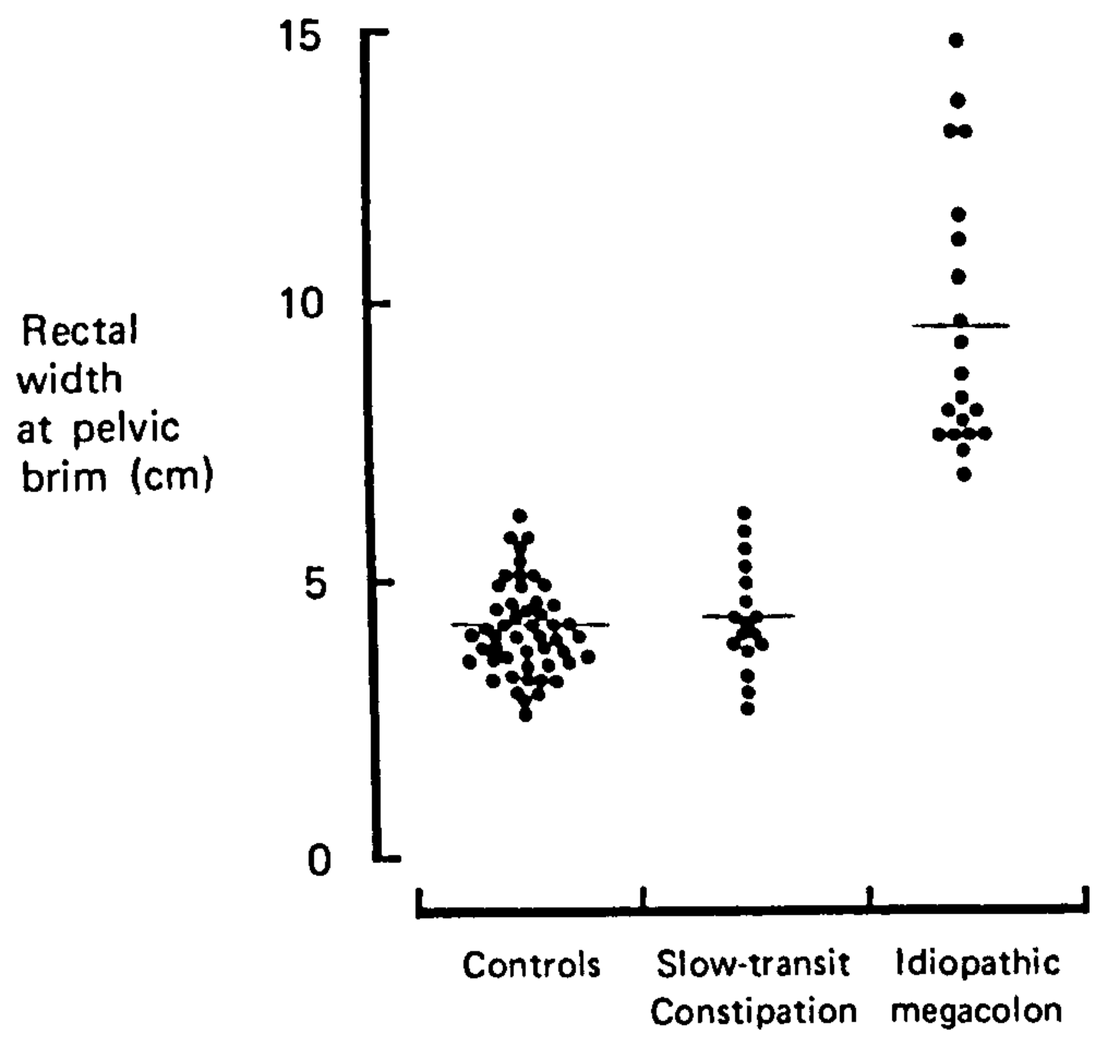


Figure 5g. BOWEL WIDTH AT THE LEVEL OF THE PELVIC BRIM IN ALL SUBJECTS. This shows clearly that measurements from the women with slow transit constipation fall into the normal range wheras all the patients with megacolon have higher values. This was the only measurement where a complete separation of the two groups was possible.

CHAPTER 6

STUDIES OF DEFAECATION

INTRODUCTION

Hurst in his monograph on Constipation and Allied Intestinal Disorders (1919) was the first to suggest that constipation could be caused by a disorder of defaecation. Some of the cases he saw probably had short segment Hirschsprung's disease and he proposed the term "anal achalasia" drawing an analogy between this and achalasia of the cardia which he and collegues at Guy's Hospital had also described (Hurst 1915). He used the general term dyschezia to describe constipation resulting from a failure to empty the rectum adequately, and proposed several causes including weakness of the pelvic floor following parturition, weakness of the abdominal muscles or diaphragm with inability to strain, a painful anal lesion, inadequate bulk of stool and hysteria. Failure of the defaecation reflex he thought could be congenital (he describes cases of idiopathic megarectum in children), or result from neurological disease such as tabes dorsalis. Other causes of constipation were classified as colonic and these included muscle weakness, colonic spasm and mechanical obstruction. His book remained the standard work on the subject for 50 years and this classification was widely accepted. However in later life he changed his mind and stated that dyschezia was probably the most important factor in all cases of constipation (Hurst 1943).

Not until after Hurst's death was the cause of

Hirschsprung's disease discovered (Swenson et al. 1948, Bodian et al. 1949) and research since then has mainly been concentrated on this disorder rather than idiopathic constipation. Important discoveries have been made about the physiology of the ano-rectal region and these will be briefly summarised insofar as they are relevant to the present study.

The Anal Sphincters.

Assumption of the erect posture has presented Man with a considerable physiological problem. In lower animals the anal sphincters are readily inhibited by colonic peristalsis and they are free to defaecate whenever the bowel is active. In those who maintain a horizontal posture there is very little activity in the external anal sphincter at rest (Browning 1983) perhaps because faeces move upwards against gravity before expulsion. It is interesting to speculate whether house training of domestic animals influences the activity of their anal sphincters. In humans however the pelvic floor muscles must resist the forces of gravity and raised intra-abdominal pressure, but relax to allow defaecation at will.

a) Anatomy

The rectum curves round the hollow of the sacrum and passes forwards so that at its junction with the anal canal it produces an angle of 80-90°. The levator ani muscles form a cradle supporting the rectum behind the anus and passing forewards to meet the pubis. The central

portion, the puborectalis muscle, makes a particularly acute angle at the ano-rectal junction. This sheet of muscle is pierced by the anal canal comprising mucosa, submucosa, and smooth muscle (the internal anal sphincter). The levator muscles are in continuity with the striated muscle of the external anal sphincter which surrounds the anal canal below the pelvic floor. There are therefore concentric tubes of smooth (involuntary) and striated (voluntary) muscle running the whole length of the anal canal. This structure is given further support by the connective tissues. (Walls 1959, Parks 1975, Williams et al. 1981).

b) The Internal Anal Sphincter.

The internal sphincter is made up of smooth muscle in continuity with the circular muscle of the rectum. This muscle is continuously active (Kerremans 1968) showing spontaneous rythmical contractions. The neurological mechanism by which this activity is maintained is still not understood (Shepherd et al. 1972, Freckner et al. 1976). During rectal distension the internal sphincter relaxes (Gowers 1877) and this reflex is mediated by local nerve pathways in the gut wall (Denny-Brown et al. 1935). Absence of local nerve pathways in patients with Hirschsprung's disease results in a failure of anal relaxation following rectal distension (Callaghan et al. 1964). The internal sphincter provides most of the pressure in the anal canal at rest (Bennett et al. 1964) but not during periods of raised intra-abdominal pressure.

b) The External Sphincter.

It is difficult to separate the puborectalis and external sphincter muscles anatomically and they are generally regarded as a functional unit. All the striated muscles of the pelvic floor are unusual in that they exhibit continuous tonic activity at rest (Floyd et al. 1953). This activity is abolished during straining but augmented during periods of raised intra-abdominal pressure, for example during coughing, as part of a spinal reflex (Parks et al. 1962). Stretch receptors have been found in both puborectalis and external sphincter muscles which probably provide the sensory input for mediation of this reflex (Winkler 1958, Walls 1959). Following rectal distension there is an increase in striated muscle activity but if the distending volume is increased activity is reduced and eventually abolished at the same time as the subject has an intolerable urge to defaecate (Porter 1962).

Rectal Sensation.

A sensation of fullness in the perineum associated with impending defaecation was first suggested by Hurst (1911) to be due to rectal distension and he thought the receptors were situated in the rectal wall. He also found that distension of the sigmoid colon above the pelvi-rectal junction produced abdominal pain rather than an urge to defaecate. Later workers claimed after studying patients with low colo-rectal anastamoses that the last 6 cm. above the ano-rectal junction were critical for a normal appreciation of rectal filling (Goligher et al. 1951) but

these findings have now been refuted. Firstly, it has been shown that adults with a colo-anal anastamosis recover normal "rectal" sensation (Lane et al. 1977). Secondly, children who have had pull-through proceedures for Hirschsprung's disease or imperforate anus develop "rectal" sensation even in the absence of a rectum, internal sphincter and external sphincter (Scharli et al. 1970, Varma et al. 1972, Bennett et al. 1973). These studies suggest that the puborectalis muscle plays the key role in "rectal" sensation.

Defaecation and Faecal Continence.

As our knowledge is still incomplete any concept of defaecation remains partly guesswork. It is thought that stool is propelled to the rectum after stimulation of colonic activity, for example after a meal or exercise (Holdstock et al. 1970) and initiates the urge to defaecate by stretching pelvic floor muscles. Stretching of the rectum also initiates the reflex inhibition of the internal anal sphincter which possibly allows the stool to descend into the sensitive upper anal canal where "sampling" occurs (Duthie 1960). Contraction of the external sphincter prevents faecal escape and stool not passed may be returned as far as the distal transverse colon, presumably by retrograde peristalsis (Halls 1965).

If defaecation is socially convenient a complex series of events takes place including adoption of the sitting posture which increases the ano-rectal angle (Tagart 1966) and relaxation of cortical inhibition. Then

intra-abdominal pressure is raised whilst bearing down and both anal sphincters relax. It is possible that the central portion of the pelvic floor relaxes to open the anus whilst the outer portion contracts raising the perineum over the stool. A wave of rectal contraction may also be initiated as a result of the stretching of the puborectalis (Scharli et al. 1970). The mechanism by which reflex inhibition of the external sphincters is coordinated with internal sphincter relaxation and colonic peristalsis is not known.

It is thought that the puborectalis muscle plays an important part in maintaining normal faecal continence. Some authors have claimed the internal sphincter has a key role and that leakage of faeces during short periods of raised intra-abdominal pressure is prevented by a "flutter-valve" mechanism (Phillips et al. 1965). Normal continence can however be enjoyed without an internal sphincter and cine-radiological studies of normal defaecation suggest that the external sphincter is responsible for maintaining continence (Kerremans 1969). It seems more likely that a "flap-valve" mechanism operates. The puborectalis muscle acts as a sling running around the back of the ano-rectal junction and when contracted will pull this forwards reducing the ano-rectal angle. Any increase in intra-abdominal pressure will then tend to depress the distal rectum and make the angle more acute as well as closing a flap of the anterior rectal mucosa over the upper anal canal (Parks 1975). It is difficult to envisage defaecation taking place whilst the puborectalis is firmly contracted in this way.

The present studies.

Many of the patients who were seen with slow transit constipation denied ever feeling any urge to defaecate and claimed that they were unable to expel a stool even when they could palpate it in the rectum. It was felt that a disorder of defaecation might be contributing to their symptoms and the following studies were therefore undertaken to develop a model of defaecation and to investigate anal sphincter function. Measurements of anal canal pressure and voluntary sphincter muscle activity were made using accepted techniques previously validated (Parks et al. 1962, Lane 1979) and now used routinely to investigate ano-rectal function at St Mark's Hospital.

PATIENTS STUDIED

In all these studies the patients were drawn from a group of women being investigated for severe constipation who fulfilled the following criteria: all had a normal barium enema, a delay in total intestinal transit time measured using radiopaque polythene pellets, a failure to respond to an increased intake of dietary fibre and normal biochemical tests such as thyroid function.

Controls

A control group for the balloon expulsion study was drawn from 15 women attending for colonoscopy. None had ano-rectal disease or a history of constipation. They were being investigated as part of another research study in

which healthy subjects had been screened for occult blood in the stool. Their ages ranged from 19 to 45.

1) ANO-RECTAL DISTENSION REFLEX

Method

A deflated party balloon mounted on a firm catheter was well lubricated and passed into the lower rectum. Air was then introduced into the balloon using a syringe attached to the catheter. The air was introduced rapidly in 50 ml. increments, each over 1 second. Measurement of anal canal pressure at 1.5 cm. from the anal verge was made using a miniature water filled balloon (0.3 x 0.7 cm.) connected via polythene tubing to a pressure transducer (Druck C-0004/21). A record was made of pressure changes with stepwise increase in rectal volume using a Devices MX4 recorder on heat sensitive paper.

Results

Twenty women were studied. All showed a normal response to rectal distension with a prompt fall in anal canal pressure (Figure 6a-b). These findings were regarded as being evidence of an intact neuromuscular plexus in the ano-rectum and excluded Hirschsprung's disease as a cause of the patients symptoms.

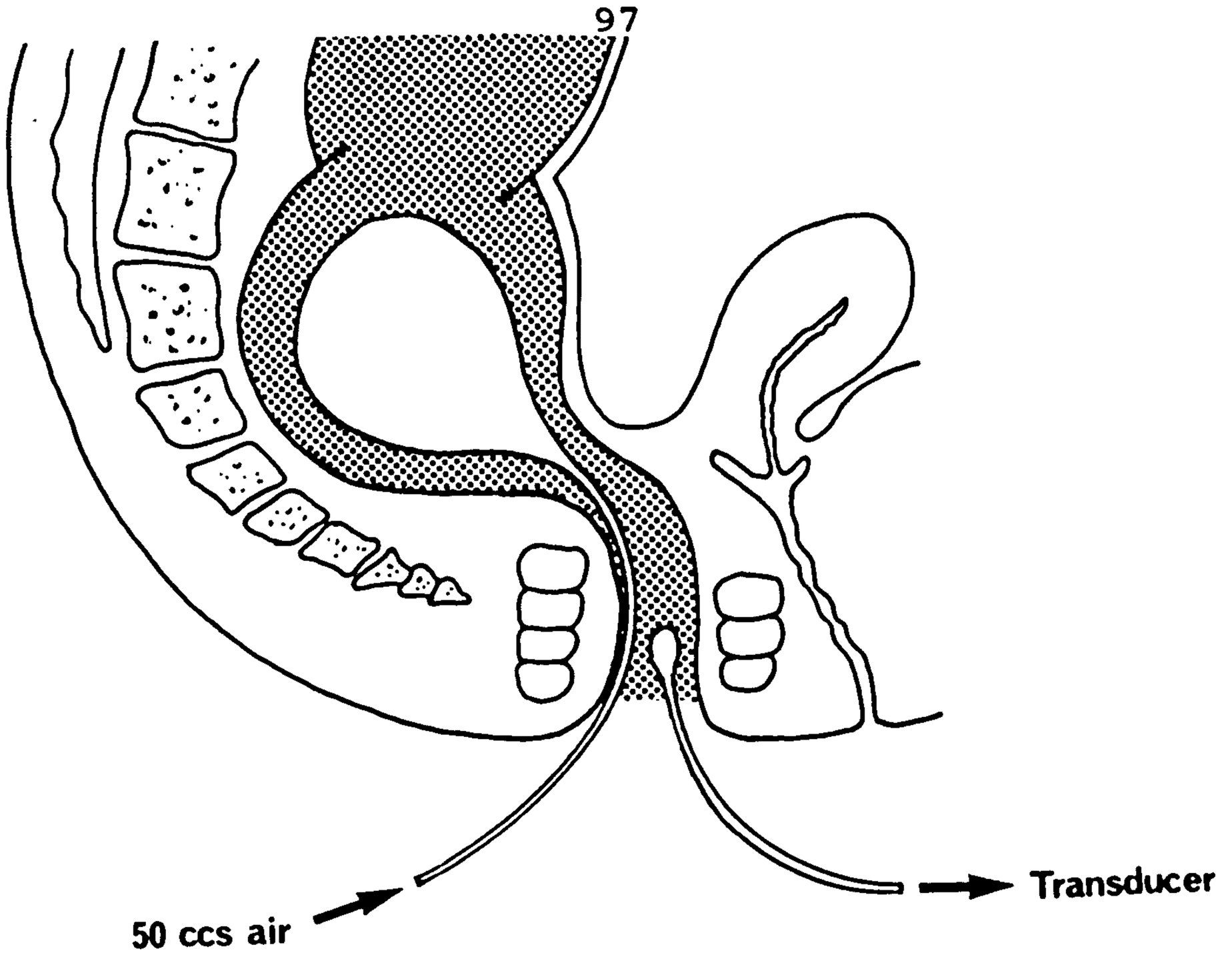


FIGURE 6a. METHOD OF MEASURING THE ANO-RECTAL DISTENSION REFLEX. The intra-rectal balloon is filled rapidly with air using a syringe in 50cc. increments. Pressure within the anal canal is recorded by means of a miniature latex balloon which is connected via a closed water filled system to the pressure transducer.

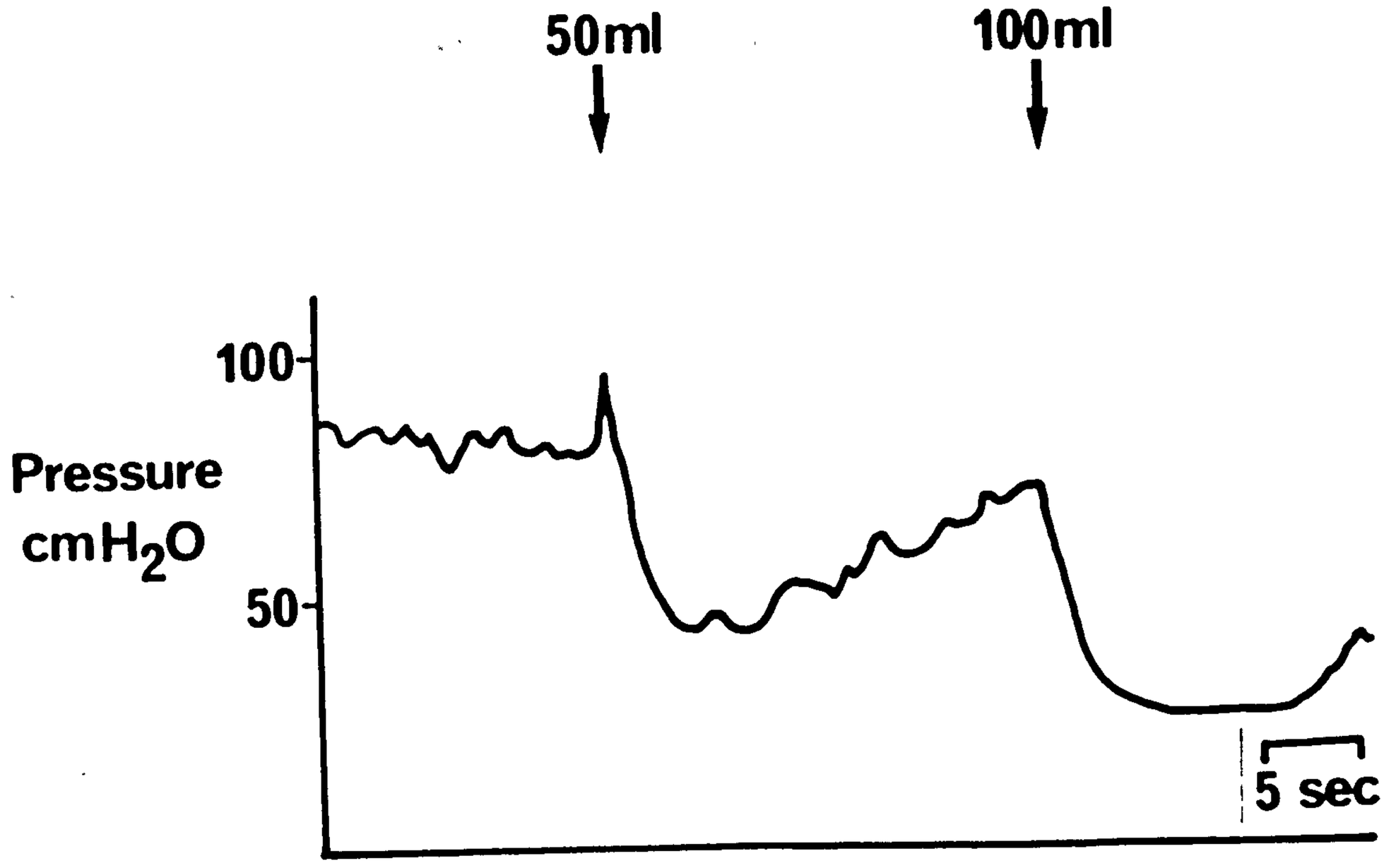


FIGURE 6b. NORMAL ANO-RECTAL DISTENSION REFLEX. This recording shows a continuous pressure trace from the anal canal at 1.5 cm from the anal verge. With successive infusions of air into the rectal balloon there is an immediate and sustained reduction in anal canal pressure caused by inhibition of the internal anal sphincter.

2) RECTAL BALLOON EXPULSION

Methods

The balloon used for this part of the study was a small childrens party balloon with a deflated diameter of 3 cm. This balloon was mounted on a firm plastic catheter so as to produce an elliptical shape when distended. The plastic catheter terminated in a 3 way tap for the introduction of water and was tied via a pulley system to a small tray holding weights (Figure 6c). When inflated with 50 ml of water the dimensions of the balloon were 5.0 x 3.5 cm. (Figure 6d). This resulted in a firm bolus which was too large to pass through the normal anal canal unless compressed and elongated during straining efforts.

Fifteen patients and 15 controls were studied by introducing the well lubricated and deflated balloon into the lower rectum whilst the patient lay in the left lateral position. The balloon was then inflated with 50 ml. of water and the patient then asked to expel it as if during normal defaecation. For the initial attempt without added weights, the subjects were allowed 5 straining efforts during 1 minute. If this proved impossible, weights were applied via the pulley and raised by increments of 50 gm. until expulsion occured. The force was not applied continuously, but after two attempts to expel the balloon at each weight the subject was allowed to relax briefly whilst the weight was removed. The position of the pulley was adjusted so that the expulsive force was applied in the long axis of the anal canal. After the straining attempt, whether successful or



FIGURE 6c. BALLOON USED TO TEST ABILITY TO DEFAECATE.
A simple rubber party balloon was used and either inflated with air to test the recto-sphincteric reflex or filled with 50cc of water to imitate a faecal bolus.

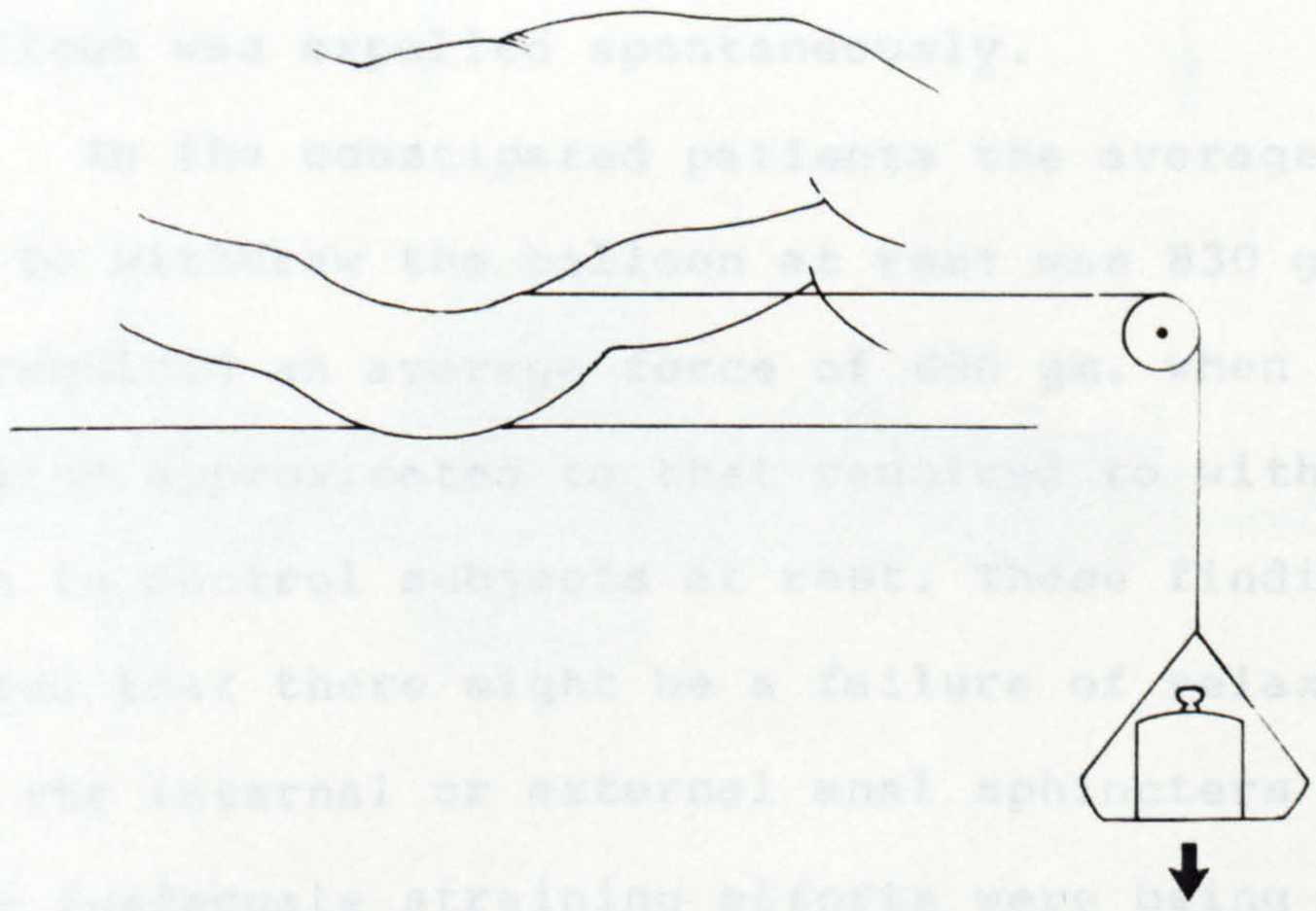


FIGURE 6d. POSITION ADOPTED FOR BALLOON EXPULSION STUDIES.
The end of the balloon was tied to a small tray holding weights via a pulley. The resulting force was applied in the long axis of the anal canal.

not, the weight needed to expel the balloon whilst the subjects were resting was examined. For this test the subjects were asked not to resist the passage of the balloon. Weights were increased again by increments of 50 gm. with each new weight applied for only 10 seconds.

Results

None of the 15 patients with slow transit constipation was able to expel the balloon whereas all the control subjects could do so. The ability of the constipated patients to expel the balloon was not affected by posture and they could not expel it in either the sitting or squatting positions. In the normal subjects (Figure 6e) an average weight of 700 gm. was needed to withdraw the balloon when relaxed. When they srained no weight was required and the balloon was expelled spontaneously.

In the constipated patients the average weight needed to withdraw the balloon at rest was 830 gm., but they still required an average force of 690 gm. when straining. This value approximated to that required to withdraw the balloon in control subjects at rest. These findings suggested that there might be a failure of relaxation of either the internal or external anal sphincters on straining or that inadequate straining efforts were being made so that intra-rectal pressure was not high enough to expel the balloon.

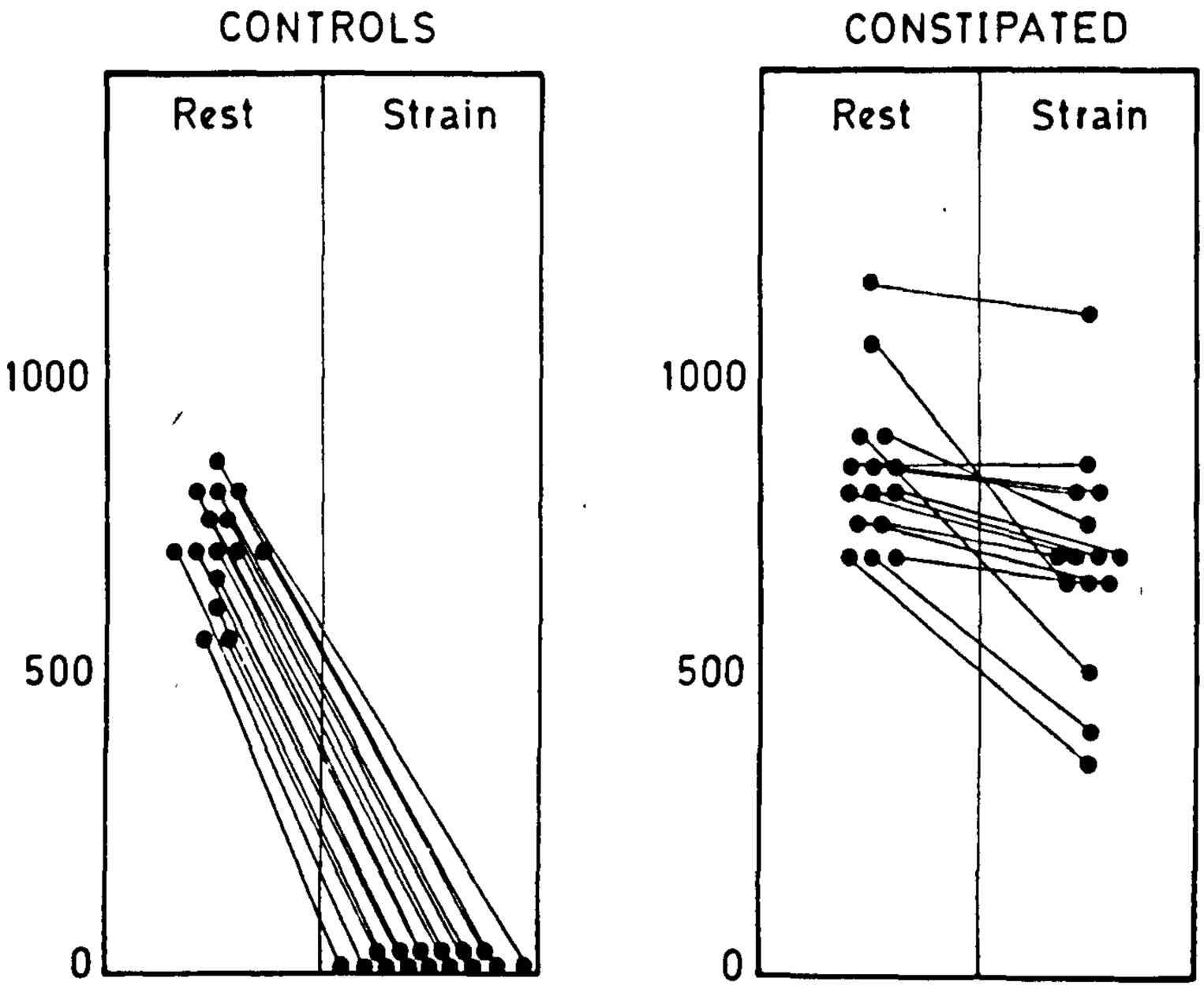


FIGURE 6e. WEIGHT NEEDED TO EXPEL A BALLOON FROM THE RECTUM IN CONSTIPATED PATIENTS AND CONTROLS. The results shown are for the weight applied via the pulley during straining attempts and when relaxed.

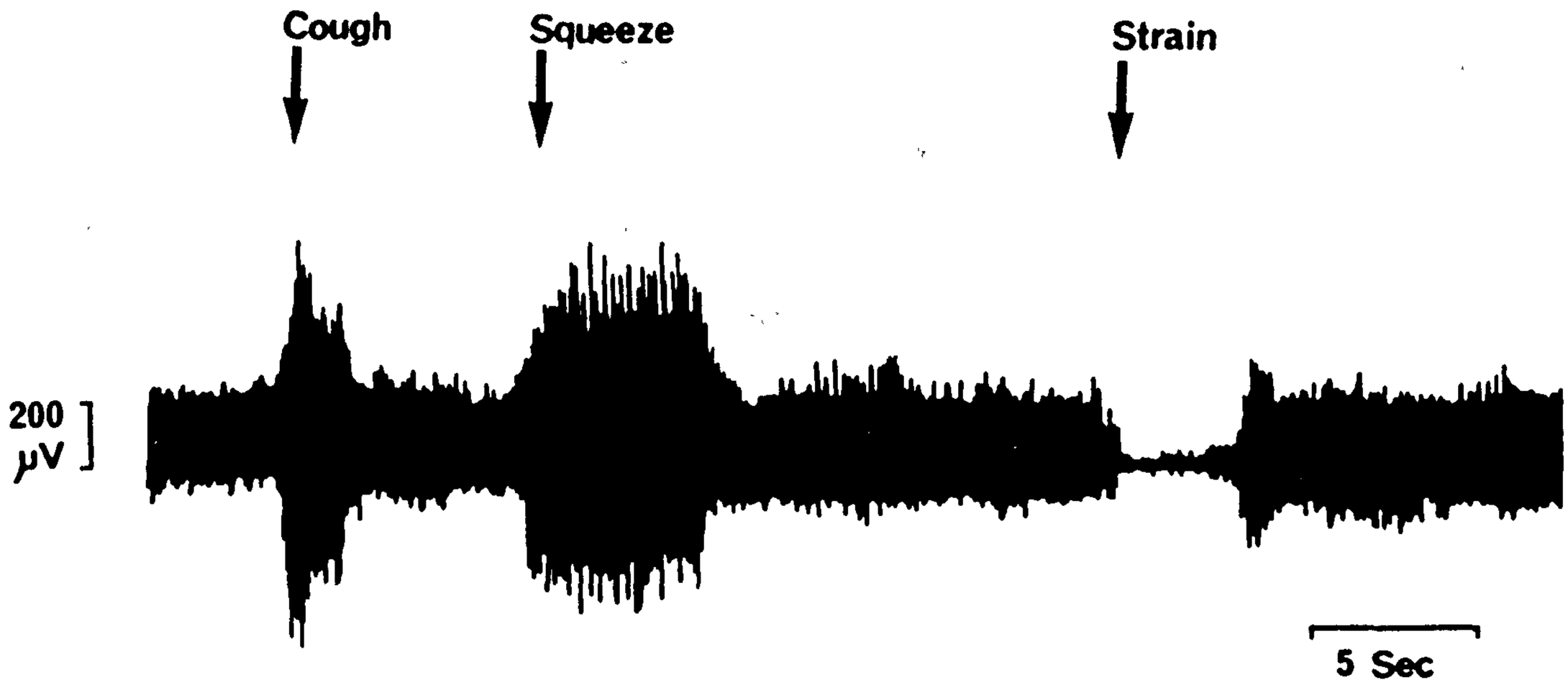


FIGURE 6f. NORMAL ELECTROMYOGRAPHY.
Electrical activity recorded from the superficial external sphincter in a normal subject at rest, during maximal voluntary contraction and on simulated defaecation.

3) MEASUREMENT OF INTRA-RECTAL AND ANAL CANAL PRESSURE DURING STRAINING.

Method

To record straining efforts a miniature balloon similar to that used to measure the ano-rectal reflex was placed inside the larger water filled balloon and attatched to a pressure recorder as described in (1) above. Pressure changes could then be determined whilst the constipated subjects attempted to expel the water filled balloon. Using a similar balloon, measurements of anal canal pressure during attempts at balloon expulsion were made in the same subjects. These readings were made at 1, 2, 3, and 4 cm. from the anal verge. The position of the pressure recording balloon was determined by means of 1 cm. divisions drawn on the catheter. At each level resting and straining pressures were noted. One minute was allowed after each straining effort and after rearrangement of the balloon in the anus for the resting pressure to equilibrate.

Results

Rectal straining pressures were recorded in 10 patients and rose by a mean of 70 ± 9 (s.e.m.) cm H2O. (see table 6a) The range was 30-120 cm H2O. These results indicated that the majority of the patients seemed to make genuine attempts to expel the balloon.

The anal canal pressure recordings showed a marked rise in anal canal pressure on attempted defaecation and that the mean maximum anal pressure was twice that of the

Table 6a

Anal canal pressures recorded at rest and during simulated defaecation in 10 patients with slow transit constipation. All figures in cm H2O.

	1 cm		2 cm		3 cm		4 cm		Rectum	
	Rest	Strain	Rest	Strain	Rest	Strain	Rest	Strain	Rest	Strain
PATIENT										
1)	15	60	35	50	25	50	15	130	-	120
2)	60	95	100	150	25	125	20	100	-	100
3)	100	200	75	150	10	60	0	40	-	40
4)	50	*	100	125	100	105	40	75	-	30
5)	50	*	150	220	80	145	40	60	-	60
6)	125	190	80	235	25	125	0	80	-	55
7)	40	*	100	175	50	100	25	75	-	80
8)	75	150	125	125	90	110	45	60	-	80
9)	25	*	110	90	110	60	40	50	-	75
10)	75	125	50	100	20	60	5	50	-	60
MEAN	52	136	90	142	53	94	23	72	-	70
s.e.m.	12	22	13	18	12	11	6	12	-	9

(* Balloon fell out during straining)

rectal pressure. This pressure gradient would prevent the passage of a stool into the anal canal and suggested a possible reason for failure of balloon expulsion was a disorder of the anal sphincters.

4) ELECTROMYOGRAPHY OF THE PELVIC FLOOR

Method

Electromyographic (EMG) recordings were made of both puborectalis and external sphincter activity in 15 patients with slow transit constipation. These recordings were made for each muscle seperately; at rest, during attempts at balloon expulsion, during coughing and during maximal voluntary contraction of the anal sphincters. Recordings were also made of straining attempts with no balloon in situ. In those patients who would permit it, an attempt was made to totally inhibit the external sphincter muscle by increasing the volume in the balloon to the limit of tolerance. Recordings were made with a Medelec MS6 EMG apparatus and a concentric needle electrode. The electrical activity was displayed on a screen and permanant records taken as required onto light sensetive paper (Kodak Linagraph type 1895). Internal calibration was provided in the apparatus and extraneous electrical activity filtered out.

The needles were inserted with the patient lying in the left lateral position. A needle electrode was introduced without local anaesthetic through the skin 1 cm. behind the anus and directed upwards until the area of maximal

electrical activity was encountered in the superficial anal sphincter. This position was regarded as representative of the external sphincter. The needle was then removed and reintroduced slightly further back and to one side. On the second occasion a gloved finger was placed into the anus until the fingertip lay at the ano-rectal junction on its posterior aspect. Using the other hand the needle was then advanced about 4 cm towards the ano-rectal junction where the puborectalis muscle could be palpated. Electrical activity could be seen to increase as the superficial external sphincter was passed, to disappear, and then to return as the puborectalis was entered. The position of maximum electrical activity was again sought and regarded as representative of puborectalis activity.

Results

In all cases a normal pattern of resting activity was seen with continuous firing of action potentials. There was also a normal response in all cases to cough with a reflex increase in electrical activity. Good responses were also seen to maximal voluntary contraction. However in none of the patients could relaxation be demonstrated on attempted defaeation whether the balloon was present or not. In contrast to normal subjects there was a paradoxical increase in activity which in some cases continued after straining efforts had ceased. (Table 6b and Figures 6f-h).

In only one patient out of 6 who cooperated could complete inhibition of the external sphincter be produced by maximal distension of the rectum. The others showed

continuous or increasing activity as the balloon was further distended (Figures 6i-j). These results in conjunction with the anal canal pressure measurements, which they complement, suggested that the a possible reason for failure of balloon expulsion in the model of defaecation used was abnormal behaviour of the striated muscles of the pelvic floor.

Table 6b.

RESULTS OF ELECTROMYOGRAPHY

The number of patients who showed increased electrical activity (++) no change (+) or reduced activity (o) on simulated defaecation.

Muscle tested	Electrical activity		
	++	+	o
PUBO-RECTALIS	15	0	0
EXTERNAL SPHINCTER	12	3	0

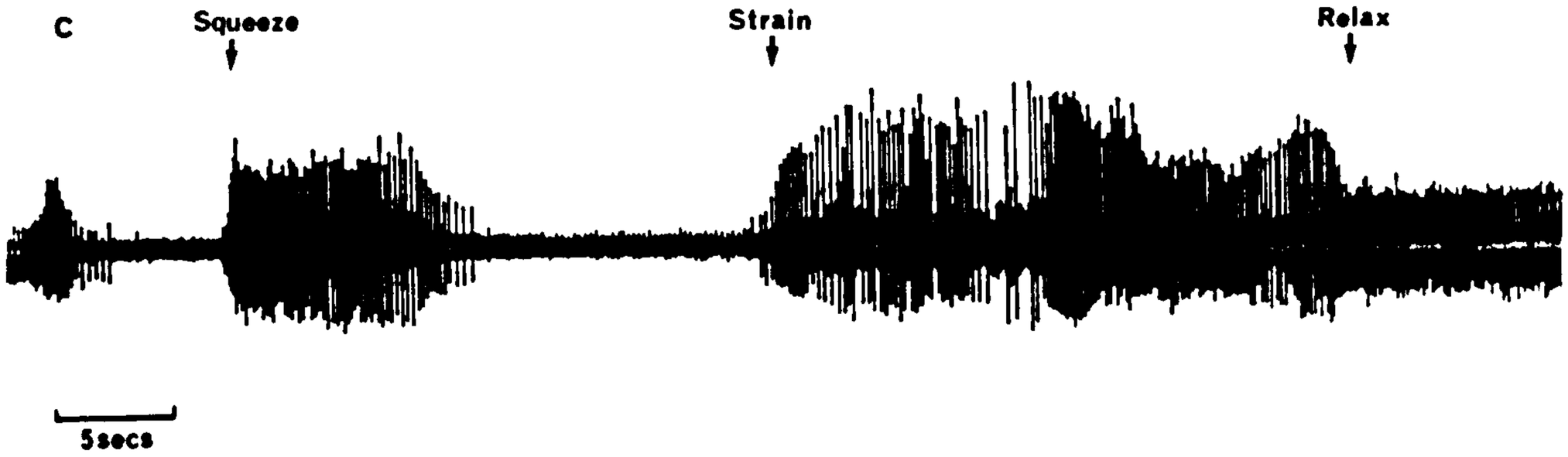


FIGURE 6g. ELECTROMYOGRAPHY IN A CONSTIPATED PATIENT (1). Electrical activity recorded from the superficial external sphincter in a patient with slow transit constipation. There is a normal response to cough and squeeze. However on straining there is marked abnormal electrical activity which continues after relaxation.

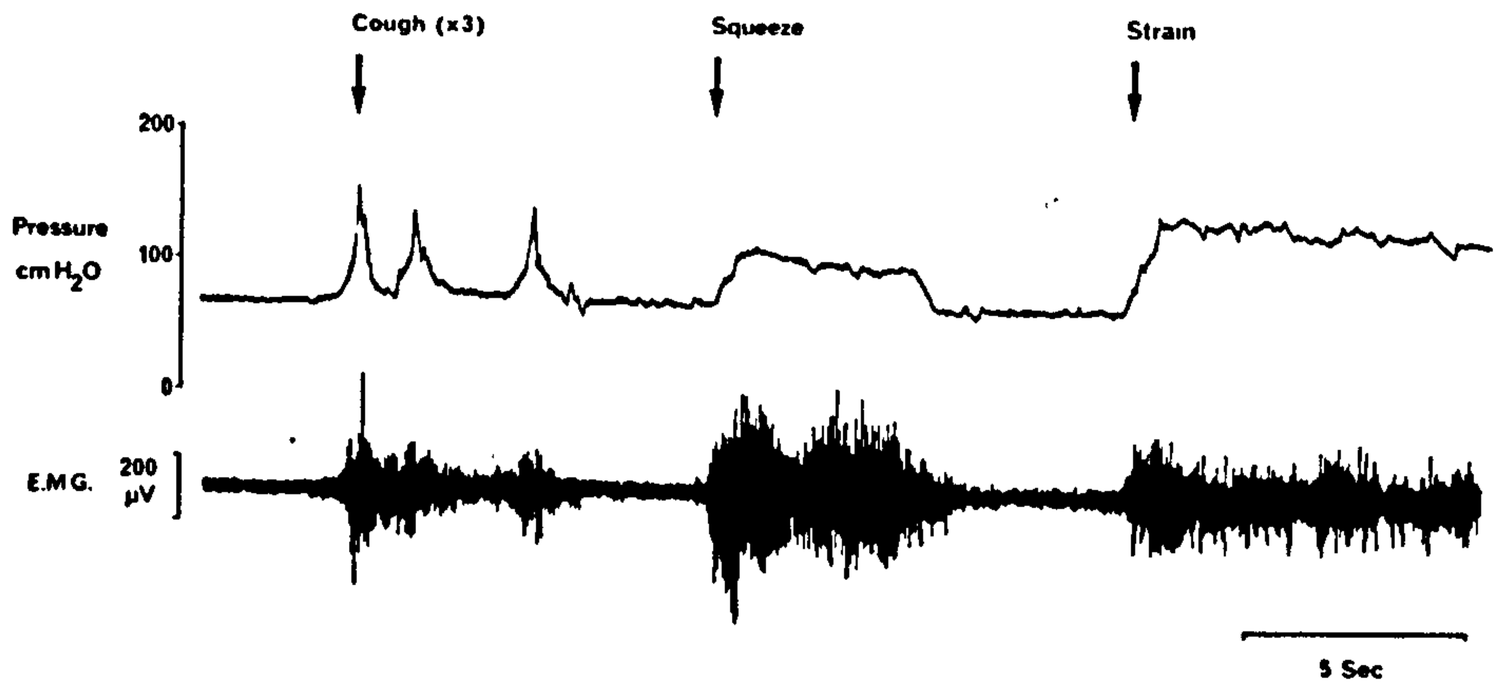


FIGURE 6h. ELECTROMYOGRAPHY IN A CONSTIPATED PATIENT (2). Electrical activity from the superficial external sphincter in a constipated patient correlated with anal canal pressure recorded 1.5 cm. from the anal margin. Abnormal electrical activity on straining is associated with a rise in anal canal pressure.

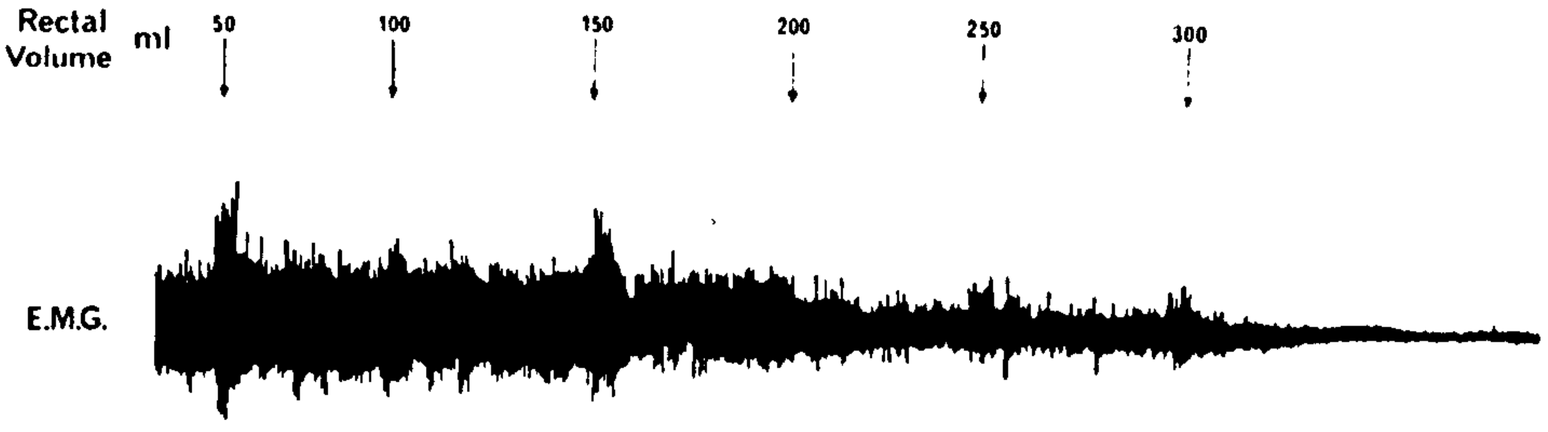


FIGURE 6i. ELECTROMYOGRAPHY ON MAXIMAL RECTAL DISTENSION (1). Continuous record of electrical activty from the external sphincter in a patient with constipation during progressive rectal distension by an air filled balloon. As the limit of tolerence is reached all activity ceases.



FIGURE 6j. ELECTROMYOGRAPHY ON MAXIMAL RECTAL DISTENSION (2). Pattern of external sphincter activity seen in 5 of the 6 patients examined. Despite distension beyond the point at which pain was felt no sphincter inhibition occurred.

5) THE BALLOON PROCTOGRAM

The position necessarily adopted for simulated defaecation in the previous studies was unphysiologial in that humans do not defaecate lying on their side. In addition it may have been embarassing for the patients, many of whom were young women, to have to attempt "defaecation" with onlookers present (though the control subjects seemed to have no difficulty). For these reasons it was felt that the balloon expulsion test needed to be modified. A radiological technique was therefore developed so that simulated defaecation could be performed on a mock lavatory seat in the sitting position normally adopted. It was also hoped to thus define the anatomy of the anal canal and rectum during straining efforts.

Method

The balloon for this study was a modified teat ended condom with a soft rubber catheter attached to the distal end and the proximal end tied off. The balloon was designed to hold 100 cc. of fluid. When filled the dimensions were approximately 3.5 x 14.0 cm. (Figure 6k). With the patient lying in the left lateral position the deflated and well lubricated balloon was introduced into the rectum. 100 cc. of a barium water mixture was then introduced into the balloon via the catheter which was afterwards sealed. It was found that the barium suspension used for barium enema examinations was too viscous to pass through the catheter. A 50/50 mixture of this suspension

with tap water produced a suitable contrast medium and as barium is heavier than water the weight of a filled balloon was approximately 150 gm. This was conveniently close to the weight of the average western stool (Burkitt et al. 1972).

Subjects were then asked to sit on a perspex radioluscent lavatory seat (Figure 61) in the position they would normally adopt for defaecation. A radio-opaque marker was placed over the pubis. In some patients gentle traction was applied to the balloon via the catheter so as to bring the narrow neck down into the anal canal. The seat was placed in a recess in the radiography room with curtains drawn to allow some privacy. Two lateral pelvic radiographs were then taken. One with the patient resting and the other during attempted defaecation of the balloon.

From these radiographs it was possible to mark the level of the muscular pelvic floor between the pubis and coccyx and to measure the ano-rectal angle (Figures 6m-o). If the two films were superimposed tracings could be made to record perineal descent as well as changes in the ano-rectal angle or anatomy of the ano-rectum during straining.

Results

Ten patients with slow transit constipation were studied. None could expel the balloon. The mean ano-rectal angle in these patients was 94 ± 3.2° (s.e.m.) at rest and 92 ± 3.6° during attempted defaecation. There was minimal perineal descent with a mean distance from the ano-rectal junction to the pubo-coccygeal line of 3.2 ± 0.5 cm. at rest and 3.4 ± 0.5 cm. on straining. Examples of the films

obtained are shown in Figures 6p-q. These pictures confirmed the finding of the expulsion tests using the smaller balloon and demonstrated that the ano-rectal angle was maintained during attempted defaecation suggesting a failure of relaxation of the puborectalis muscle.

ADDITIONAL STUDIES ON OTHER PATIENTS

a) Ballon expulsion after colectomy (50cc.).

Seven patients with slow transit constipation who had already undergone sub-total colectomy with ileo-rectal or caeco-rectal anastamosis were examined. In 5 of them constipation had been relieved to a greater or lesser extent. Two of these now had more than 5 bowel actions daily. The results at rest and on straining in this group were as follows.

	Rest	Strain	
1)	1300	1200	
2)	700	800	
3)	700	800	Weights applied to expel
4)	800	850	the balloons (gm.)
5)	400	650	
6)	550	850	
7)	400	600	

These results suggested that any pelvic floor problem had not been affected by colectomy. Failure of colonic propulsion on straining could therefore play no part in the apparent defaecatory disorder. The patients had mostly been helped by operation and two had diarrhoea. The success of colectomy may have resulted from the development of semi-formed stool which was easier to pass.

b) Balloon expulsion test in other types of constipation.

Seventeen other constipated patients were studied with the 50cc. balloon to determine whether the defaecatory problem was confined to patients with slow transit constipation. Eight had idiopathic megacolon and 9 a normal barium enema and normal colonic transit time (irritable bowel syndrome).

Of the 8 patients with idiopathic megacolon none could expel the balloon, and the results were as follows:

	Rest	Strain	
1)	750	500	
2)	750	650	
3)	800	500	
4)	850	850	Weights applied to expel the balloons (gm.)
5)	800	450	
6)	750	600	
7)	1500	550	
8)	650	550	

Of 9 patients with the irritable bowel syndrome 7 passed the balloon. The weights applied during resting and straining in the other 2 were as follows:

	Rest	Strain
1)	750	300
2)	750	500

These results suggest that difficulty in defaecation is not confined to patients with a normal barium enema and slow intestinal transit time. However there is a problem in assessing the results in those patients with a grossly dilated rectum which will be discussed below.

c) The balloon proctogram in patients with faecal incontinence and other pelvic floor problems.

Previous studies discussed in the introduction to this chapter have suggested that the puborectalis is of

paramount importance in maintaining faecal continence. During the balloon proctogram tests the oportunity was taken to examine patients with other types of pelvic floor disorder. It was felt this was important both to confirm the usefulness of the technique in clinical practice and to investigate further the behaviour of the pelvic floor. It would be expected that patients with neuropathic faecal incontience might show exactly the opposite picture to those with severe constipation.

Twelve such patients were therefore studied before and after the operation of post-anal repair which is meant to shorten the puborectalis muscle and thus restore the ano-rectal angle (Parks 1975). Before surgery all the patients found great difficulty in retaining the balloon. Pictures were only taken at rest as on attempted expulsion the balloon was rapidly extruded before the film could be exposed. Comparison of the resting films before and after operation showed that the mean ano-rectal angle had reduced from 135 ± 4.4°(s.e.m.) to 103 ± 4.1°, and the distance between the ano-rectal junction and pubo-coccygeal line from 4.6 ± 0.4 cm. to 3.1 ± 0.4 cm. (Figures 6r-s).

These findings matched the clinical results of the operation (all patients had faecal continence restored) and confirmed that the balloon proctogram was recording a clinically useful picture of pelvic floor muscle activity. This was further supported by examination of patients who complained of difficulty in defaecation because of rectal prolapse or the descending perineum syndrome (Figures 6t-u).

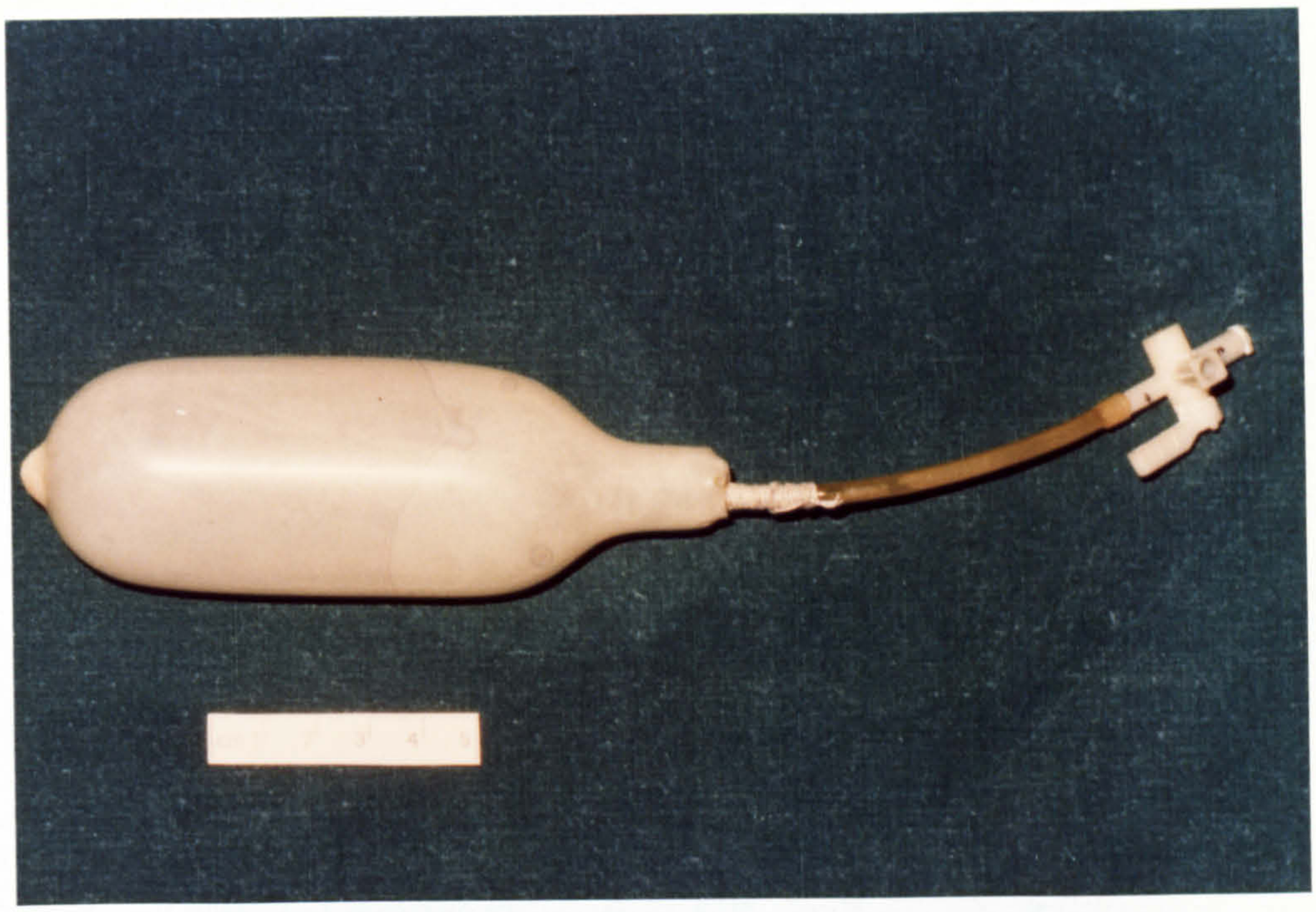


FIGURE 6k. BALLOON USED FOR DEFAECATING BALOON PROCTOGRAM.
100 cc. of a barium/water mixture is introduced via the catheter after the deflated balloon has been introduced into the rectum.

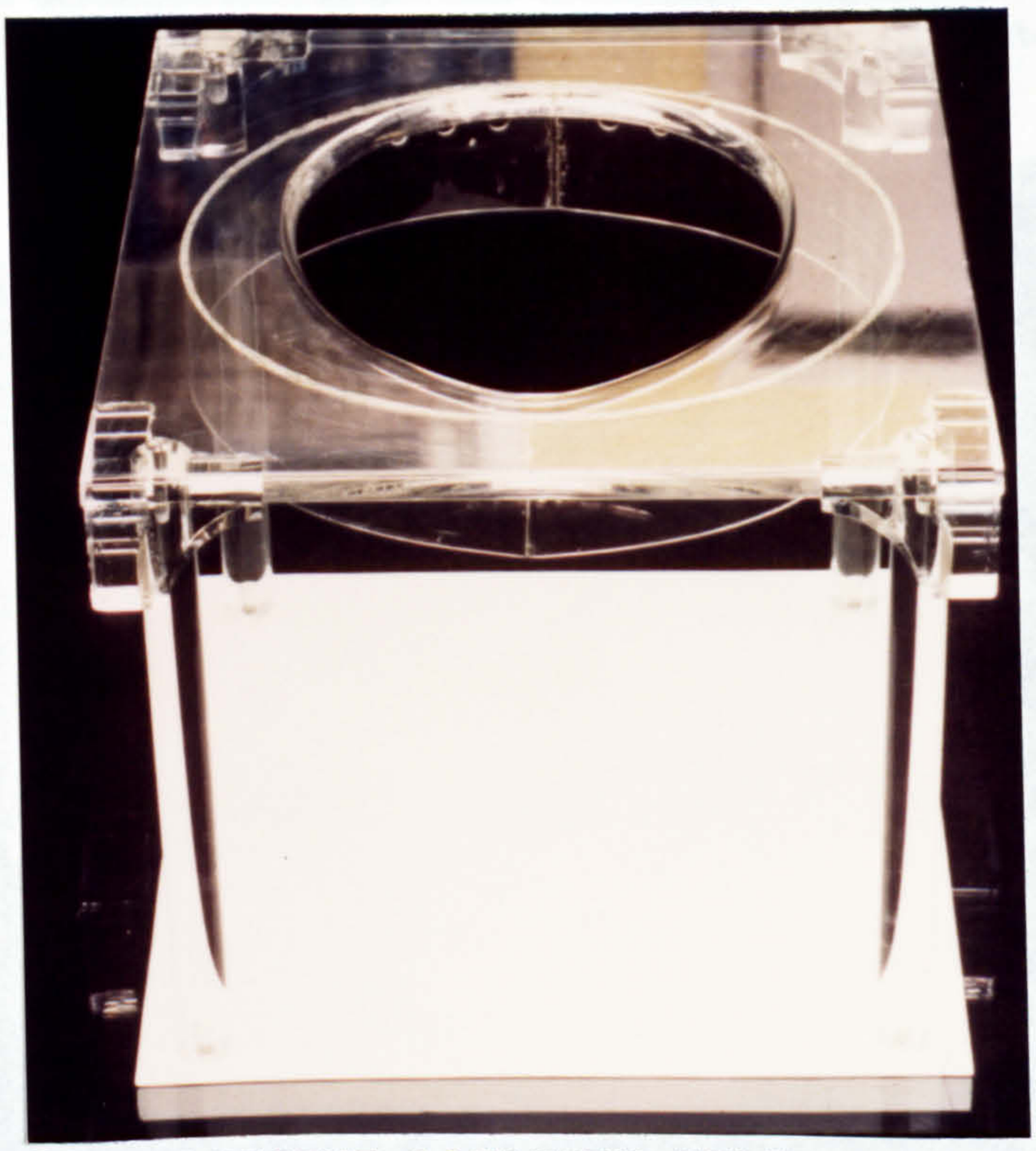


FIGURE 6l. RADIOLUSCENT LAVATORY SEAT.
This mock lavatory seat was designed for simulated defaecation in the position usually adopted by Europeans. The top is made from perspex which causes only minimal shadowing on the x-ray plate.

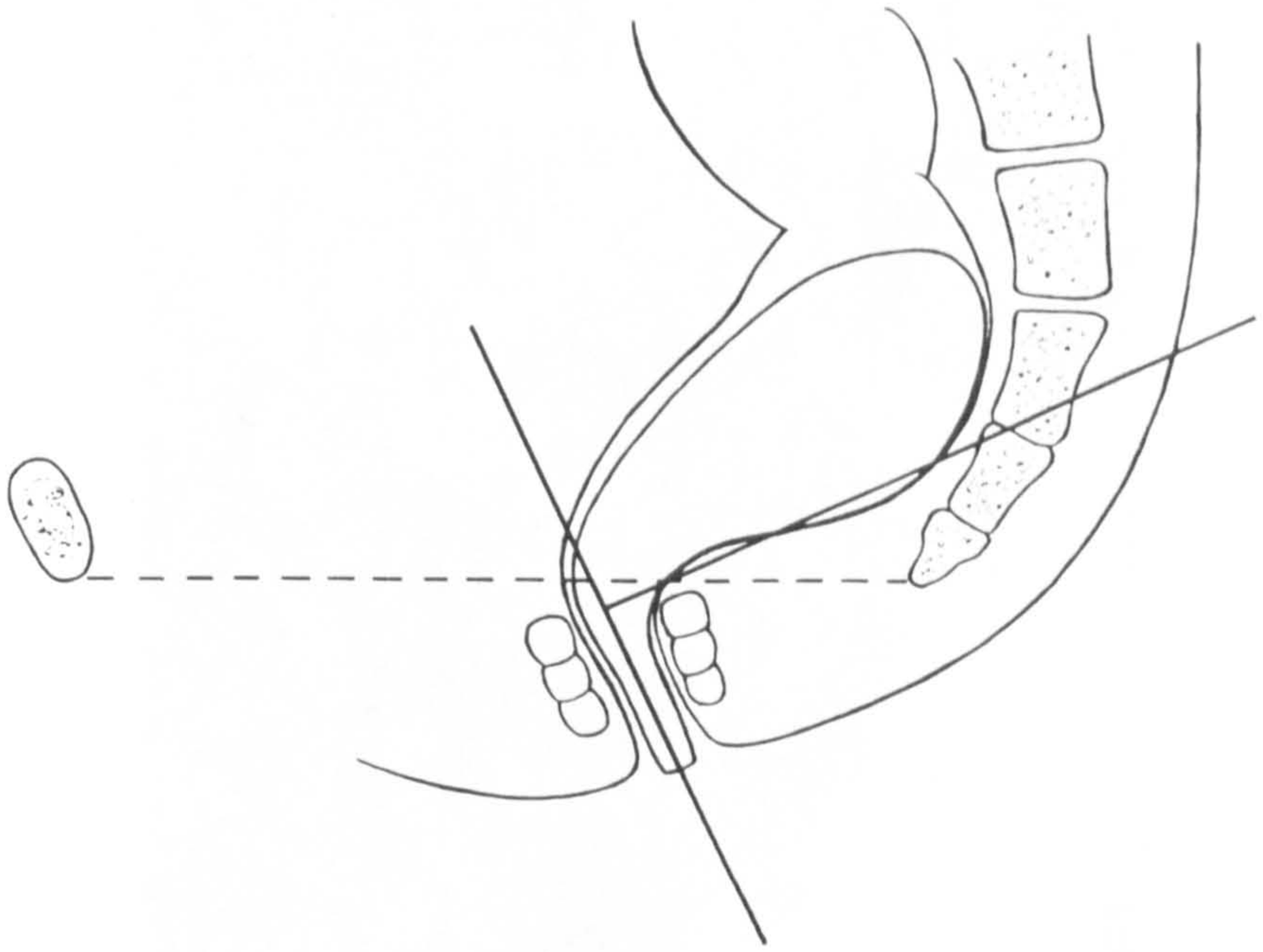


FIGURE 6m. MEASUREMENT OF ANO-RECTAL ANGLE.
This diagram shows the position of the balloon filling the lower rectum and the anal canal. The pelvic floor muscles lie close to the dotted line (pubo-coccygeal line). The ano-rectal angle is that between the lower border of the distal rectum and the midline of the anal canal in its luminal axis.

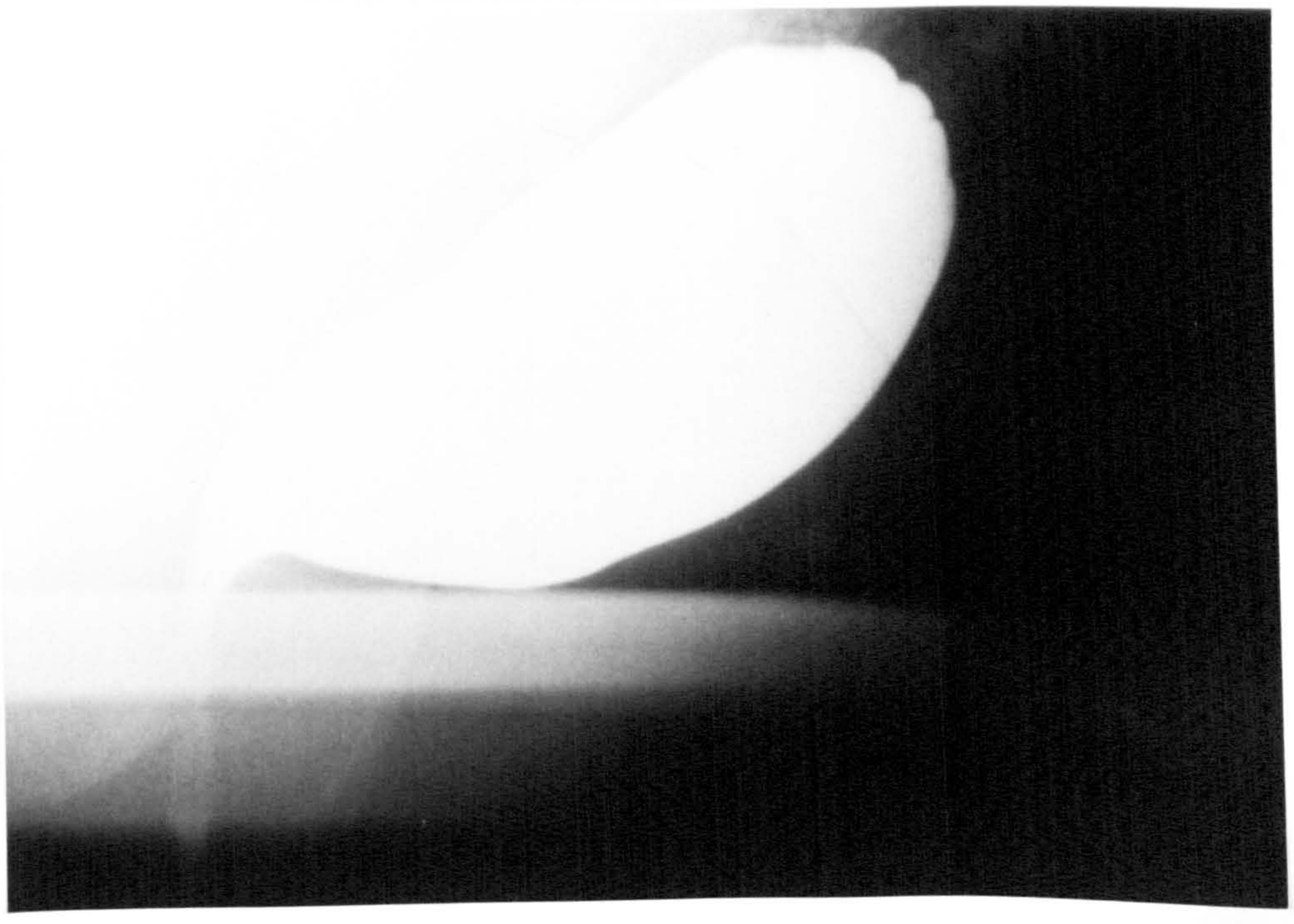


FIGURE 6n. BALLOON PROCTOGRAM: NORMAL SUBJECT AT REST.
This demonstrates clearly a 90° angle between the anal canal and distal rectum. The horizontal shadow below the rectum is from the perspex lavatory seat.



FIGURE 6o. BALLOON PROCTOGRAM: NORMAL DEFAECATION.
This shows a photograph taken whilst screening a normal subject. On simulated defaecation the pelvic floor was seen to descend and then the ano-rectal angle was obliterated. At the moment of defaecation illustrated the barium filled balloon is seen passing through the anal canal with minimal distortion.

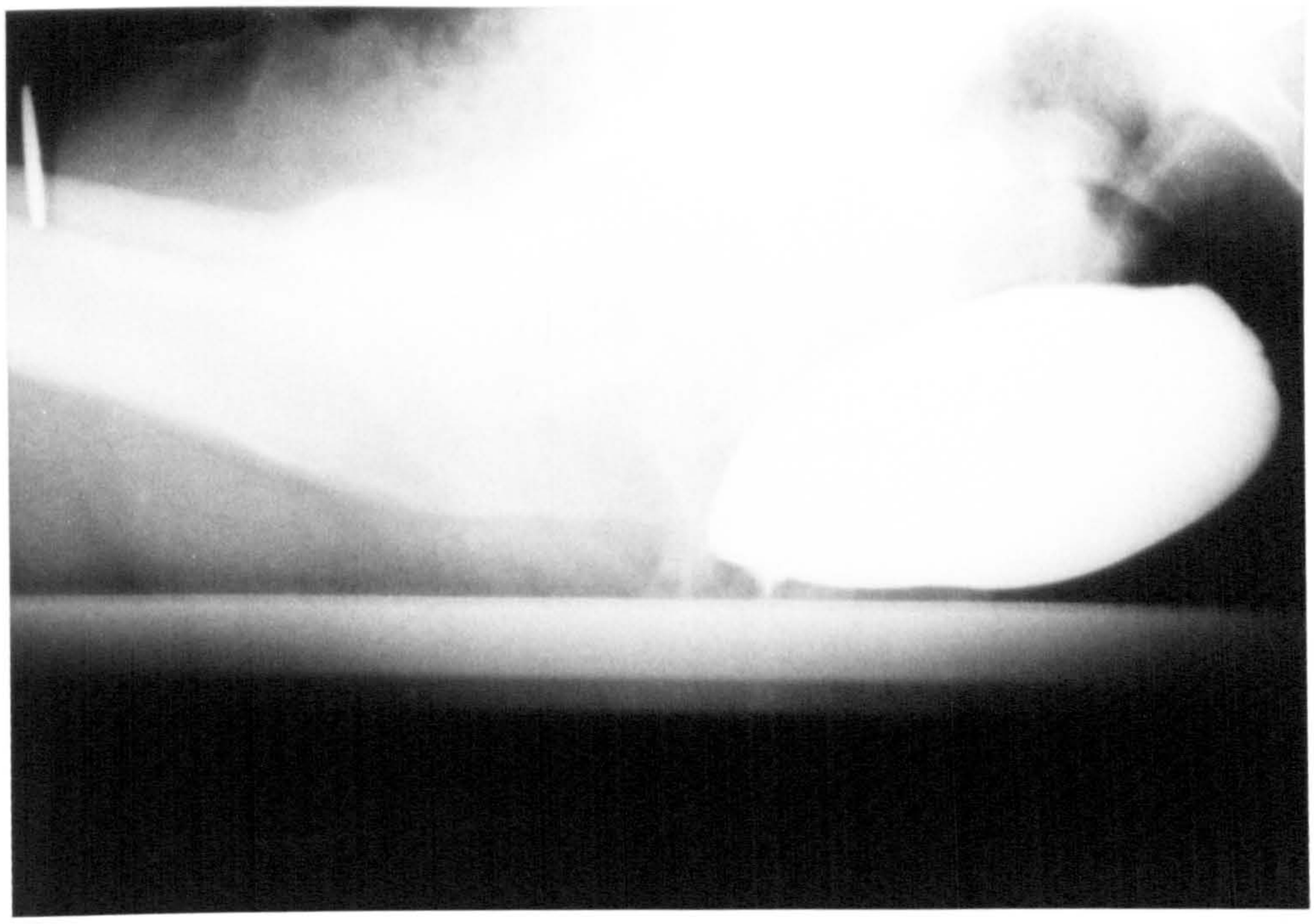


FIGURE 6p. BALLOON PROCTOGRAM: SLOW TRANSIT CONSTIPAION 1. Resting film taken from a patient with slow transit constipation. The rectum is well filled and shows a small rectocoele. The anal canal is tightly closed and the ano-rectal angle 90°.

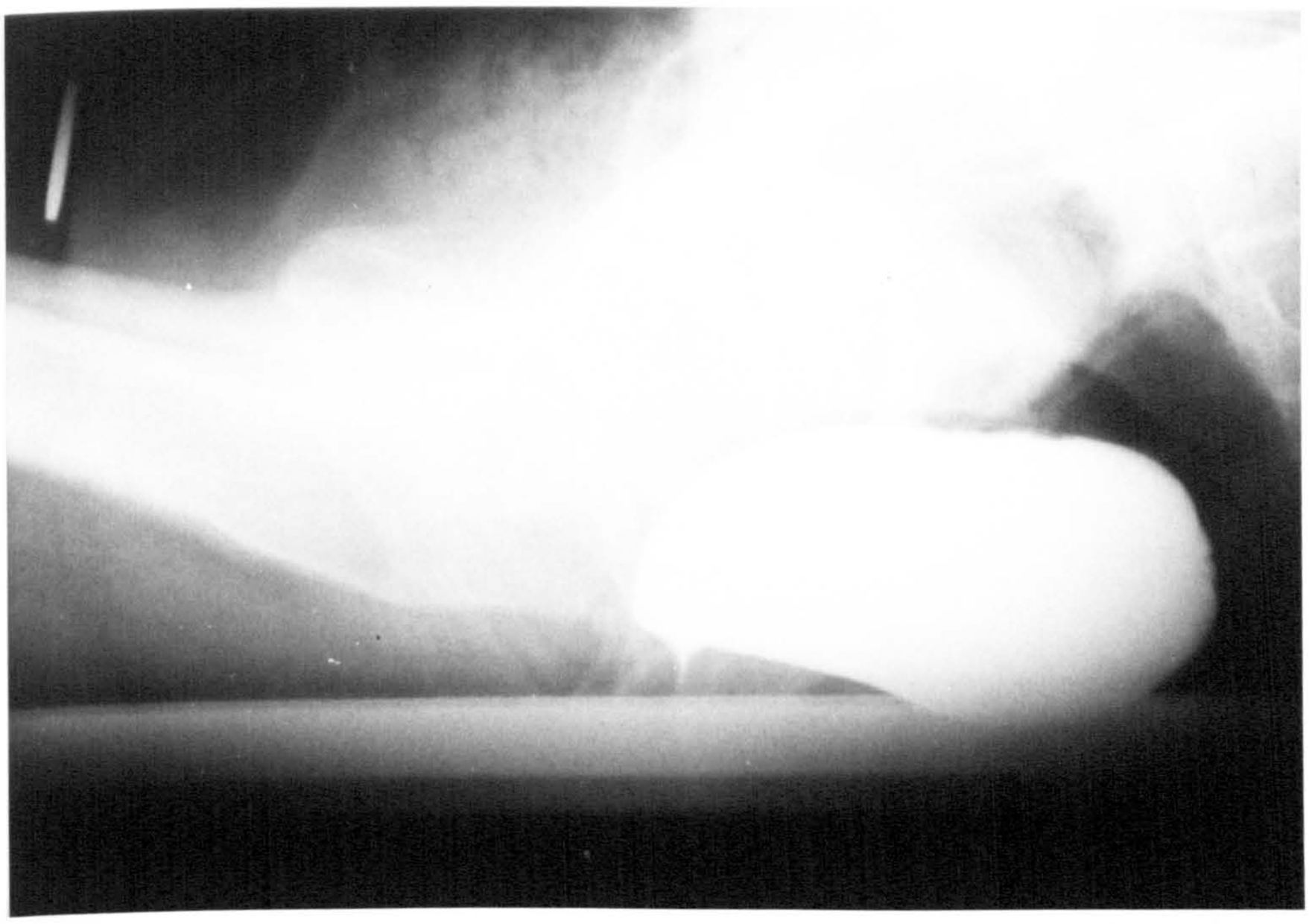


FIGURE 6q. BALLOON PROCTOGRAM: SLOW TRANSIT CONSTIPATION 2. The second film taken during straining shows the distal rectum to have descended slightly, but the anal canal remains tightly shut with the ano-rectal angle becoming more acute.

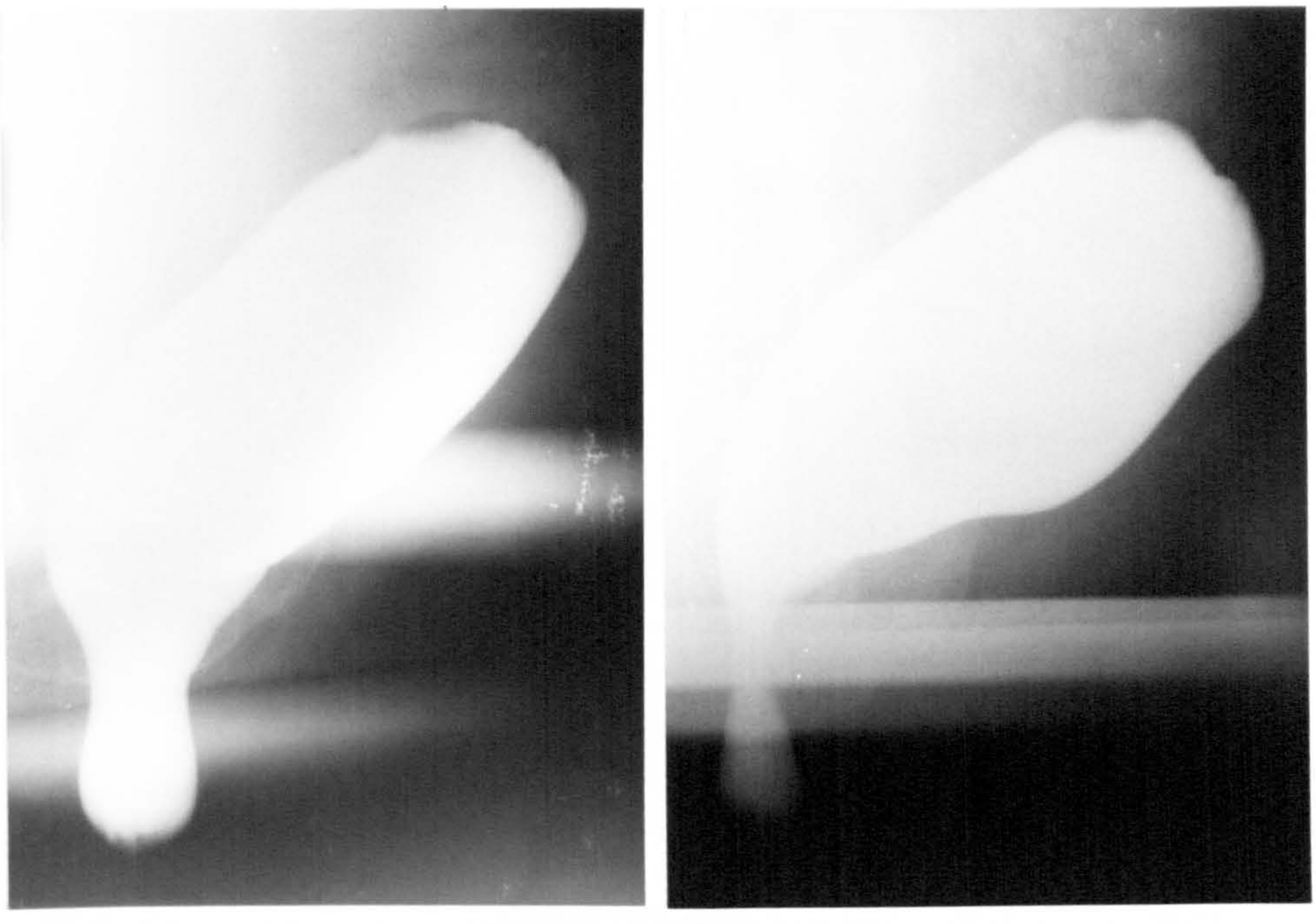


FIGURE 6r. BALLOON PROCTOGRAM: FAECAL INCONTINENCE 1. These films show the appearance of the resting proctograms in a lady of 53 before and after the operation of post anal repair.

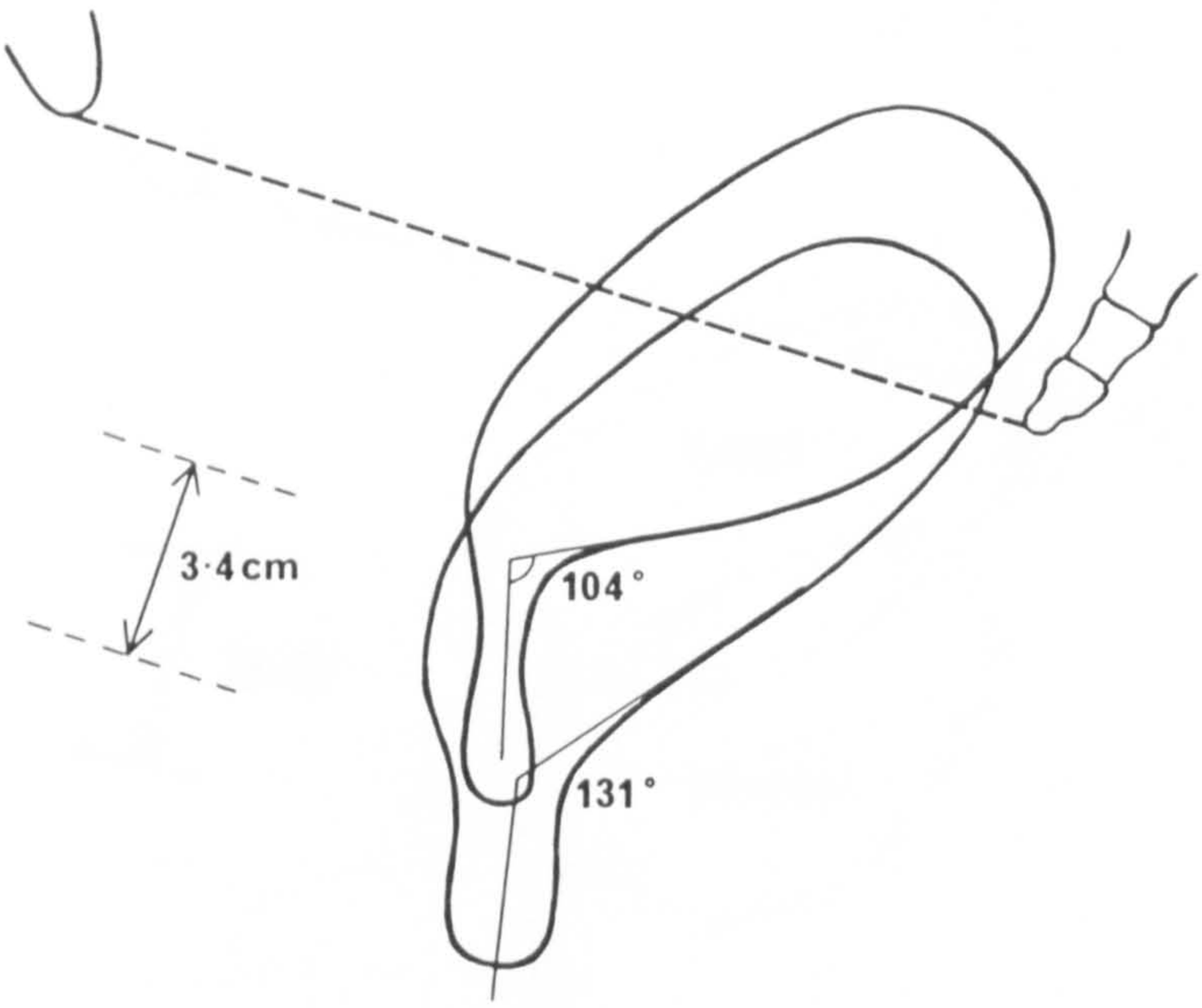


FIGURE 6s. BALLOON PROCTOGRAM: FAECAL INCONTINENCE 2. This diagram is an example of the results obtained by superimposing films from the same patient. This can be done to show the effects of straining, or the result of an operation. These traces were from the patient shown in Figure 6r above.

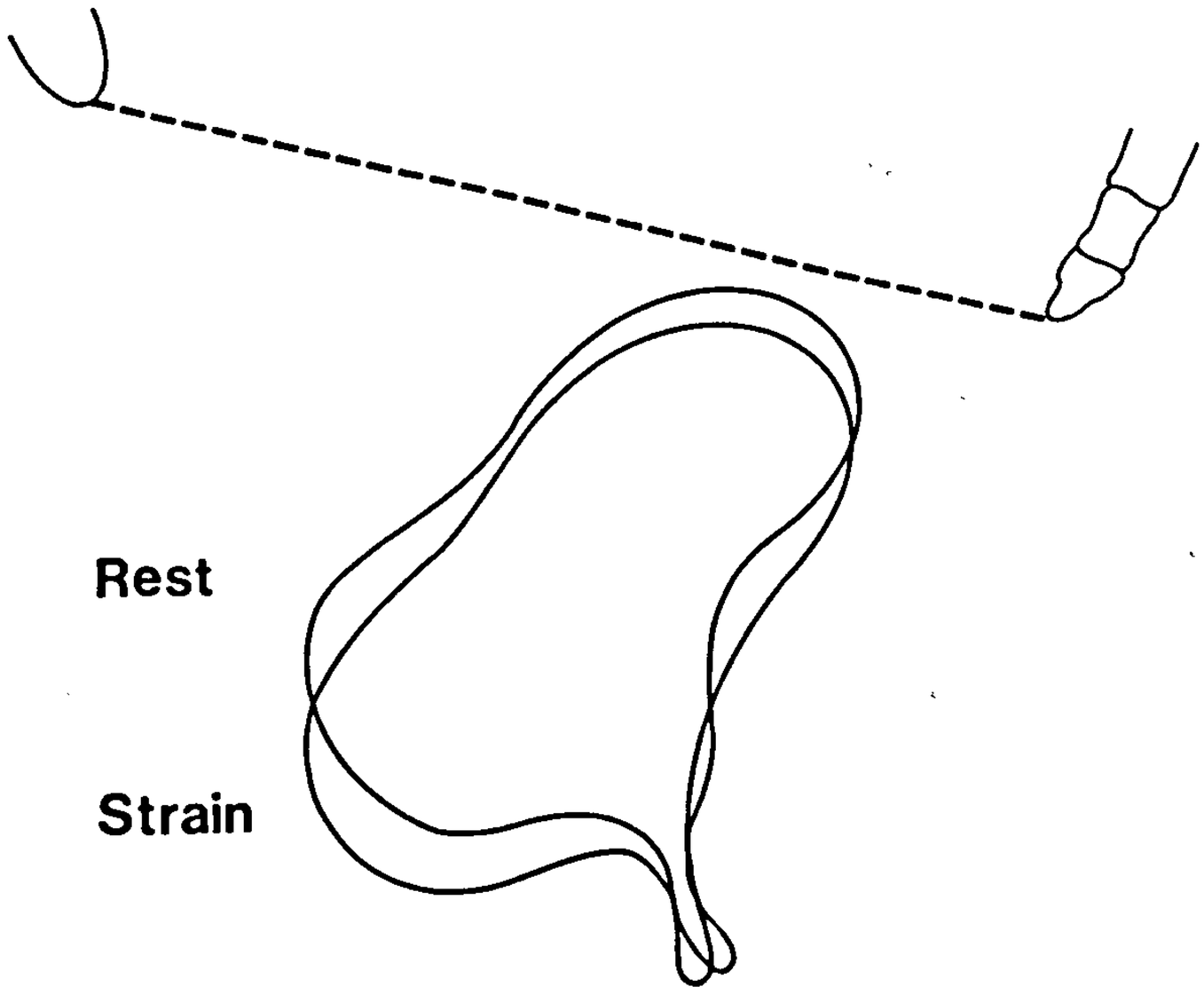


FIGURE 6t. BALLOON PROCTOGRAM: RECTAL PROLAPSE.
Example of resting and straining films from a patient with rectal prolapse. There is a huge rectocoele and on straining this distends further but there is no relaxation of the anal canal.

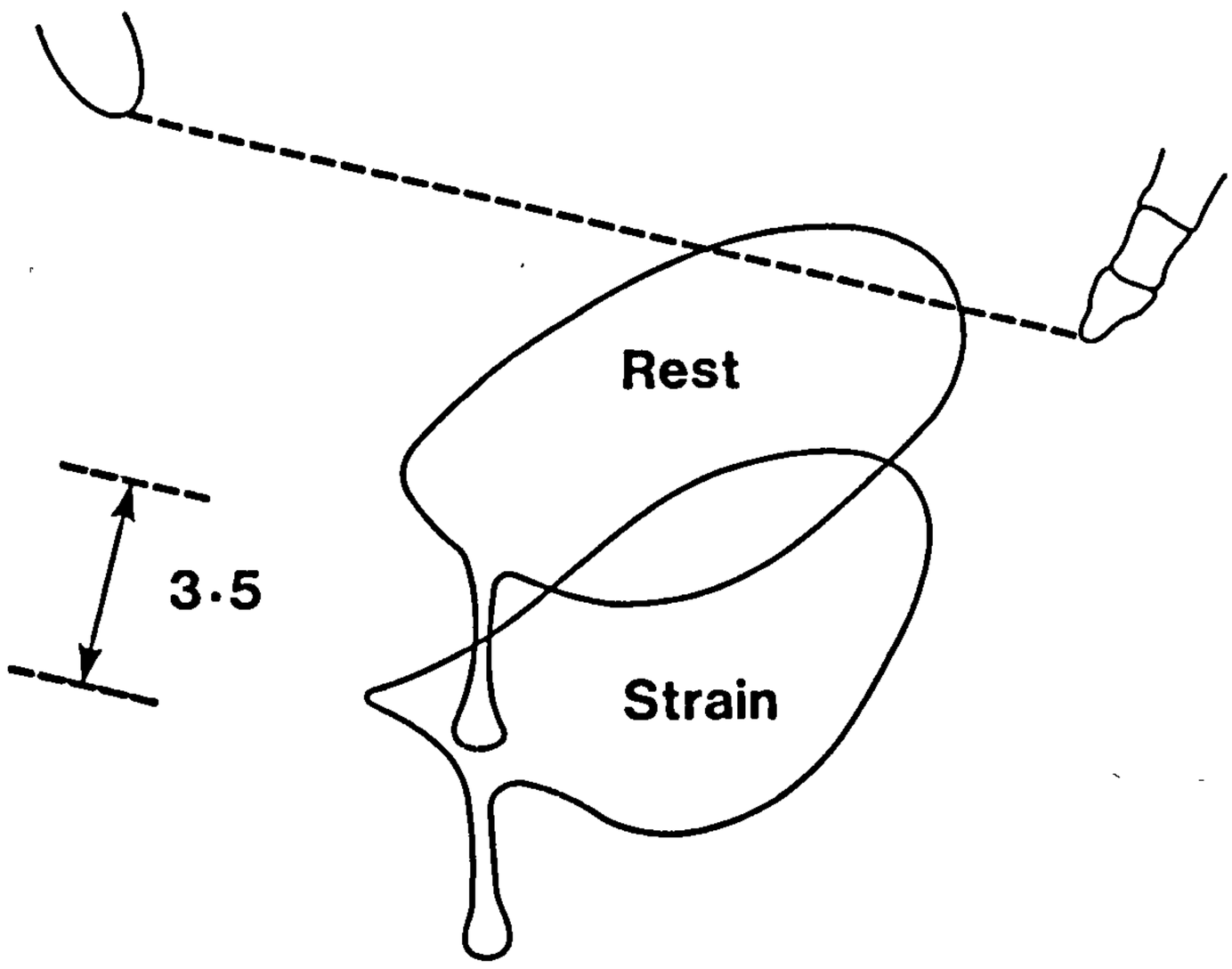


FIGURE 6u. BALLOON PROCTOGRAM: DESCENDING PERINEUM.
In this patient there is marked descent of the whole pelvic floor on straining with bulging of the posterior perineum. Defaecation cannot however take place as the anus remains tightly closed.

DISCUSSION

It is now possible to provide an explanation for the symptoms of some patients complaining of chronic constipation and to support Hurst's claim that a disorder of defaecation might be responsible in many of them. Since the discovery of agangionosis causing failure of internal sphincter muscle relaxation, patients with a short segment of disease (possibly his anal achalasia) have been treated by ano-rectal myectomy with success (Bentley 1966, Lynn 1975). Because of the clinical similarity between these patients and others with idiopathic megacolon some have suggested that a failure of internal sphincter relaxation might also the cause of symptoms in the latter group. This view has been supported by some reportedly successful operations (Shandling et al. 1969). The idea that a defaecatory disorder or "outlet obstruction" is the cause of constipation was carried further by one group who performed ano-rectal myectomy on all groups of patients with chronic symptoms (Martelli et al. 1978b).

Some patients with idiopathic megacolon (particularly children) are helped by division of the internal sphincter which suggests that it may be behaving abnormally in this condition. This idea has been given further support by the demonstration of abnormal sphincter relaxation on progressive distension of the rectum in adults with idiopathic megacolon (Lane 1979). It has yet to be determined whether this abnormality is secondary to the gross dilatation of the rectum. Cleveland (1889) was the

first to suggest forceful dilatation of the anus for constipation secondary to anal spasm and Hurst (1919) later recommended the same treatment for anal achalasia. It has now become common practice for surgeons to treat idiopathic megarectum and megacolon in this way (Clayden et al. 1976). The success of this procedure, particularly in children may be because the stretch disrupts smooth muscle fibres in the internal anal sphincter.

However in cases of slow transit constipation, experience of ano-rectal myectomy has been disapointing. (See Chapter 14). A review of the paper by Martelli et al. (1978b) also shows a significant number of failures in their patients with slow colonic transit time. The results presented above indicate a possible reason for these failures in that the "obstruction" is provided by the striated muscle of the external anal sphincter and not the smooth muscle of the internal sphincter.

The argument that studies such as those described are not physiological cannot be rebutted. It would be unreasonable to expect any patient to behave normally with their buttocks exposed and a needle stuck in the external sphincter. The pelvic floor muscles are under voluntary control and could have been contracted abnormally because of embarrassment or the stress of the procedures. In answer to this, all that can be said is that inhibition of the pelvic floor muscles on straining has been described as a phenomenon using identical methods to these, and that in other groups of patients attending the same department for ano-rectal physiology studies about 2/3 demonstrate this

inhibition (Henry 1980). These other patients, most of whom were awaiting surgery would have been under similar apprehensions. Kerremans (1969) claimed that inhibition of external sphincter activity on simulated defaecation is seen in less than half of normal subjects but his experimental method differed from that routinely adopted in this country. Ihre (1974) who used concentric needle electrodes similar to those used in the present study found inhibition on attempted defaecation in 8 out of 15 control subjects. All investigators agree that inhibition is seen in some normal subjects and it therefore seems unusual that it was not recorded in any of the constipated women. On the contrary in most cases there was increased activity in both muscles examined. This pattern of behaviour was noted by Kerremans (1969) in some control subjects and it is therefore possible that it is a normal variant. Increased electrical activity on straining has been previously reported in another group of patients with the solitary ulcer syndrome (Rutter 1975) raising the possibility that a failure of pelvic floor relaxation on defaecation might be responsible for more than one clinical disorder.

It would have been ideal to find a group of normal young women to undergo the same studies, but it proved impossible to find volunteers for what were very embarassing tests. It was also on ethical grounds not possible to perform lateral pelvic radiographs on normal young women who had not had children. EMG studies during forceful balloon expulsion were also not permitted on volunteers.

The main evidence for a defaecatory disorder in

slow transit constipation is that of the balloon expulsion study, for which there are controls. The other evidence supports but does not prove the idea that the striated muscles are at fault. Four of the patients studied had previously undergone internal sphincterotomy and 3 ano-rectal myectomy. The fact that colectomy and ileo-rectal anastamosis or internal sphincterotomy does not help these patients to expel the balloons suggests the problem must lie in the rectum or the striated pelvic floor muscles. The pictures obtained with the balloon proctogram indicate the latter to be the most likely.

If a disorder of the striated pelvic floor muscles is confirmed as the cause of these patients symptoms then the next step must be to determine whether this is an abnormal reflex or under voluntary control. It is possible that these patients deliberately impede the passage of faeces because of a psychological disturbance or that they suffer from an unusual "habit" disorder perhaps resulting from unfortunate experiences in childhood. Blake (1900) noted that ordinary people were unable to defaecate when under emotional strain. He attributed this to spasm of the anal sphincters and coined the term "anal stuttering" to describe it. Beddard (1910) elaborating on a list of causes of constipation derived from Hurst noted that anal spasm could be responsible. Neurotic subjects were said to be prone to this problem which could be cured by forcible anal dilatation under anaesthesia. He drew an analogy between this problem and vaginismus and suggested that resistant cases might be helped by hypnotic suggestion.

There is now increasing interest in the possibility of using biofeedback retraining in patients with functional disorders. Constipated children with megarectum have been successfully trained to increase intra-abdominal pressure to expel a simulated stool with an apparent improvement in their clinical condition (Olness et al. 1980). Normal adults have been trained to inhibit the contraction of the external sphincter that occurs when the rectum is distended (Whitehead et al. 1982b) and adaptation of this technique may prove helpful for the patients described here.

CHAPTER 7

THE PROCTOMETROGRAM

INTRODUCTION

The studies in Chapter 5 demonstrated a measureable difference between the rectal size of patients with megacolon and those with slow transit constipation. For future research purposes it was felt that a routine method of measuring rectal size would be helpful, particularly if this did not involve irradiation. Many patients with constipation were referred after barium enema had been performed at another hospital. Differences in the technique used by various radiologists made these radiographs unsuitable for comparison and repeat studies would have given an unnecessary dose of pelvic irradiation to the young women studied. A non-radiological method of measuring rectal area could have been used in these patients and might also be repeated at intervals to monitor changes following treatment.

Measurement of rectal capacity is routinely performed by inflating a latex balloon with air and awaiting the subjects response. The results of this investigation for some of the constipated patients studied is given in Table 7a. The major difficulty with this method for research studies is that it is a subjective measurement. Response is dependent on the patients' understanding of terms used by the investigator and many find difficulty in differentiating irritation of the anal canal by the catheter from rectal

distension when trying to distinguish the threshold of sensation. In addition the rate of filling may affect the response. Not surprisingly in different centres the results for normal subjects have varied widely (Farthing et al. 1978, Kullmann et al. 1981).

The rectum and bladder share a similar innervation because of their common embryological origin. It has been known for many years that instillation of water into the bladder causes a characteristic pressure/volume curve in neurogenic disturbances (Rose 1927). Because of its greater size, the colon is more difficult to fill, and the presence of large quantities of stool may distort the recordings. Nevertheless, it has been shown that it is possible to perform a colonmetrogram in the same way, and that the pattern of the curve mimics that of the cystometrogram (White et al. 1940).

Swenson et al. (1955) were the first to notice that many patients with idiopathic megacolon could also have an enlarged bladder. Though several investigators had measured colonic and rectal elasticity, it was not until recently that an attempt was made to correlate these findings with the cystometrogram (Bubrick et al. 1980). In this study it was shown that confining the infused fluid to the rectal ampulla by a latex balloon gave very similar pressure/volume curves in the rectum to those obtained on cystometry in patients with a neurogenic bladder. One patient with chronic constipation was included and showed a hyporeflexic curve with both investigations. This suggested that an adaption of this technique might be of value in studying patients with

different types of chronic constipation.

METHODS

i) Choice of balloon.

Unlike the cystometrogram, it was necessary to confine infused fluid to the lower rectum in a balloon. Review of the paper by Bubrick et al. showed that they had used a balloon with a capacity of over 400 cc. This seemed to be too large, as the balloon could be distorted during filling and possibly only distend at its distal end. The resulting pressure curve might then reflect changes at the recto-sigmoid junction rather than the rectal ampulla. Comparison of a party balloon with a condom showed that thickness of rubber in the balloon wall has a marked effect on the pressure/volume curve outside the body (Figure 7a). All balloons were found to have an initial resistance after which the curve was flat. The smallest rise found was in the condom. Enlarging the size of the balloon only served to move the eventual pressure rise to the right. As high volumes were anticipated in patients with megacolon this would mean a distortion entering in the middle of the tracing which would have been difficult to subtract. Bench testing of the condom showed that if a small (50 cc.) capacity balloon was constructed, the pressure rise was minimal in the first 30 seconds as fluid was introduced at a rate of 150 ml/minute (Figure 7a). Therafter, a flat trace continued up to 4000 cc. when the balloon burst. This was far in excess of the volumes that were likely to be used in the rectum and this balloon was therefore selected for the

study. The balloon was then mounted on a soft plastic catheter through which water could be introduced.

ii) Pressure recording and rate of flow.

A separate miniature balloon (0.3 x 0.7 cm.) was placed inside the main one to record pressure changes inside the rectum. This was filled with water and connected via nylon tubing in a closed system to a pressure transducer (Druck C-0004/21) the output of which was amplified and recorded on heat sensitive paper using a Devices MX4 recorder. The apparatus used is illustrated in Figure 7b.

Tension generated by the gut wall is known to be affected by the rate of distension (Lipkin et al. 1962). The maximal rate of fill in this study was decided by the limitations of the pump available whose maximal flow rate was 150 cc./minute. Thus a normal sized rectum with a capacity of 250-300 cc. would take about 2 minutes to fill. Lower rates of filling were initially studied but abandoned. It was found that patients with megacolon might require up to ten minutes to complete filling at slower rates of infusion and this led to loss of compliance. Any movement or coughing during the study interfered with the record and patients found it difficult to keep still for long periods.

iii) Method of study.

The catheter holding the balloon was marked at 7.5 cm. from the centre of the balloon. Apposition of this mark to the anal verge resulted in the balloon lying between 5 and 10 cm from the anal verge during filling. This ensured

that the lower part of the rectum only was distended. The studies were performed with the patients in the left lateral position and the balloon and tubes were well lubricated before insertion. Stool was cleared from the rectum by enema or glycerine suppository prior to the studies and no stimulant laxative or suppository was allowed beforehand. Before water was introduced patients were asked to relax, and to avoid any movement, speaking or coughing. They were instructed to try and accommodate as much water as possible but to signal for the infusion to stop as soon as they experienced pain or the distension became intolerable. A trial run was given first to familiarise the patients with the technique and then two full studies performed.

PATIENTS STUDIED

Five control patients were studied. who were attending for colonoscopic polypectomy or follow up and had no ano-rectal disease. All had a normal bowel habit and denied straining at stool. There were 2 men and 3 women in this group. 32 patients with chronic constipation were studied, all of whom were attending the outpatients or receiving inpatient treatment at St Mark's Hospital. They were divided into three groups as follows:

a) Idiopathic Megacolon (10).

These patients had all had megacolon diagnosed by barium enema. The X-rays were re-examined and all showed a rectal width at the pelvic brim greater than 7.0 cm. This confirmed that they were part of the group with megacolon as defined in Chapter 5. The sex ratio was equal, with 5 men

and 5 women. In all cases Hirschsprung's disease had been excluded by the finding of a normal recto-sphincteric reflex.

b) Slow Transit constipation (12).

These patients all had a barium enema of normal calibre as defined in Chapter 5. They also had an abnormal gut transit study with a delay in the excretion of polythene markers. All were women.

c) Irritable Bowel Syndrome (10).

These patients had a bowel of normal width as defined in Chapter 5 and also a normal gut transit study. They had failed to respond to a high residue diet and were therefore regarded as suffering from the irritable bowel syndrome. There were 2 men and 8 women in this group.

RESULTS

Control patients.

In the controls infusion of fluid produced a sigmoid curve (Figure 7c). None tolerated a volume greater than 300 cc. and the highest pressure recorded was 90 cm H2O at this volume.

Constipated patients

In the majority of patients with slow transit constipation a normal curve was seen (Figure 7d). One patient however stopped the study at 180 cc. with an intrarectal pressure of only 60 cm H2O, and two had rather flatter curves acommodating 360 and 400 cc. of water

respectively. Those with megacolon had a markedly different pattern (Figure 7f). Mean intrarectal pressure at 300 cc. in this group was only 24 cm H2O. All tolerated more than 500 cc. and one even 1000 cc. (at which point the investigator's courage failed). For those with the irritable bowel syndrome the results were also markedly different. None could tolerate a volume above 180 cc. At this point however, pressure had risen to the values seen in controls at twice that volume (Figure 7f). The repeated studies indicated that the test was reasonably reproducible (Figure 7g).

When the mean values for each group were compared it was found that there were significant differences between the groups of constipated patients (Figure 7h). For example, after inflation to 180 cc. mean rectal pressures were as follows: Controls 39.4 $\pm$ 6.5 Cm H20 (s.e.m.), Megacolon 19.6 $\pm$ 3.0 ($p<0.01$), Irritable Bowel Syndrome 81.5 $\pm$ 4.7 ($p<0.01$), Slow Transit Constipation 44.8 $\pm$ 3.5 (NS).

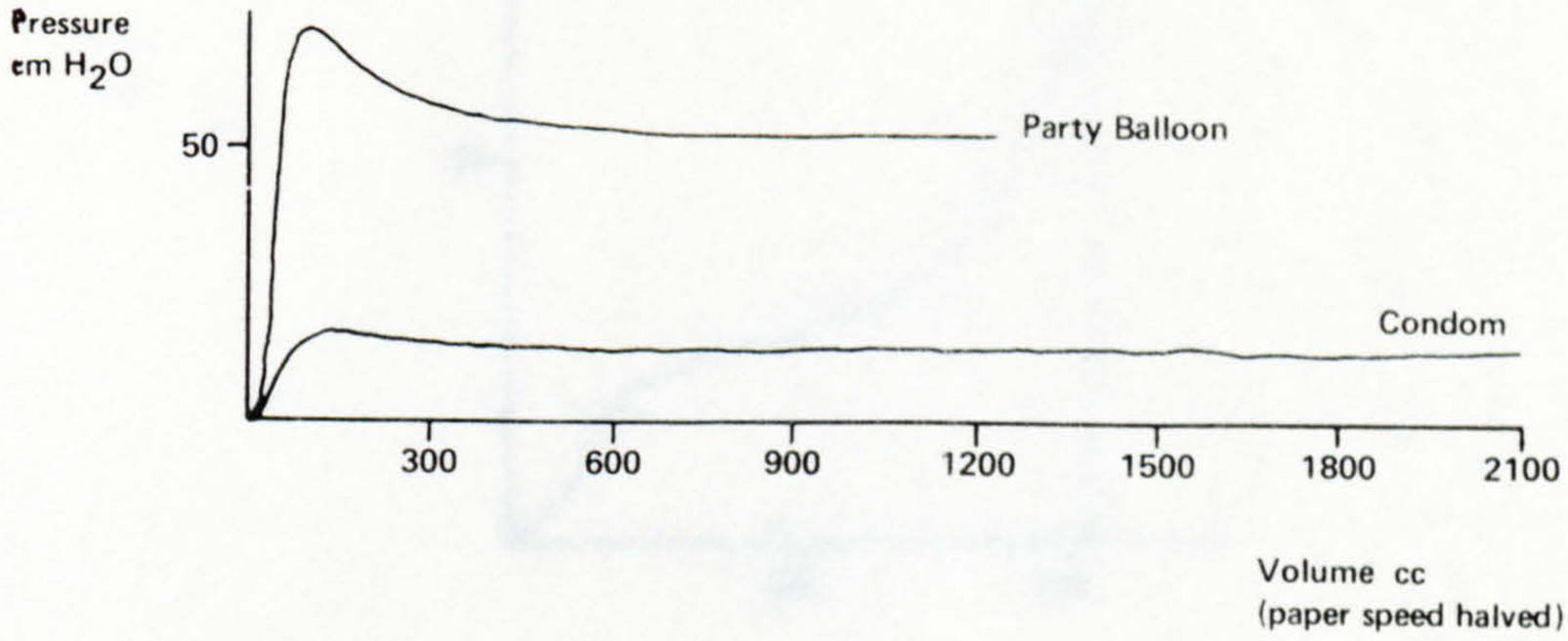


FIGURE 7a. BENCH TESTS ON BALLOONS. The results obtained by filling balloons with water outside the rectum at a fixed rate of 150 cc/minute. The initial rise in pressure using a party balloon was unacceptable, however after an early rise of 20 cm H20 the curve using a condom is flat.

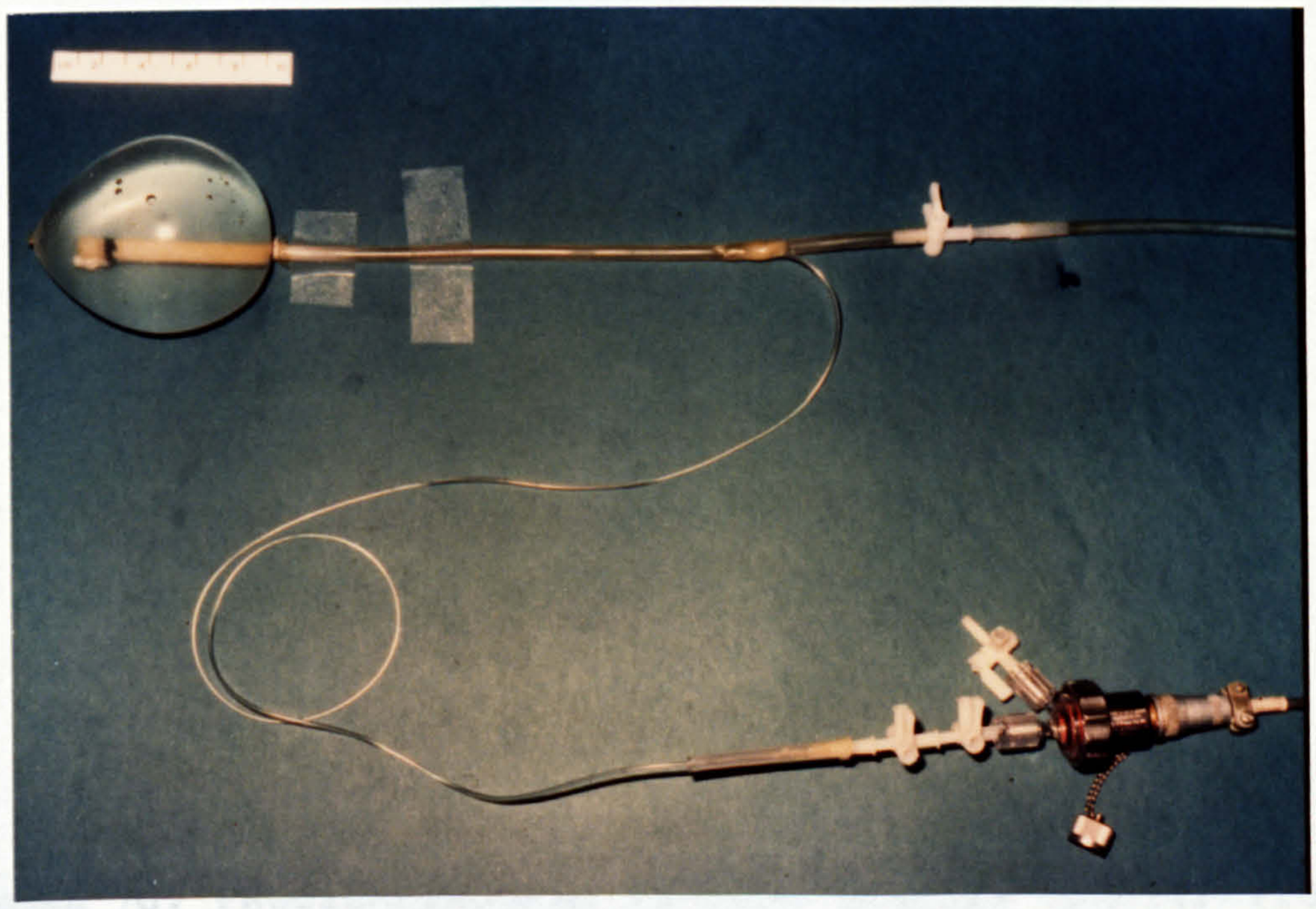


FIGURE 7b. PROCTOMETROGRAM APPARATUS. A 3 inch section of condom rubber has been used to make a small (apx 30 cc) balloon here seen distended to 300 cc. Water from the pump enters through the central catheter. A miniature pressure recording balloon inside is connected to the pressure transducer (below).

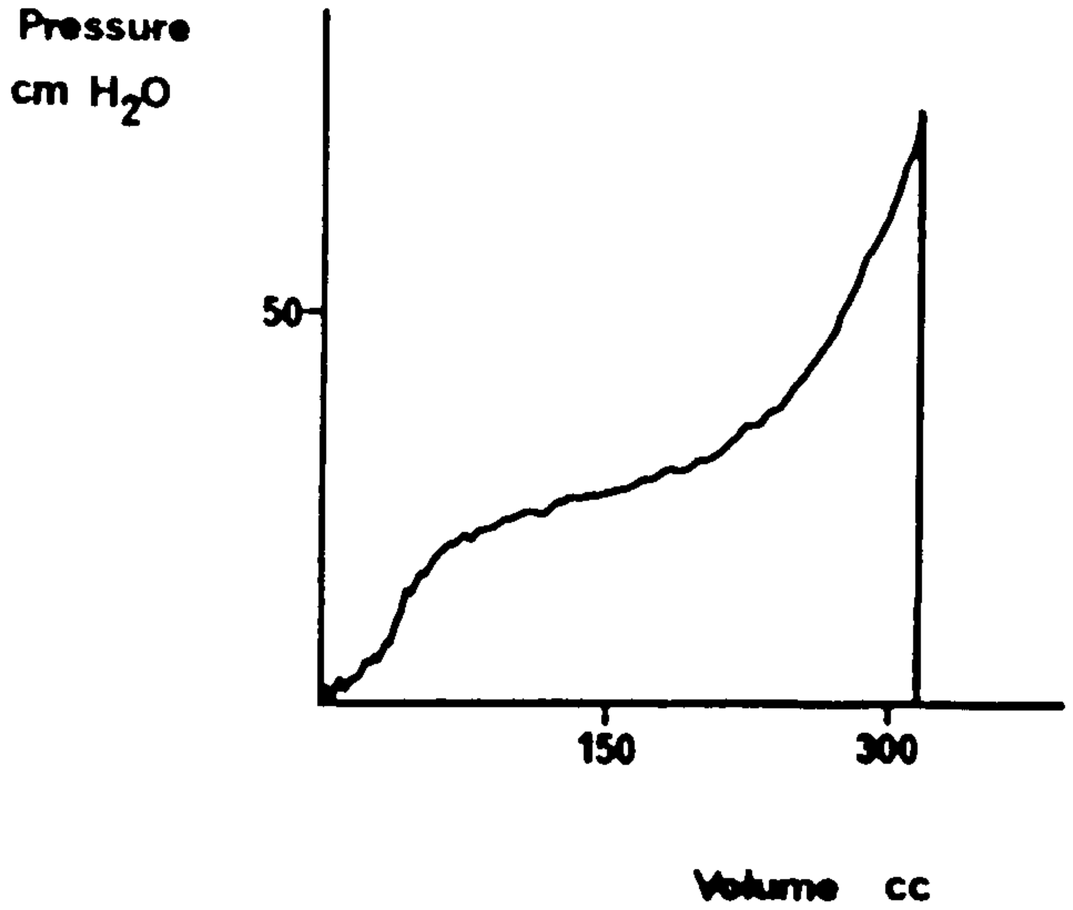


FIGURE 7c. NORMAL PROCTOMETROGRAM
Results in a control subject showing an initial slow rise in pressure followed by a more rapid rise before pain terminated the study. The final pressure was 80 cm H20 after 305 cc of water had been infused.

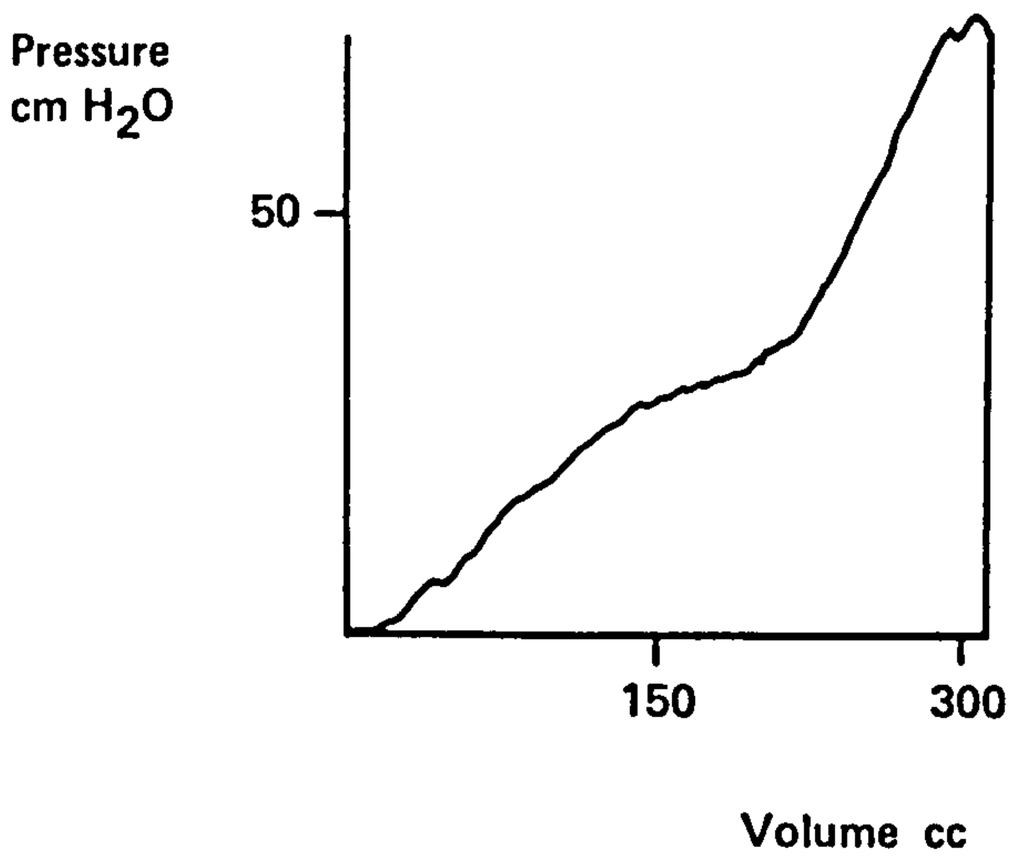


FIGURE 7d. PROCTOMETROGRAM IN SLOW TRANSIT CONSTIPATION
This shows a normal response from a young girl with severe constipation who opened her bowels only once a month. The final pressure was 75 cm H20 at a volume of 305 cc of water.

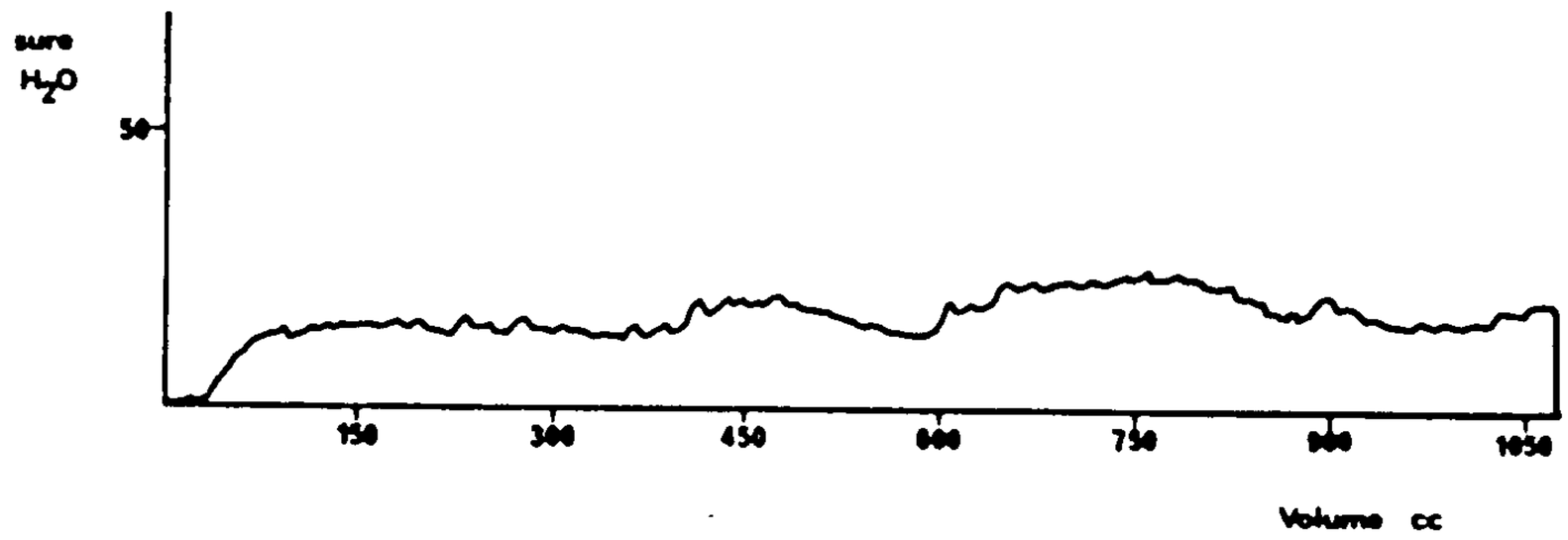


FIGURE 7e. PROCTOMETROGRAM IN IDIOPATHIC MEGACOLON
Results from a man with severe constipation associated with megabowel. There is no appreciable contribution to pressure changes from the rectum. The study was abandoned after 1000 cc of water had been instilled and the final pressure reading was 18 cm H20.

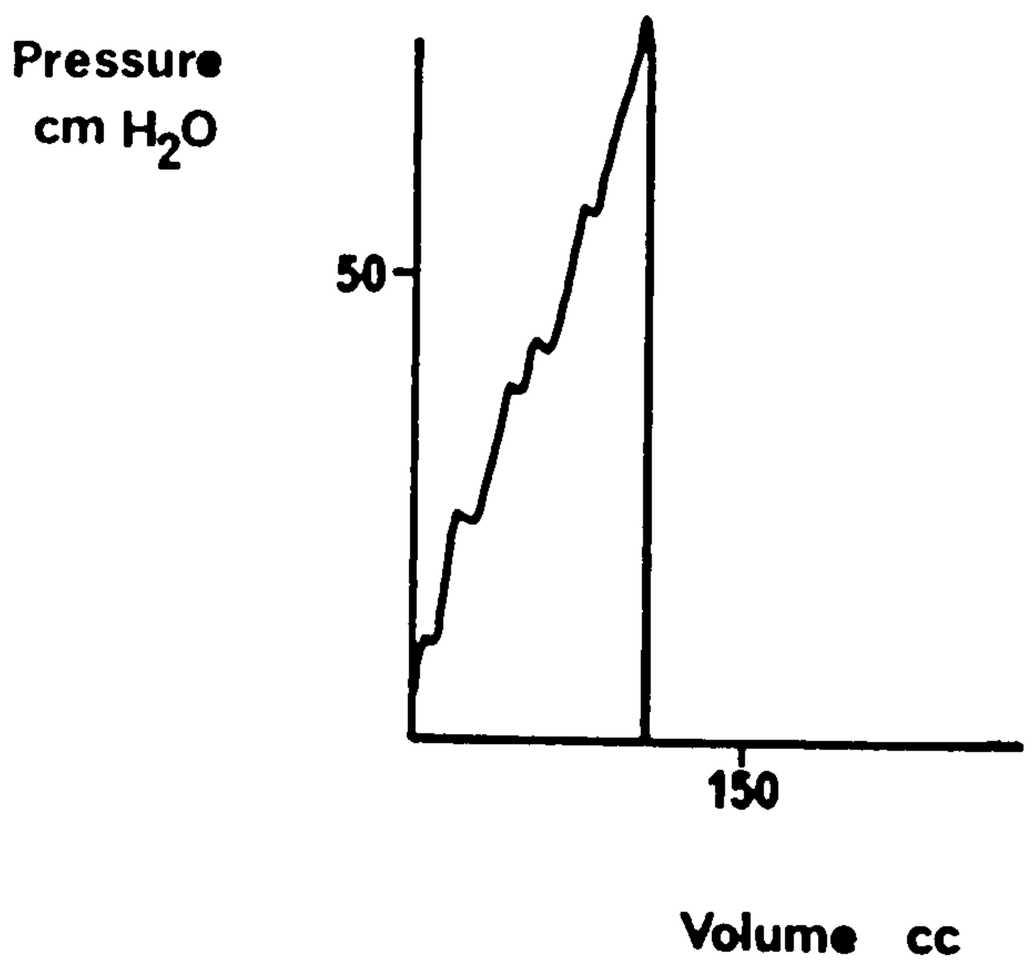


FIGURE 7f. PROCTOMETROGRAM IN IRRITABLE BOWEL SYNDROME
Results obtained from a woman with severe abdominal pain and constipation whose bowel transit study was normal. There was an immediate and sustained rise in rectal pressure and the study was abandoned after only 100 cc of water had been infused. The final pressure was 80 cm H20.

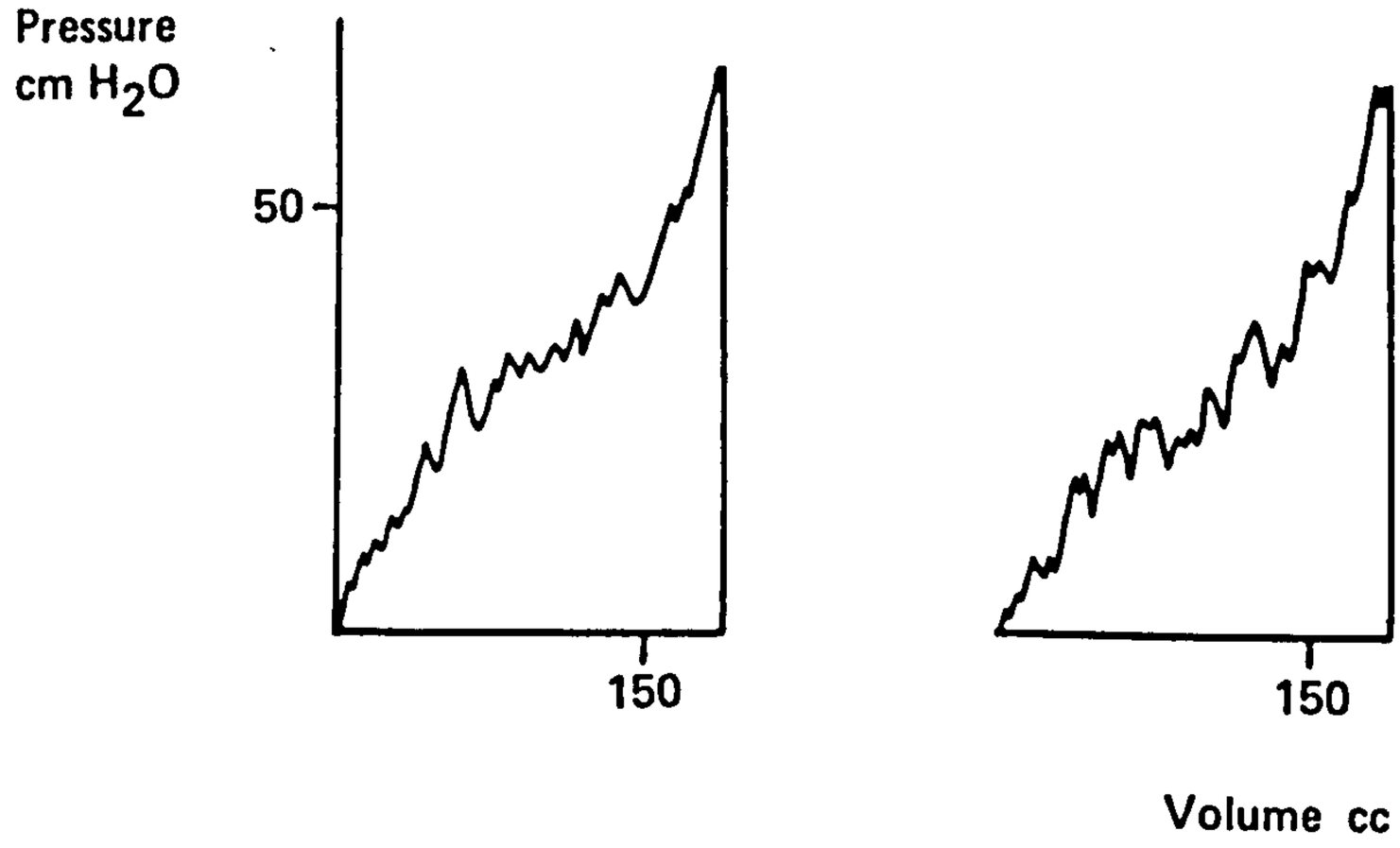


FIGURE 7g. REPEATED STUDIES (IRITABLE BOWEL)
Proctometrograms performed on the same patient 5 minutes apart. Despite the fact that in this case there appears to have been some rectal muscle spasm the final pressures and volumes are the same.

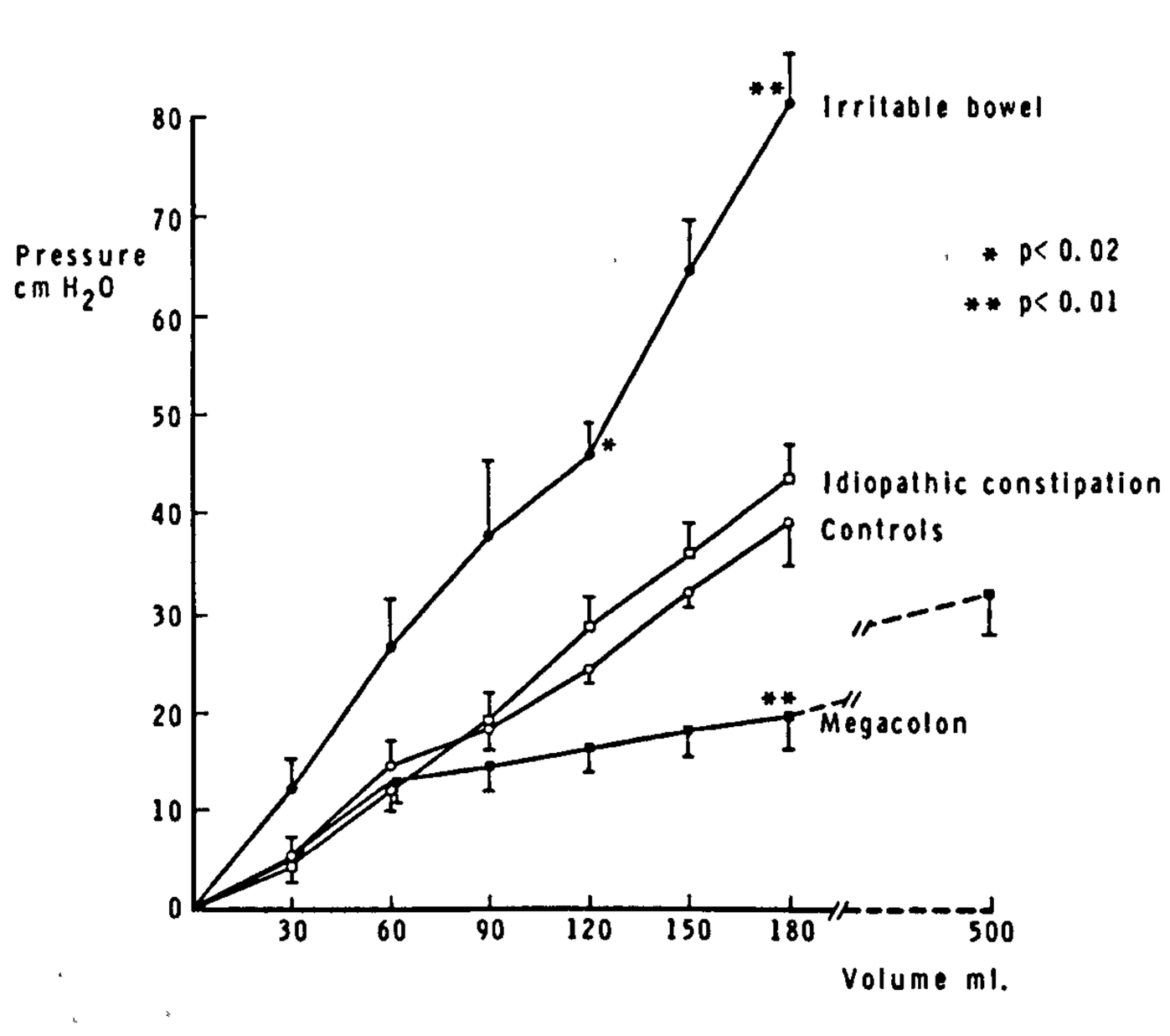


FIGURE 7h. RESULTS IN ALL PATIENTS
The mean values for the 3 patient groups and controls are shown up to 180 cc as no IBS patient could continue after this. At this point the pressure differences are highly significant (IBS and Megacolon $p<0.01$ v controls or STC). At 500 cc the mean pressure in the patients with megacolon had not risen as high as that found after 180 cc in controls.

		Constant sensation (cc.)	Discomfort (cc.)
SLOW TRANSIT CONSTIPATION		100	340
		90	250
		50	240
		130	350
		220	450
		50	140
		150	200
		100	300
		100	300
		150	400
		50	200
		110	300
		50	230
		150	330
		50	180
		180	400
		50	200
		100	220
		150	350
		150	350
		60	360
		200	420
		60	100
		80	200
		200	450
		180	360
	Mean	113 ± 10	293 ± 18
IDIOPATHIC MEGACOLON		170	340
		600	1000
		150	550
		90	550
		150	800
		150	750
		150	700
		250	450
	Mean	213 ± 57	642 ± 95

Table 7a.
Results of rectal sensation in slow transit constipation and idiopathic megacolon obtained by inflating a rubber balloon with air in the rectal ampulla. The rate of filling was approximately 10 cc./second. Normal subjects are aware of a sensation of constant filling after 30 to 60 cc. have been introduced, and complain of discomfort or an intolerable urge to defaecate with a volume of 200 to 300 cc.

DISCUSSION

This study was performed to find if a reproducible and objective method of measuring rectal capacity could be developed. The results suggest the proctometrogram fulfils those requirements and could be a useful non-radiological method of assessing patients with chronic constipation. The results clearly support the radiological findings in Chapter 5 suggesting that idiopathic megacolon and slow transit constipation are separate disorders.

There was an overlap between the results in patients with slow transit constipation and those with the irritable bowel syndrome which unfortunately will not allow this to be used as a differential test. However the markedly abnormal curves in many of the latter group suggests a significant difference in rectal function between constipated patients with normal and delayed gut transit rates. Taken together with gut transit studies and balloon expulsion tests, the proctometrogram might thus help to separate patients with slow transit constipation from other patients complaining of constipation so as to provide a more rigorous definition of the disorder for future research. There is however sometimes difficulty in distinguishing these groups clinically and it is possible that they represent the two ends of a wide spectrum of a more common disorder.

Other investigators have used traces such as this to calculate the elasticity of the rectum (Arhan et al. 1976) though the methods used here are probably too crude for this. If the law of Laplace is modified for a cone

(assuming the lower rectum to adopt this shape) then the figures obtained can be used to give an approximation of the tension in the rectal wall (Hopkins 1966). A plot of wall tension against volume does not however significantly alter the results given above.

The reason why some patients with chronic constipation develop a huge rectum whilst others with equally prolonged and severe symptoms do not is unknown. Lane (1979) found higher rectal pressures on distension in patients with chronic constipation but normal rectal size as compared with those having an enlarged rectum. He postulated that rectal contractility at first increased to overcome internal sphincter obstruction and that later the rectal muscle weakenes and passively relaxes resulting in development of the megacolon. Those patients whom he studied without megacolon may have had an irritable bowel as no transit studies were done. His theory also fails to account for the large number of children and adolescents with megacolon or to explain why there are no men with slow transit constipation who then go on to develop a megacolon.

Theories suggesting that internal anal sphincter disorders can cause idiopathic megacolon also fail to explain the associated enlargement of the bladder in many patients (Swenson et al. 1955). A prospective study of bladder function in patients with idiopathic megacolon has not been done and some might have evidence of neuropathy. It is possible that there may be an analogy between the hypotonic proctometrograms of patients with idiopathic megacolon and the flat cystometrograms found in patients

with lower motor neurone bladder dysfunction.

The hypertonic traces found in many of the patients with the irritable bowel syndrome correlate with previous studies showing such patients to have a lower threshold for pain on distension of the bowel (Ritchie 1973). It is interesting to see that they experience pain at the same intra-rectal pressure as normals. This suggests that their appreciation of pain is appropriate, but the behaviour of their rectal wall is not. Further studies to define possible abnormal behaviour in this and other parts of the gut seem indicated. The rectum is however the most easily accessible part of the bowel and study of rectal compliance might provide a useful screening investigation for patients attending gastroenterology outpatients.

CHAPTER 8

COLONIC MOTILITY STUDIES

INTRODUCTION

Human colonic motility has been extensively studied during the last 40 years. Most investigators have found that pressure wave activity is increased in patients with constipation and reduced in those with diarrhoea (e.g. Chaudhary et al. 1961, Connell 1962, Wangel et al. 1965, Waller et al. 1972). Such investigations were however without diagnostic value as there was a wide overlap between patients and normal subjects. Recently doubt has been cast on the consensus view with the demonstration that colonic motility in the majority of constipated subjects is within the normal range (Meunier et al. 1979).

All these studies suffered from a failure to define constipation adequately and some did not exclude dietary constipation by a trial of a high residue diet. There were also differences in the methodology. Most were carried out before gut transit time measurements became routine and none examined colonic motility in slow transit constipation. It was therefore felt that another study to look specifically at this group would be worthwhile.

The electrophysiology of the colon has attracted interest recently in functional bowel disease (Snape et al. 1976, 1977, Taylor et al. 1978, Bueno et al. 1980, Latimer et al. 1981). At the time the present study was started however, it was not felt that sufficient progress had been

made in this field. The relationship of electrical events to colonic movement was not clear, nor was there any agreement on the significance of recorded abnormalities. Consequently the findings in this group of constipated women would have been difficult to interpret. Motility was therefore assessed using pressure recording devices with similar methodology to that of previous investigators. This enabled the results to be compared with an established body of data such as that compiled by Connell (1961a, 1961b, 1962, 1963, 1964, 1965).

The reported failure of laxatives by many patients in the questionnaire (Chapter 3) was puzzling. Previous studies had shown that laxatives such as Senna, Bisacodyl and Oxyphenisatin can act by stimulating the colon directly (Hardcastle et al. 1968). This activity was blocked by prior application of lignocaine suggesting the effect was mediated via the submucosal nerve plexus. It was decided to test the constipated patients in the same way to find if their colons were capable of responding to laxatives.

PATIENTS STUDIED

In order to compare the results with previous studies it was decided to include some patients with functional diarrhoea as well as constipated patients who had a normal gut transit time. The details of the four groups were as follows:

a) Controls

Five women (mean age 33.1 years) with a normal bowel habit were recruited from patients attending hospital

for other conditions. All denied straining at stool and their mean reported weekly bowel frequency was 6.2.

b) Functional Diarrhoea

Five patients (3F 2M, mean age 39.2 years) with chronic diarrhoea were studied. All had been fully investigated to exclude known causes of diarhoea and were regarded as suffering from the irritable bowel syndrome. None had any episodes of constipation. Their mean reported weekly bowel frequency was 63.

c) Constipation

Twenty-eight patients referred for investigation of chronic constipation were studied. In all cases the barium enema had shown a bowel of normal calibre, and none had responded to an increased intake of dietary fibre. All other primary causes of constipation had been excluded. Bowel transit studies were performed and the group divided on the basis of the results.

One group (19 patients, all female, mean age 30.0 years) had a prolonged gut transit time. Their main complaints were of difficulty in evacuation and infrequent bowel movements and their mean spontaneous weekly bowel frequency was 0.5. The other group (9 patients, 8F 1M, mean age 36.4 years) had a normal whole gut transit time. Severe abdominal pain was a more marked feature than in the first group, but they also complained of difficulty in evacuation and a sensation of incomplete emptying of the rectum. Their mean spontaneous weekly bowel frequency was 4.3.

METHODS

No medication was allowed for 48 hours before the studies. Following a 12 hour fast and without bowel preparation, three miniature pressure recording balloons (0.7 x 1.2 cm.) were introduced into the rectum and sigmoid colon via a sigmoidoscope. The balloons were made of latex and filled with water. Nylon inelastic tubing (internal diameter 1mm.) was used to connect each balloon to a pressure transducer (Druck C-0004/21) the output of which was amplified and recorded on heat sensitive paper using a Devices MX4 multi-channel recorder. A fourth channel was used to record respiratory excursion using a strain gauge transducer fitted round the chest. This enabled artefacts caused by movement or respiration to be recognised.

During the studies the subjects were asked to lie on their left hand side, and no reading or other diversion was allowed. After a 30 minute wait for equilibration, to exclude artefacts caused by sigmoidoscopy, recordings were made of intraluminal pressure changes at 15, 20 and 25 cm. from the anal verge over one hour. In the group with slow transit constipation alone Bisacodyl was then introduced. This was chosen because Senna requires prior hydrolysis and Oxyphenisatin has been withdrawn. A large dose (10 mg.) of Bisacodyl was chosen to counter possible later critiscism that failure to respond might have been due to insufficient stimulation. It was injected through a fine nylon tube attached to the recording apparatus into the lumen of the colon at 25 cm from the anus. Recordings of pressure wave activity were then continued for a further 30 minutes. One

patient did not take part in this study as she refused further investigation.

The activity of the colon was then assessed from the resulting pressure traces and expressed as a motility index. This was calculated by measuring the pressure waves greater than 10 cm. of water in all 3 leads. The height and width of each wave were multiplied together and divided by 2 to give an approximation of the area under the curve (Chaudary et al. 1961). Statistical significance was assessed using the rank sum test.

RESULTS

a) Fasting activity

The resting motility index over one hour for all subjects is shown in figure 8a. In the control subjects the mean value was 1,803 ± 297 (s.e.m.), range 932 - 2,593. The values in many of the patients with slow transit constipation were below the normal range but there was no significant difference between the groups (mean motility index 397 ± 91, range 20 - 1,140). In contrast 6 of the 9 patients with constipation but normal transit time had values greater than controls. The mean motility index of this group was significantly higher than both the controls and the constipated patients with slow gut transit time (mean motility index 11,934 ± 3,066, range 1,831 - 27,510; $p<0.02$ v controls and $p<0.01$ v slow transit constipation).

The values for the 5 patients with functional diarrhoea were mostly below the normal range but the

difference was not significant (mean motility index 591 ± 145, range 278 - 1125). Examples of the traces obtained are given in figures 8c-f. Figure 8b shows a comparison between the ages and fasting motility indices for all the constipated patients.

b) Response to Bisacodyl

The response to the introduction of intraluminal bisacodyl into the sigmoid colon is shown in Figure 8g. In normal subjects there is an immediate response with some disorganised activity that progresses within a few minutes to powerful peristaltic waves progressing caudally. Some of the constipated patients showed this reaction whilst others demonstrated an attenuated response (Figure 8h) and some showed no changes at all (Figure 8i). Changes in the motility index over 30 minutes before and after introduction of bisacodyl were assessed for the patients with slow transit constipation and are shown in Figure 8j. A separation has been made between those patients in whom peristaltic waves were set up and those in whom there was no such response. As might be expected there was a significant rise in the mean motility index for those patients showing a response:

	Before	After
Response	262 ± 146	7,201 ± 1,874
No response	201 ± 54	153 ± 68
	N.S.	p<0.001

The mean age of the 7 who showed no response was 35 years compared with 28 years in the responders. The non-responders also had a longer history of constipation,

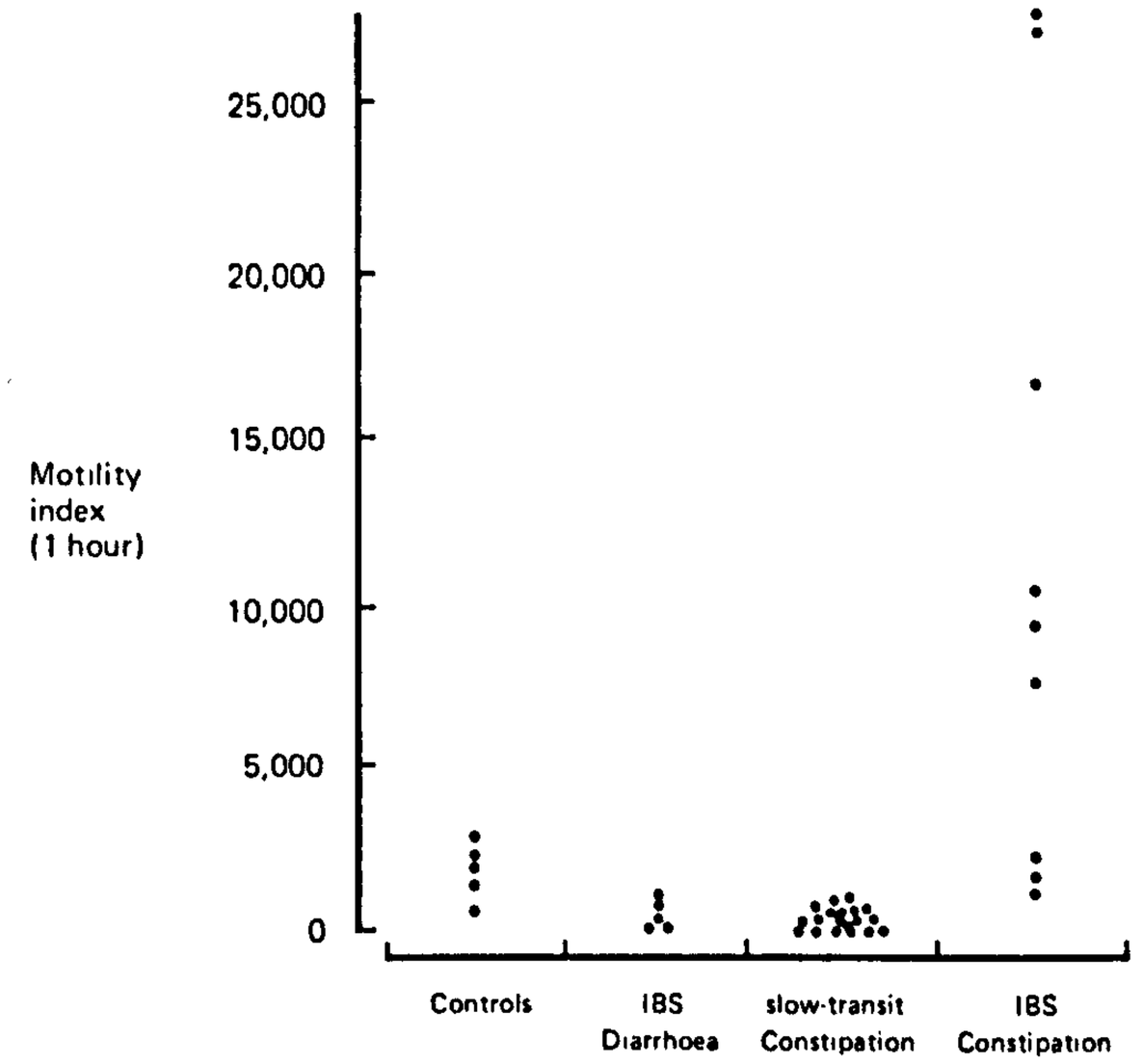


FIGURE 8a. FASTING COLONIC ACTIVITY.
The motility indices for all the groups studied measured for one hour after equilibration and following a 12 hour fast.

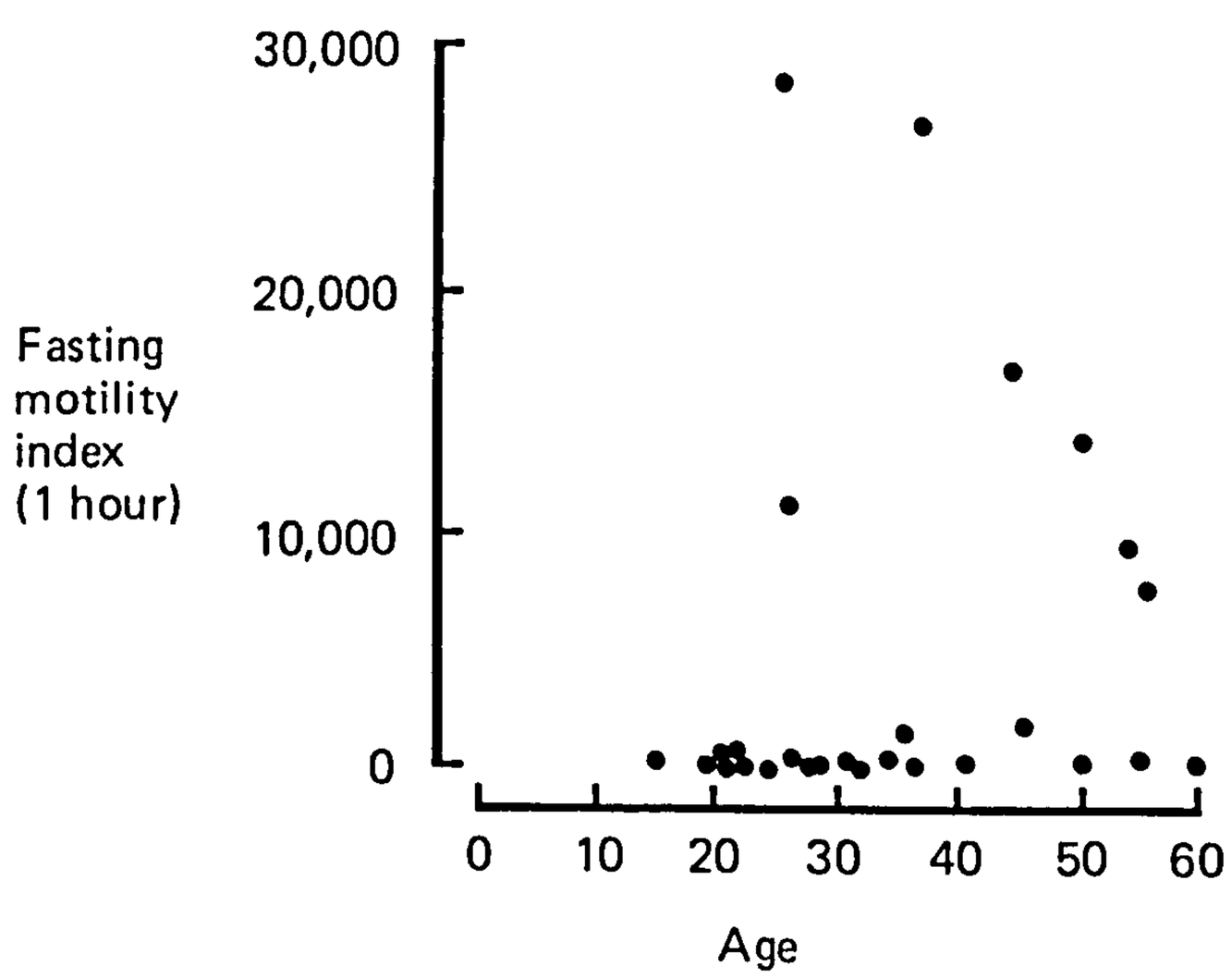


FIGURE 8b. EFFECT OF AGE ON COLONIC ACTIVITY.
A plot of the motility index for each constipated patient against their age. This demonstrates that reduced activity is seen at all ages and not solely in the older patients.

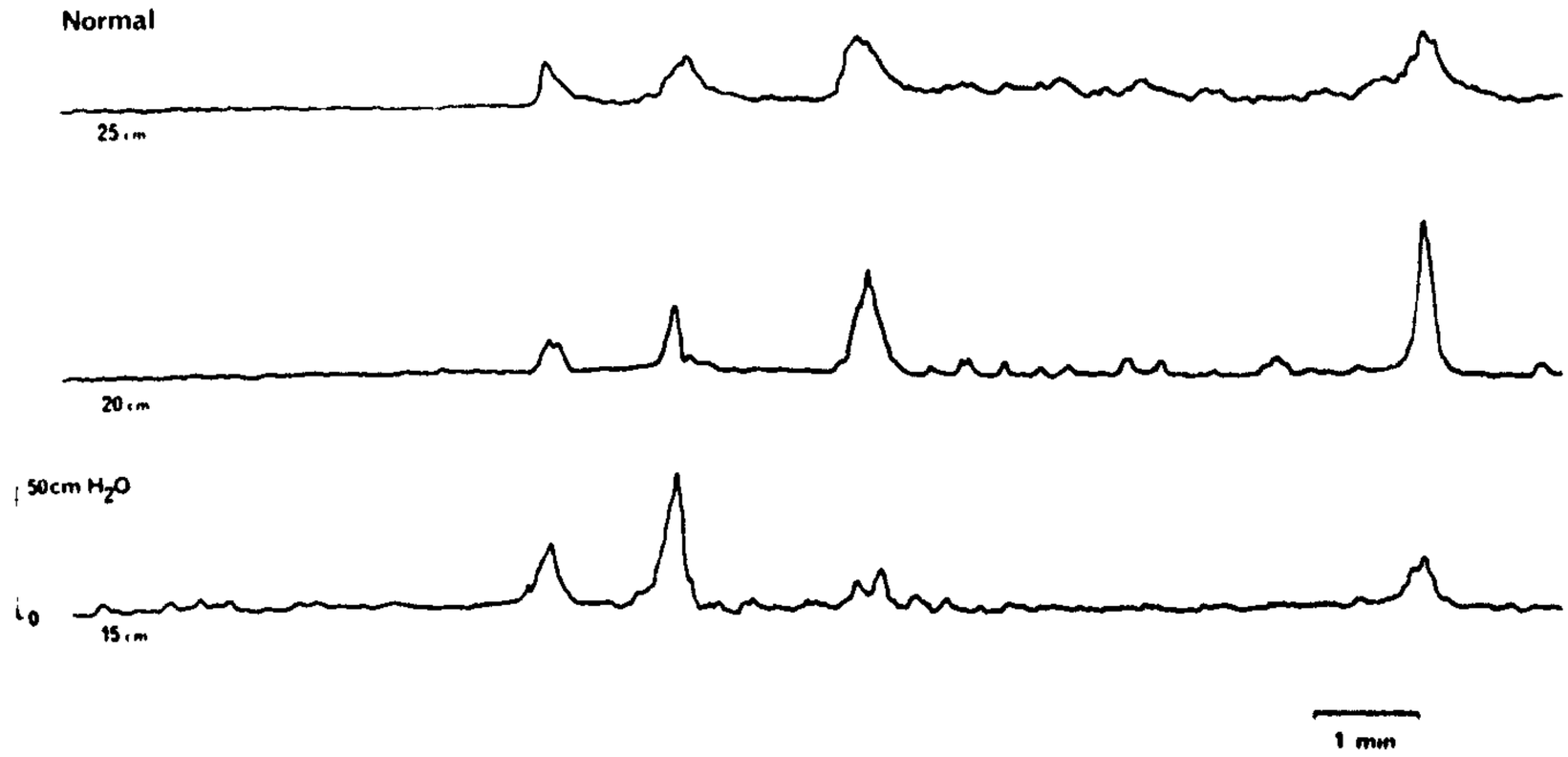


FIGURE 8c. NORMAL COLONIC MOTILITY.
Sample from the traces obtained in one of the normal subjects. (In all traces figures on left indicate distance of pressure probe from anal verge. Height of wave indicates pressure at that point given in cm H20.)

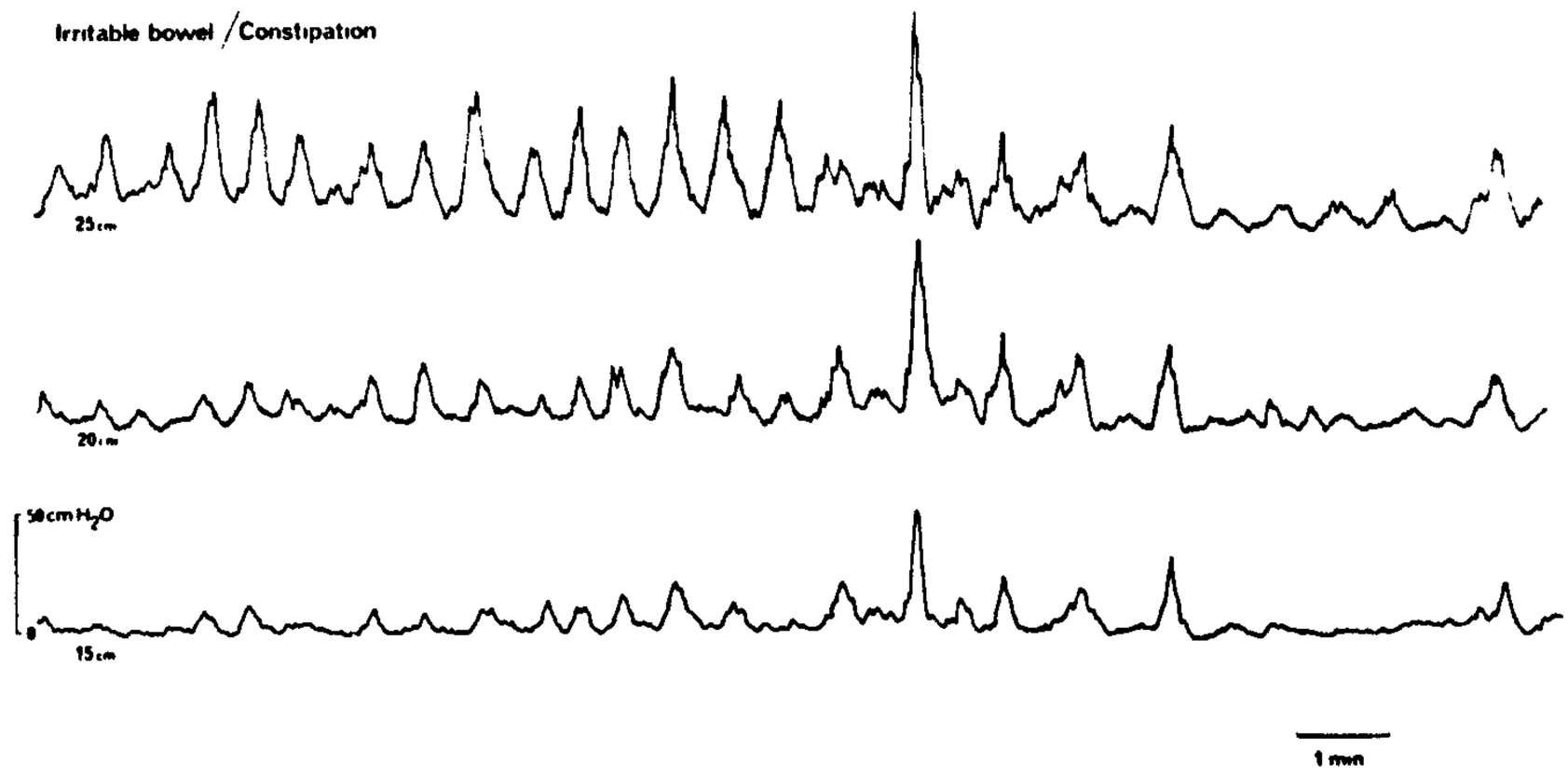


FIGURE 8d. COLONIC MOTILITY IN IRRITABLE BOWEL SYNDROME WITH CONSTIPATION.
Irregular and uncordinated activity was seen in all three traces for the duration of the recording.

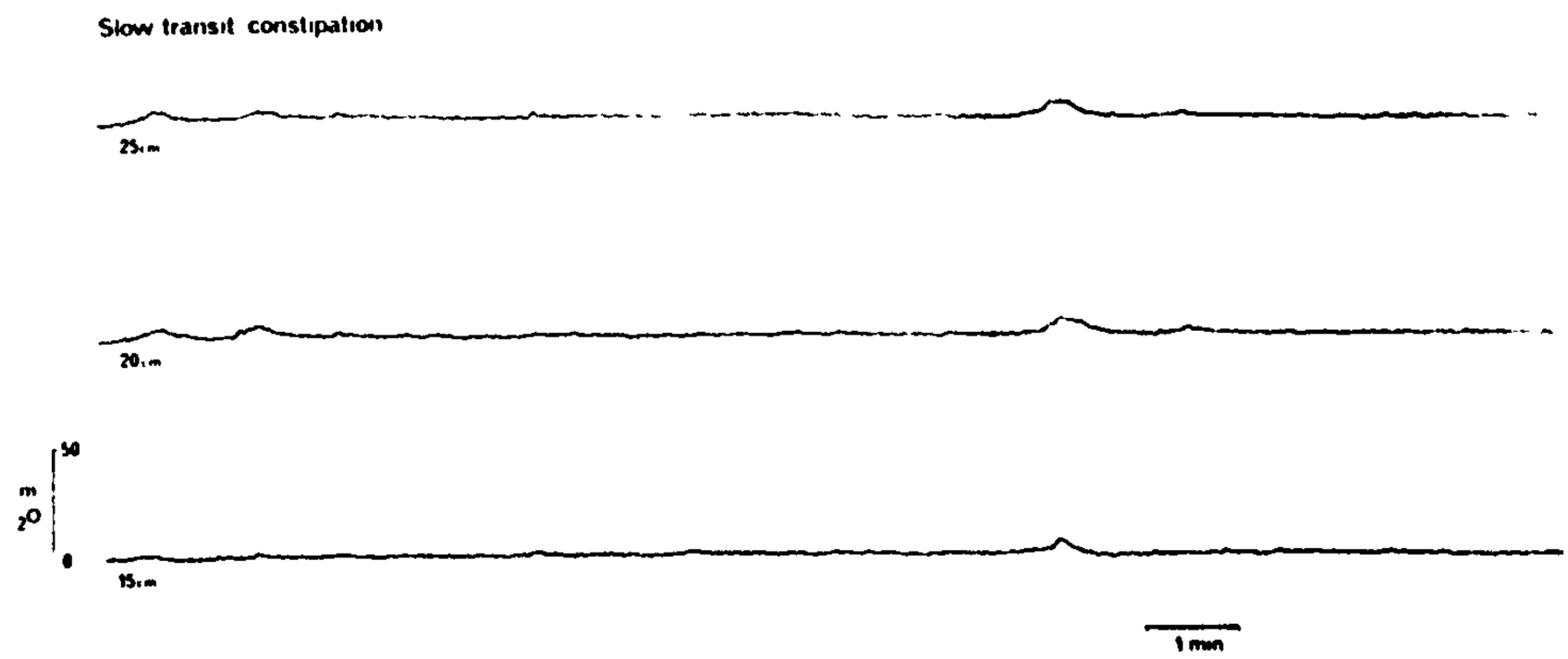


FIGURE 8e. COLONIC MOTILITY IN SLOW TRANSIT CONSTIPATION.
In this girl with constipation and a markedly prolonged whole gut transit rate no significant pressure changes were seen in the sigmoid colon throughout the recording.

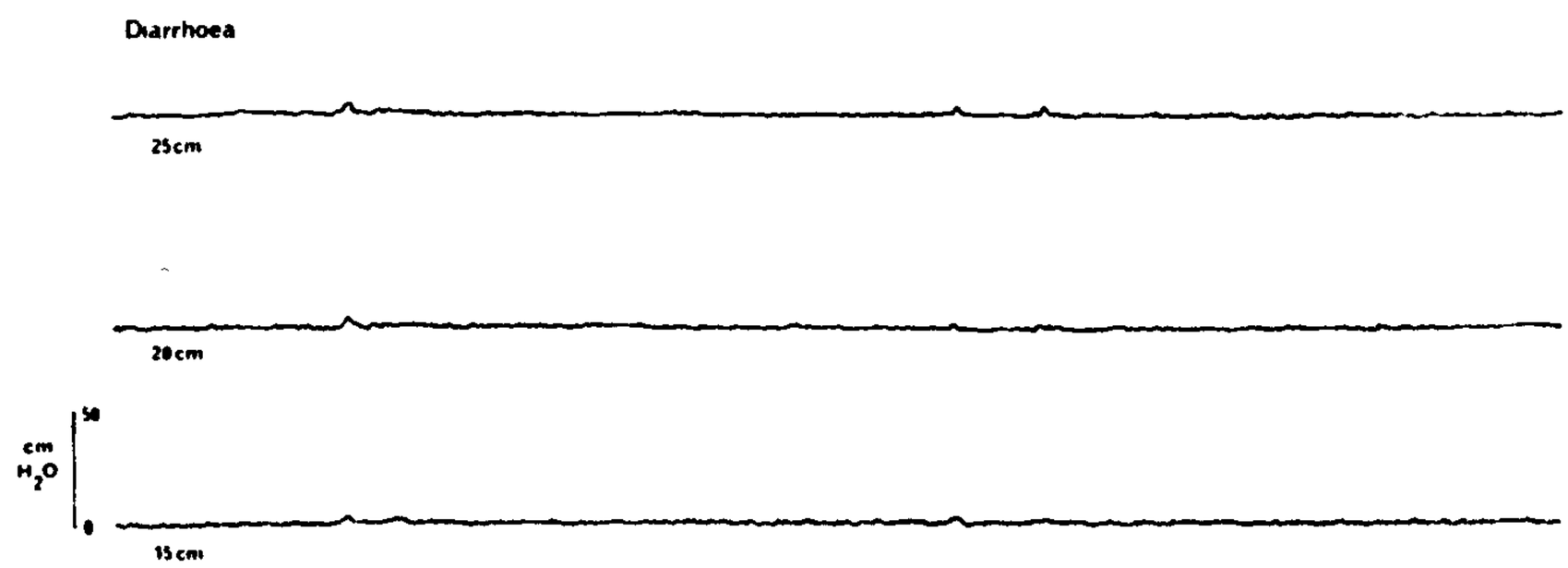


FIGURE 8f. COLONIC MOTILITY IN IRRITABLE BOWEL SYNDROME WITH DIARRHOEA.
In this patient who reported 12 bowel actions daily no spontaneous pressure changes occured throughout the recording.

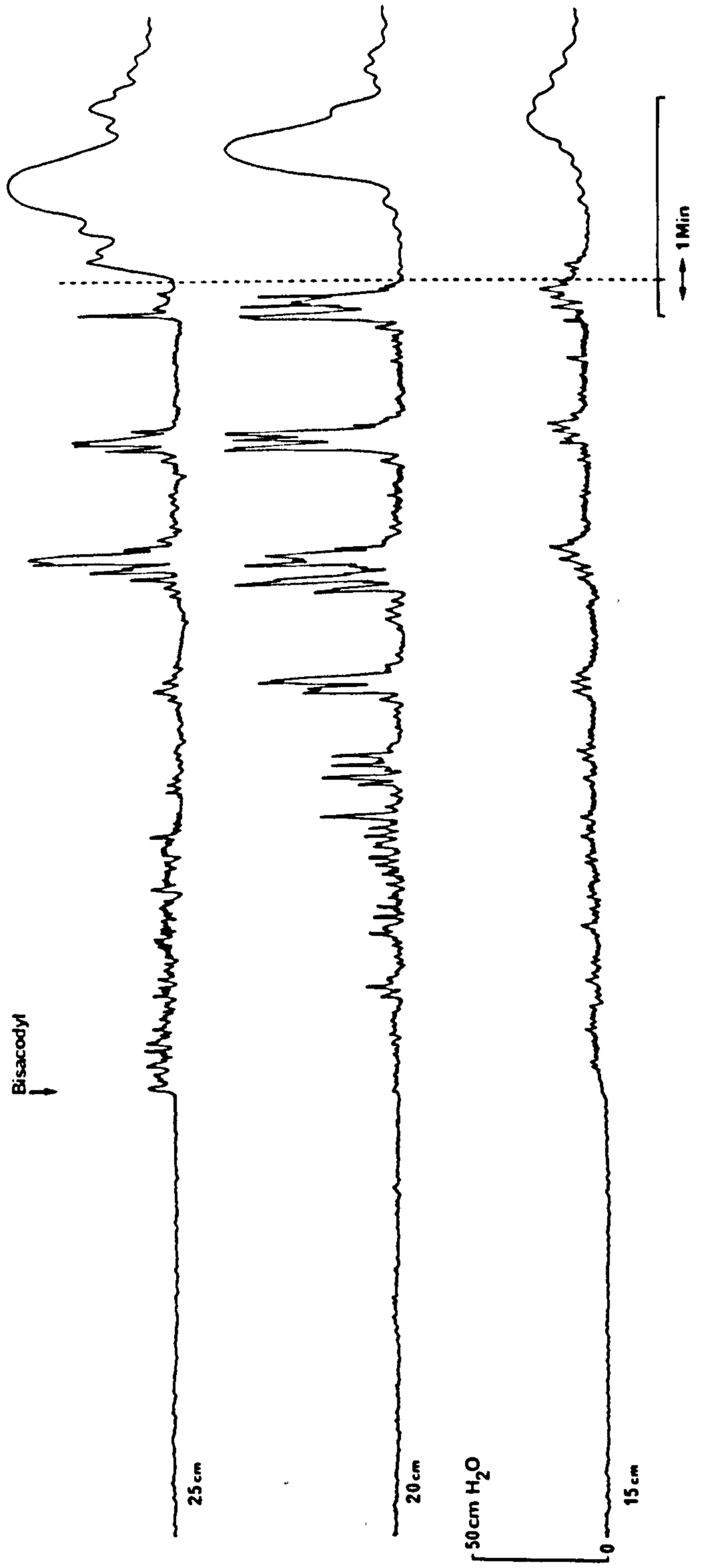


Figure 8g. NORMAL RESPONSE TO BISACODYL.
This trace shows the normal response to the introduction of bisacodyl to the sigmoid colon. There is an immediate response which develops to produce peristaltic waves progressing caudally. At the end of the record the paper speed has been increased to demonstrate the direction of the pressure waves.

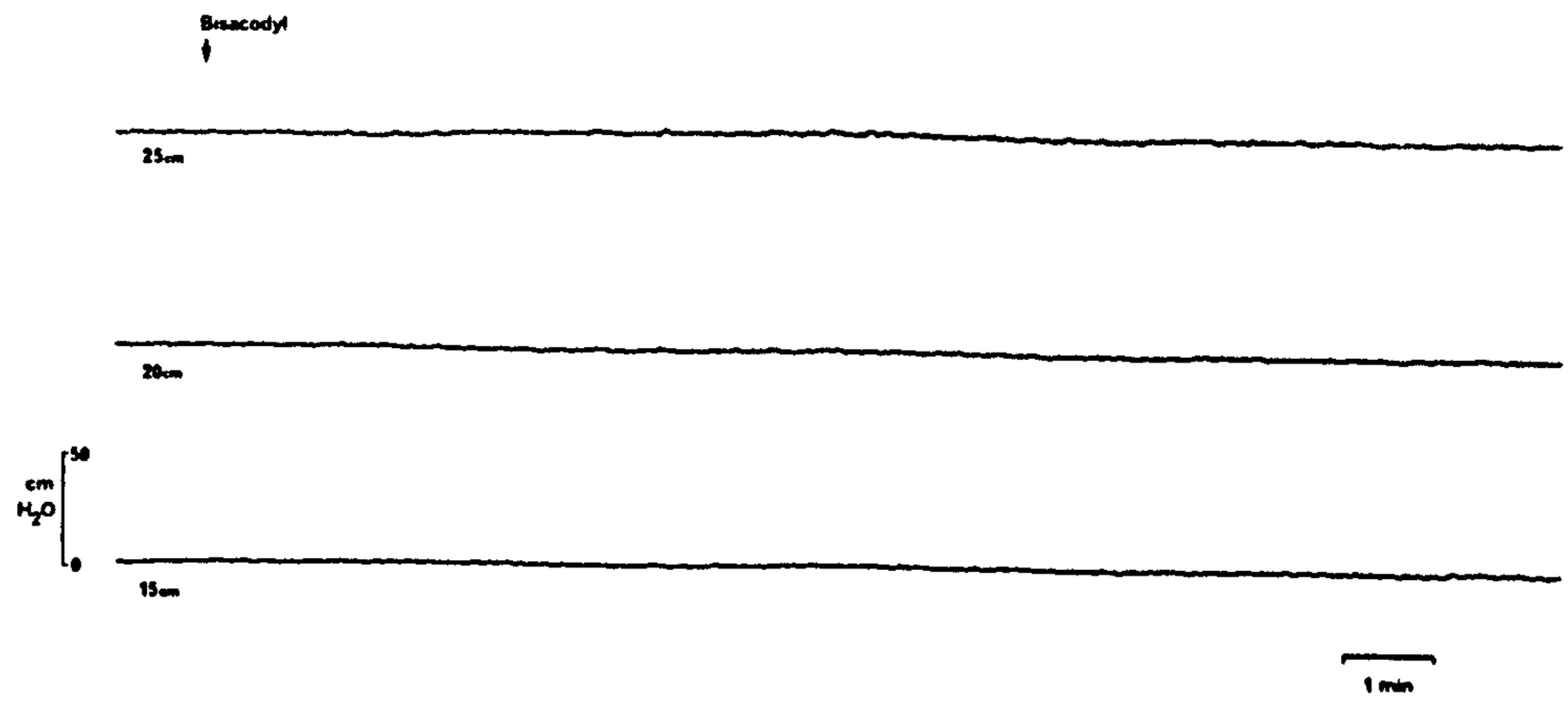


FIGURE 8h. RESPONSE TO BISACODYL (1).
In this patient with slow transit constipation the introduction of 10 mg. bisacodyl at 25 cm. from the anus had no observable effect on colonic pressure wave activity.

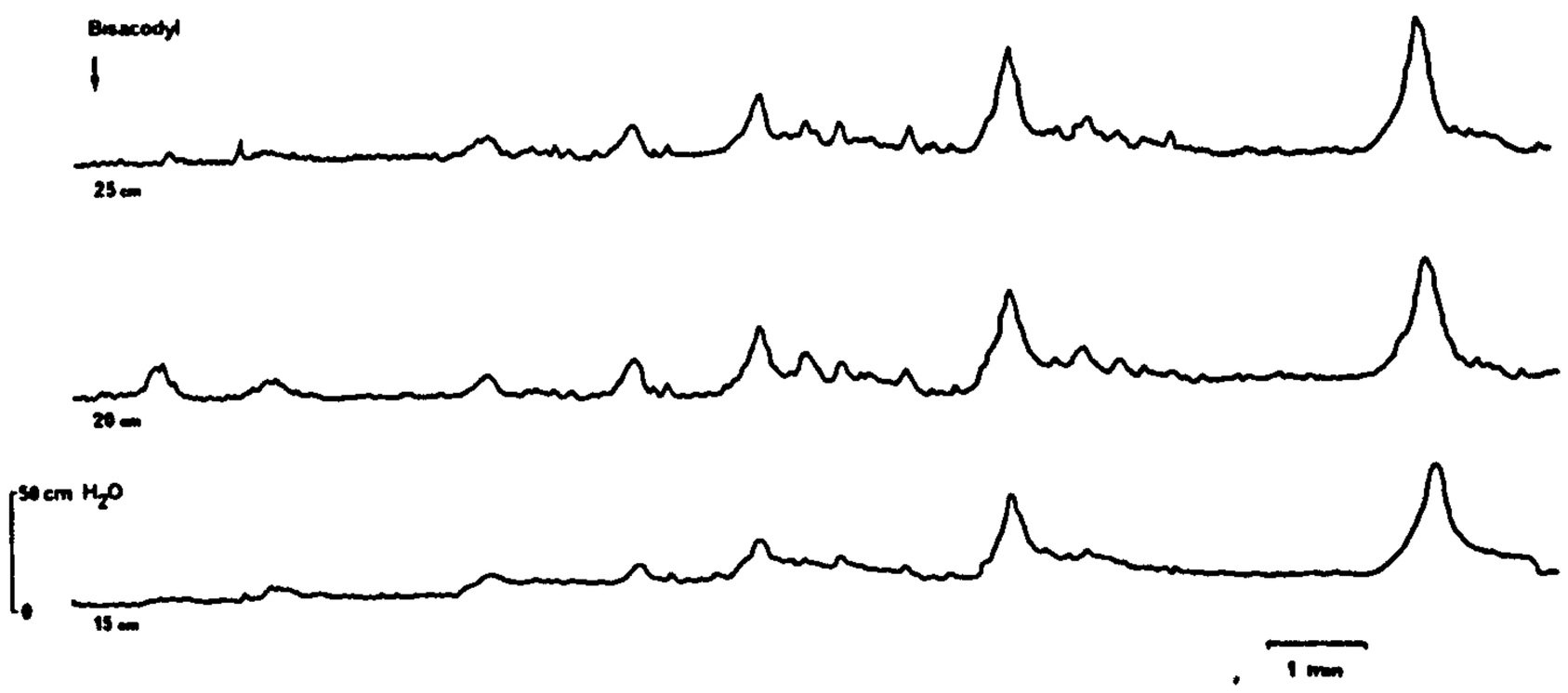


FIGURE 8i. RESPONSE TO BISACODYL (2)
In this patient with slow transit constipation the introduction of bisacodyl lead to the development of peristaltic waves which are seen to be progressing caudally.

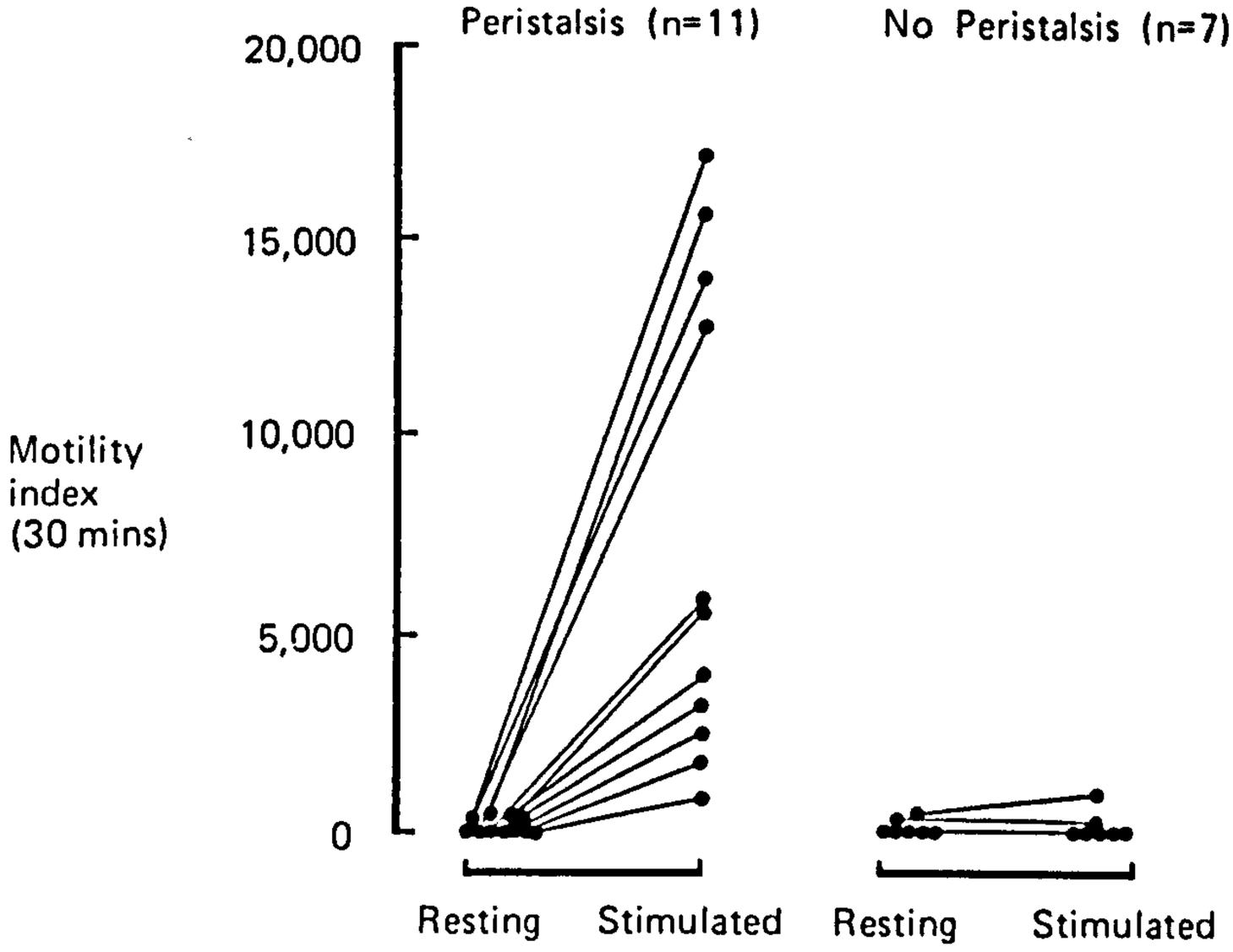


FIGURE 8j. RESPONSE TO BISACODYL (MOTILITY INDICES). The motility indices for 18 patients with slow transit constipation divided into 2 groups. On the left those who developed peristalsis after stimulation with intraluminal bisacodyl and on the right those who did not. The lines connect the recorded activity for each patient for the 30 minutes before and after stimulation.

having been symptomatic for a mean period of 18 years compared with 12 years in the rest. Neither of these differences were however statistically significant. A careful history of laxative use did reveal that 6/7 non-responders had been given laxatives before the age of 10, compared with only 2/11 of those who developed peristaltic waves ($p<0.02$). One other curious observation was that three patients developed colonic type pain during the 30 minutes after introduction of bisacodyl, but without showing any increase in colonic pressure wave activity or peristalsis. This suggests that in these patients the drug might have been absorbed systemically and then stimulated the proximal colon.

DISCUSSION

Movements of the colon are of two main types: mass movements and segmenting constrictions. Although these were described over 75 years ago, the regulation of colonic motor activity is still not properly understood. In particular, the role of the intrinsic and extrinsic nerves is uncertain, and their relationship to the recently dicovered gut regulatory peptides has yet to be elucidated.

Mass peristalsis was first observed by Holzknecht (1909) as an extremely rare occurence. He noticed rapid movement of colonic content along the transverse colon with temporary abolition of segmentation. This has since been shown to occur after meals and exercise (Hertz et al. 1913, Holdstock et al. 1970) as well as in response to laxatives

(Ritchie 1972). In the latter study mass movements were seen to correspond on motility records to high pressure peristaltic waves which moved caudally. Most bowel movements occur after meals (Rendtorff et al. 1966) possibly following a mass movement which propels stool to the rectum. One mode of action for stimulant laxatives may therefore be the generation of an artificial mass movement.

Segmenting constrictions hold colonic content and can propel it in either direction (Case 1913, Barclay 1935). In this way residue can be mixed and absorption enhanced. These muscular constrictions, and the consequent movements of stool and gas, result in pressure changes on motility records which may not correlate with the movements of the bowel wall (Ritchie et al. 1962). Segmenting activity is affected by many factors; increasing in response to emotion, drugs such as prostigmine and opiates, some peptide hormones and to distension of the rectum. Activity may be reduced by drugs such as atropine, 5-hydroxytryptamine and some groups of prostaglandins (Misiewicz 1975).

Present knowledge about the neural control of gut motility suggests that the autonomic nervous system has a major role. Sympathetic nerves are mainly inhibitory and parasympathetic excitatory but bilateral sympathectomy does not appear to affect bowel function and vagotomy has little effect on colonic function (Alvarez 1958, Rattan 1981). However, constipation is a feature of a generalised autonomic neuropathy (Bannister 1984). Damage to the sacral parasympathetic nerves, which supply the sigmoid colon and rectum, can lead to loss of rectal sensation and failure of

colonic motility with an inability to defaecate (Devroede 1974).

The importance of the intrinsic nervous system is best illustrated by the failure of colonic peristalsis in Hirschsprung's disease when there is a deficiency of the myenteric plexus from birth. Acquired damage whether from drugs or in Chagas' disease has a similar effect (Smith 1972). In some of these conditions the peptide containing nerves are also damaged, but the contribution of peptide containing cells and nerve fibres inside and outside the plexus to the coordination of peristalsis is unknown (Reimann 1980, Long et al. 1980, Bishop et al. 1981).

The motility findings in the women with slow transit constipation were unexpected as they were amongst the most severely constipated patients attending the hospital. If colonic hypersegmentation is a major factor in the pathogenesis of constipation then they might have been expected to demonstrate this to extreme. The immediate conclusions to be drawn therefore are either that constipation is not associated with colonic hypermotility, that this form of constipation is not a colonic problem, or that the inactivity has contributed to the symptoms of these patients.

The findings of previous investigators have been supported by the results in those patients with the irritable bowel syndrome and constipation with normal transit time. In addition the inactivity in those with diarrhoea is confirmed. This makes it unlikely that differences in methodology resulted in the unusual findings

in the slow transit group. It is important to point out that 3 of the irritable bowel group had normal studies, and that if the results on the other 6 were excluded one might draw the conclusion that there was very little difference between any of the groups. Some of the constipated patients had traces that were completely flat and indistinguishable from those of the patients with diarrhoea. This must cast doubt on the idea that diarrhoea is solely a consequence of lack of colonic segmentation in functional bowel disorders.

Next the possibility that the results are artefactual must be considered. Recording colonic pressures with balloons has come under considerable criticism in the past. Open ended perfused tubes are preferred by some but may easily be blocked by stool, particularly in constipated patients like these who had no bowel preparation. Connell (1962) argued that a miniature balloon not obstructing the lumen gives the most reliable result. Ideally some sort of strain gauge transducer is needed that could be attached directly to the colonic wall. At present this seems technically impossible and may explain the current enthusiasm for electromyography. It is accepted though that this study, like others previously, has measured colonic pressures and not necessarily movement. Progressive waves passing from one section to another are however almost certainly indicative of peristalsis.

Another objection to be considered is that the colon was too wide for pressure changes to be detected. It has been shown that patients with idiopathic megacolon exhibit hypomotile records using the same methods (Connell

1961b). This may be because the bowel lumen is so wide that the walls do not meet during constriction and thus pressure in an isolated segment recorded by the balloon cannot rise. This objection can be countered by the studies in Chapter 5 which have shown that the lumen of the rectum and colon is of normal diameter in patients with slow transit constipation.

Although the difference between the mean motility index of the controls and the slow transit group was not statistically significant a number of the patients had records that were almost completely flat at rest. The fact that some patients with constipation can have flat traces has been recorded previously, though its association with delayed intestinal transit has not been noted. In the original paper reporting the paradoxical colonic motility of patients with diarrhoea and constipation, a few patients with constipation were noted to have hypomotile traces (Connell 1962). On analysing his data he arbitrarily divided the constipated patients into those above and below 40 years of age. The older group were found to have significantly less activity in the sigmoid colon. This difference he then postulated might reflect a progression of the disorder or the effect of prolonged laxative use. The results of the present study show that hypomotility can be a feature of young constipated patients as well (Figure 8b). Many had laxatives in childhood and the idea that hypomotility reflects laxative induced damage could therefore still be correct.

In another more recent study 8 out of 49

chronically constipated patients were found to have hypomotile records after a meal (Meunier et al. 1979). The barium enemas were said to be normal, though megacolon was not mentioned nor defined and a high residue diet was not given to exclude dietary constipation. No transit studies were performed, so it is difficult to relate the findings to the present work. All their hypomotile group were women and had abused laxatives. Of interest however is the fact that a prolonged fast was used, as in the present work, and they found little difference between the fasting records of the constipated patients and controls.

In addition to idiopathic megacolon flat motility records have been reported in patients following transection of the spinal cord (Connell 1963). This occurred in those with high cord lesions, but not in others with lower lesions whose activity was increased. The explanation given for this was that there was failure of inhibition of the lumbar outflow with high cord lesions which allowed uncontrolled inhibitory activity. On the other hand eliminating the lumbar outflow with a low cord lesion leaves the sacral tracts uninhibited and results in overactivity. In addition it was noted that patients with paraplegia following an intrathecal alcohol block (which would damage fibres to both groups) had the least activity of all. Some of these effects may have been due to widening of the colon as paraplegics are prone to faecal retention and megacolon.

The studies with bisacodyl were therefore performed to investigate whether the lack of activity was due to a defect in the intrinsic nerves of the bowel wall rather than

the extrinsic nerves. This seemed the most likely explanation in view of the known effects of chronic laxative use on the myenteric plexus (Smith 1972). The fact that high pressure peristaltic waves were produced in some patients is evidence against there being a methodological fault leading to apparent hypomotility.

The failure of some patients to respond to a very high dose of Bisacodyl suggested the possibility of a myenteric plexus lesion in these cases. It also showed that these patients were correct in claiming that stimulant laxatives did not seem to help them. Further studies were therefore carried out to investigate this possibility and are presented with a discussion of the possible significance of the motility findings in Chapter 9.

CHAPTER 9

EXAMINATION OF THE MYENTERIC PLEXUS

INTRODUCTION

Conventional histological examination of gut tissue relies on paraffin sections which are cut in the vertical plane. By this method it is possible to demonstrate the absence of ganglion cells in the myenteric plexus in conditions such as Hirschsprung's disease and Chagas' disease (Bodian et al. 1951, Martins-Campos et al. 1973). However when the neuronal loss is not so great no abnormality may be seen, and the pathologist then has no idea of the extent of any damage.

Smith (1967) has pioneered the application of a technique of silver impregnation to the examination of the myenteric plexus. The anatomy of the plexus is thus demonstrated by taking sections in the horizontal plane, exposing a large number of ganglion cells. The neuropathology of several conditions has been defined when often conventional histopathological techniques showed no abnormality (Smith 1972). Of particular interest to the present study are changes demonstrated in patients who have abused laxatives (Smith 1973) or suffer from an autonomic neuropathy (Smith 1982).

In a previous study of the resected colons of 20 patients with idiopathic megacolon 8 showed an abnormality of the plexus. Five of these had changes which were presumed secondary to laxatives, but there were 3 other cases with an

unusual pathology. This was a loss of argyrophil cells, with the remainder pale and swollen and an increase in the number of Schwann cells (Smith 1972). A further report gave details of 4 other patients with idiopathic megacolon who had a quite distinct anomaly of the plexus, thought to be due to a developmental defect (Smith et al. 1977). No previous study had looked at the neuropathology of idiopathic constipation without megacolon. It was decided to do this and to take the opportunity to compare the pathology with colonic function in life.

PATIENTS STUDIED

12 patients underwent colectomy during the time the other studies in this thesis were carried out. All have been included in the 21 patients described in Chapter 14 which gives the clinical results of surgery. All were women with a mean age of 29 years and had been symptomatic on average for 14 years. In all cases the ano-rectal distension reflex was normal excluding Hirschsprung's diease. Barium enema examinations had shown a colon and rectum of normal calibre excluding megacolon as the cause of their symptoms. Whole gut transit rate measured with radiopaque polythene pellets had been shown to be markedly prolonged. Biochemical tests and physical examination had excluded other primary causes for their symptoms. Surgical treatment had been advised with reluctance after an average attendance at St Mark's hospital of three years during which time all medical treatment had been ineffective.

METHODS

a) Pathology

The technique used to examine the tissue was that described by Scofield (1960) and modified by Smith (1972). The details of the staining method are given in appendix 2. The colons were opened flat whilst fresh and fixed in formalin. 12 pieces of tissue 1cm. by 2cm. were selected from representative areas of the colon. These were then placed flat and cut on a dissecting microtome. 50 micron sections were cut until the level of the myenteric plexus was reached. Sections through the plexus were then prepared using the silver stain which shows neural tissue black against a brown background. The anatomy of the myenteric plexus was then examined. The sections were read 'blind' by an experienced neuropathologist (Dr Barbara Smith) who was ignorant of the case histories and of the results of the motility studies prior to surgery.

b) Motility studies

All 12 patients had undergone colonic motility studies prior to operation and are included in the series of 19 patients with slow transit constipation described in Chapter 8. For the purposes of comparison with the neuropathology, a simple classification of the motility findings was devised. The colonic activity in the resting phase was described as normal if there were spontaneous pressure waves or flat if there was no spontaneous activity over the whole hour. The response to Bisacodyl was then classified as follows: i) Good: Immediate and marked

increase in colonic pressure wave activity with peristalsis progressing caudally. ii) Moderate: Delayed response with less marked increase in activity but still some peristaltic waves. iii) Poor: Small increase in activity but without the development of any peristaltic waves. iv) Flat: No observable effect.

RESULTS

Details of the pathological findings and motility studies for each patient are shown in Table 9a. There were no gross pathological changes and all the colons appeared entirely normal to the naked eye (Figures 9a-b and appendix 1). Routine histopathological examination showed no abnormalities apart from microscopic melanosis coli in one patient. All except one patient had some abnormality of the myenteric plexus on silver staining. The changes in the severe cases consisted of complete loss of the argyrophil plexus with a marked increase in Schwann cells indicating that extrinsic damage to the plexus had occurred. Some argyrophobe cells remained and conventional paraffin sections had shown normal ganglion cells to be present. The plexus damage was most marked distally exept for two cases where the transverse colon was worst affected. In some of the cases there was also evidence of mild laxative induced damage.

The motility studies on 7 of the patients showed a completely flat trace in the resting state. Of these 6 showed no response to the introduction of bisacodyl. This inactivity did not however correlate with the pathological

findings. The patient who showed the best response to bisacodyl (Case 11) had a severely abnormal plexus with a marked reduction in cell numbers and no axonal processes. Some cases with only a mild abnormality had a flat record with no response. However the only patient with a normal plexus (Case 7) did have a normal motility trace and a good response to stimulation. Examples of the normal appearence of the myenteric plexus on silver stain and of the abnormal findings in the constipated patients are given in Figures 9c-d.

The pathological changes were in some ways similar to those previously described in patients with cathartic colon exept that this usually presents at a later age. The area of colon affected was also different, as the worst changes in anthraquinone induced damage appear in the ascending colon. In addition in cathartic colon the muscle wall is thinned and there is colonic dilatation (Smith 1973). The other striking finding is that there was no melanosis coli in these patients wheras severe melanosis is a feature of cathartic colon. Laxative damage seen in younger patients usually has a different histological picture, with large pale neurones rather than the shrunken cells seen here (Smith 1972). The main differences between the three groups are summarised in Table 9b.



FIGURE 9a. COLECTOMY SPECIMEN 1.
Colon removed from a patient with slow transit constipation demonstrating that the lenghth and diameter are normal.

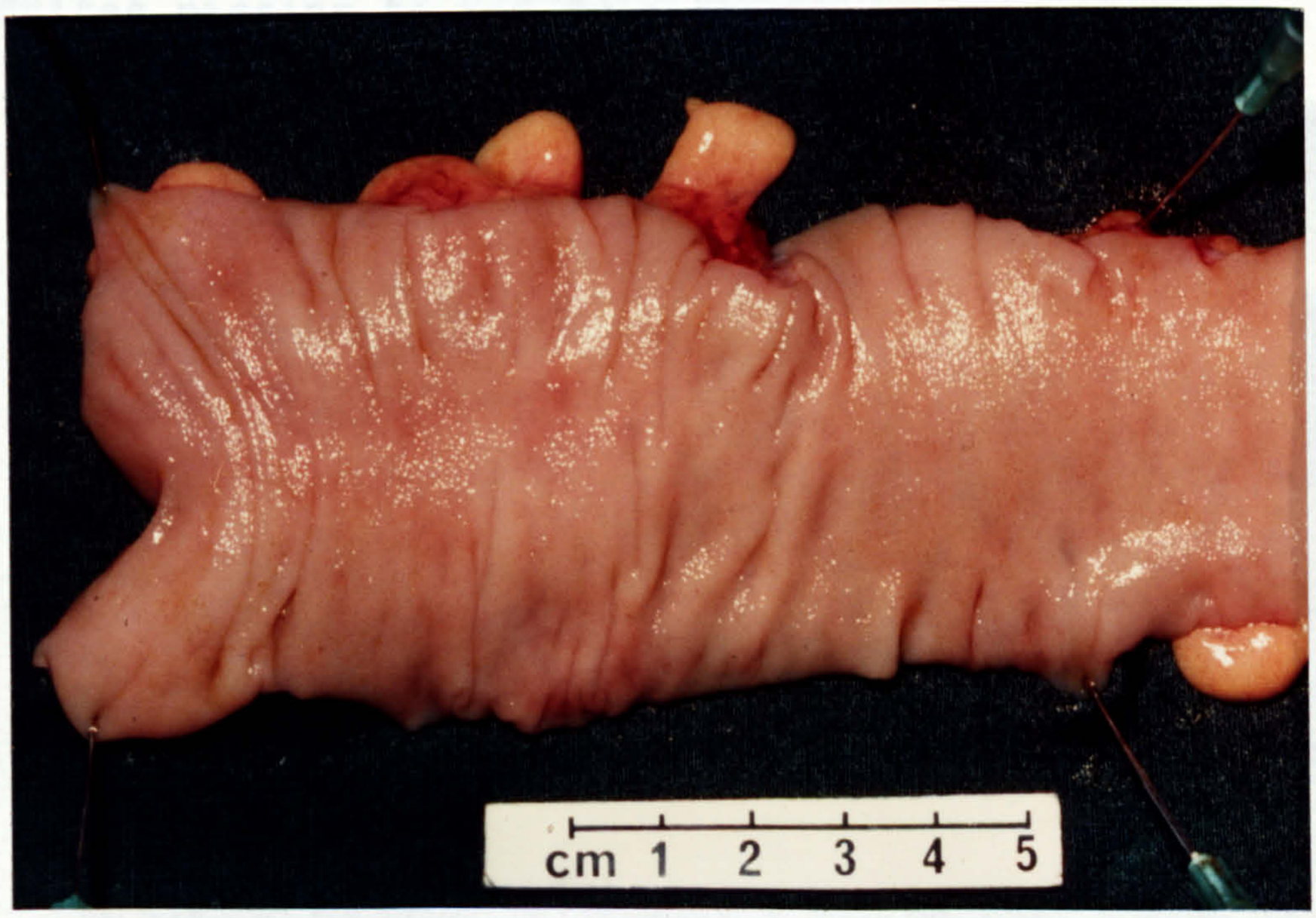


FIGURE 9b. COLECTOMY SPECIMEN 2.
Opened portion of the sigmoid colon showing a normal mucosa.

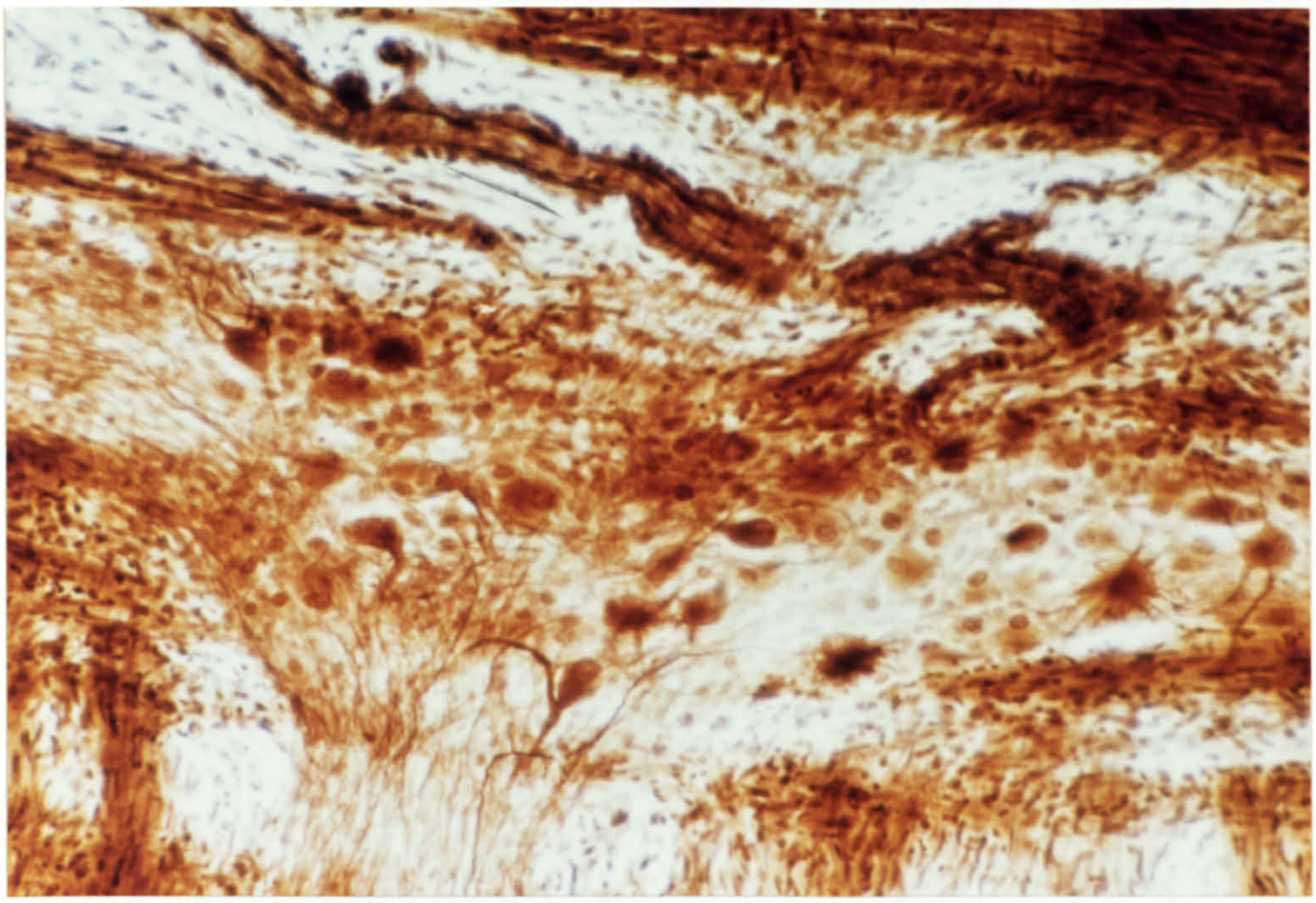


FIGURE 9c. NORMAL MYENTERIC PLEXUS.
Section from a control subject (colon removed for carcinoma) showing a mesh of nerve fibres entering the inter-muscular plane. Numerous argyrophil cells are seen with axons and dendrites passing to and from them.

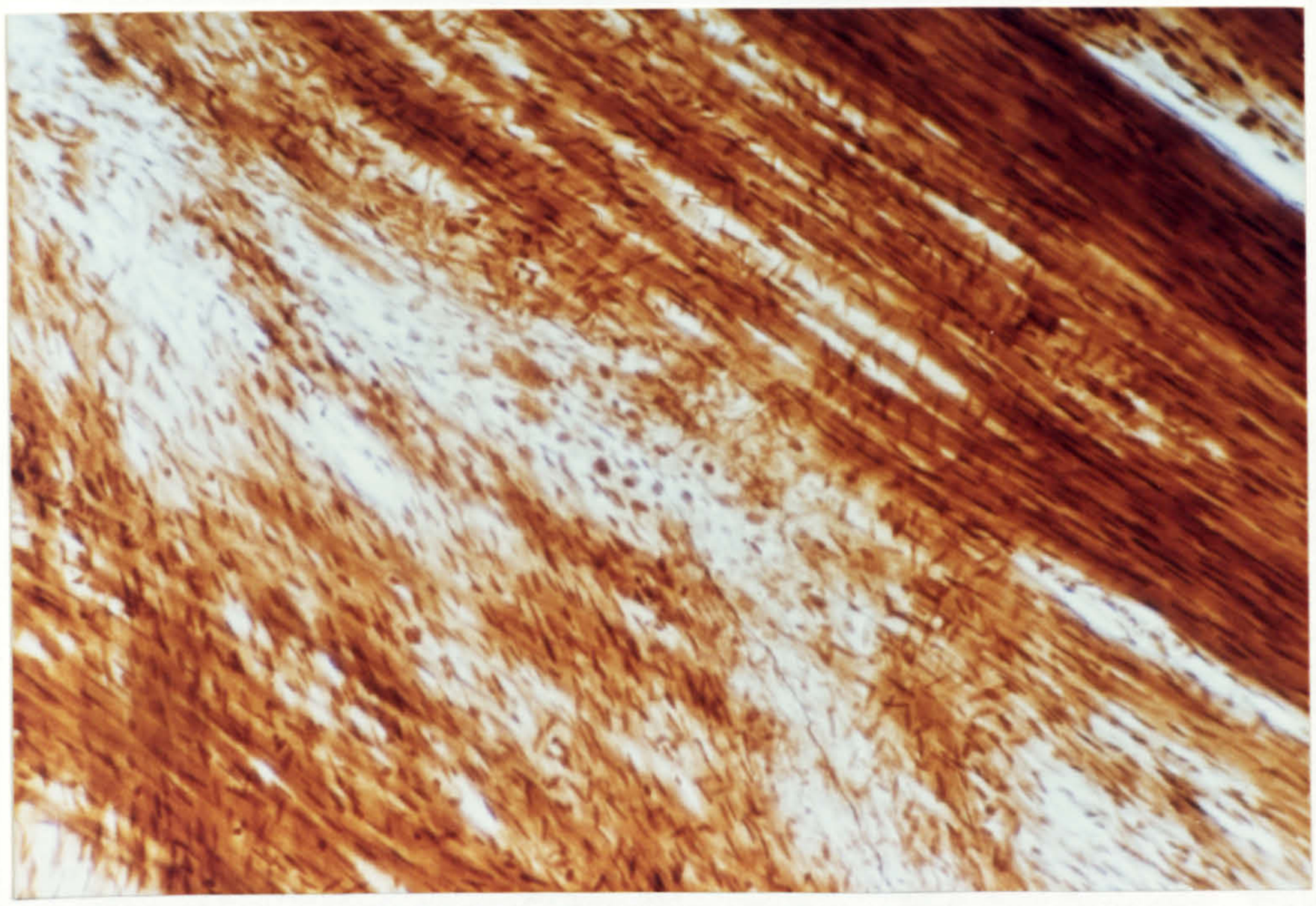


FIGURE 9d. MYENTERIC PLEXUS IN CONSTIPATED PATIENT.
Section from a 21 year old girl with slow transit constipation (Case 5). A single nerve fibre only is seen entering the inter-muscular plane where the ganglia should be. Two abnormal cells are seen in the centre which have not taken up the silver stain properly. This pattern was found along the whole length of the colon.

TABLE 9a

Details of the cases studied correlating the pathological findings with pre-operative colonic motility. The ages of the patients at the time of operation are given together with the length of history of constipation (LOH). A summary of the neuropathologists report on each colon is given indicating the appearence of the ganglion cells and their processes (axons and dendrites). The presence of scwann cell proliferation indicates axonal loss. Finally the presence or absence of melanosis coli on parrafin section is noted.

CASE	AGE	LOH	PATHOLOGY				MOTILITY	
			Cell numbers / shape	Processes	Schwannosis	Melanosis	Fasting	Stimulated
1	42	38	Reduced and Shrunken	Reduced	Yes	No	FLAT	FLAT
2	53	31	Markedly reduced but normal size	Reduced	Yes	No	FLAT	FLAT
3	55	30	Mild reduction shrunken/deformed	Reduced	No	No	FLAT	FLAT
4	22	18	Mildly reduced shrunken/deformed	Reduced	No	No	FLAT	FLAT
5	21	17	Scanty, pale and shrunken	Reduced	Yes	No	FLAT	FLAT
6	35	15	Normal number but shrunken	Reduced	No	No	FLAT	FLAT
7	28	11	Normal	Normal	No	No	Normal	Good response
8	35	7	Scanty and shrunken	Reduced	Yes	No	FLAT	Good response
9	23	7	Moderate reduction but normal shape	Reduced	Yes	No	Normal	Poor response
10	21	6	Normal number but small and dark	Stumpy	No	No	Normal	Mod. response
11	19	5	Markedly reduced and stunted	None	Yes	Mild	Normal	Good response
12	19	3	Mildly reduced and shrunken	Reduced	No	No	Normal	Poor response

TABLE 9b

Comparison of changes reported previously in older patients with cathartic colon or severe laxative abuse at a young age (Smith 1972, 1973) with the present study.

	LAXATIVE DAMAGE		SLOW TRANSIT
	Mild	Severe	
AGE	20-30	50-70	20-40
CELLS	Pale swollen	Small dark	Mixed picture most dark and shrunken
AXONS	Normal	Reduced	Reduced
SCWANNOSIS	No	Yes	Yes
MELANOSIS COLI	Yes	Very severe	No
AREA AFFECTED	--- Right side of colon ---		Recto-sigmoid

DISCUSSION

This study has shown a distinctive abnormality of the myenteric plexus in some patients with severe idiopathic constipation. The pathology of the autonomic nervous system can be difficult to interpret but there is no doubt that the loss of axons and neurones with Schwann cell proliferation seen in some of these patients represents acquired damage to the plexus. The picture is not that of a failure of development where the plexus would show many neuroblasts and non-argyrophil cells in the ganglia and also little or no argyrophil plexus (Smith 1972).

Interpretation of the changes when some of the argyrophil plexus is retained but the cell morphology is abnormal is particularly difficult. Neurones may be flattened, shrunken or irregular in shape with clubbed or absent processes. The axons may show swellings and the plexus have fewer fibres than normal. In such cases the opinion of an experienced neuropathologist is the only way of assessing the changes and this is obviously subjective. The technique of staining is difficult and unreliable, the result being affected by the thickness of the tissue and unstable reagents. This study has benefited from the opinion of an expert and pioneer in the field, but for future studies some method of quantification of cell loss will be needed, and this may be possible with a histochemical technique such as the immunological stain for neurone specific enolase.

The bisacodyl stimulation test has not been shown to correlate well with the amount of neuronal damage. This

was disappointing but may be because patients differ in the amount of damage needed to cause symptoms or loss of peristalsis. Alternatively, cells not shown up by this method (the argyrophobe cells) may be important and loss of both groups may have to be severe before peristalsis fails. It is also possible tha the submucosal plexus, not shown here, is important. This is another reason why a histochemical technique that shows up all the ganglion cells or nerve fibres and defines the neurotransmitters contained in them might be better.

All that can be said from this study is that an abnormal response to bisacodyl is found in every case to be associated with plexus damage though the converse is not true. The finding of a flat trace before and after stimulation would therefore provide some evidence to support surgical treatment. It seems however from the present study that it is unusual in any case for physicians to recommend a patient for colectomy who does not have myenteric plexus damage. The results of surgical treatment in this group of patients can be good (Chapter 14) and the finding of a neurological disorder might give a rational ground for advising colectomy in those patients most severely affected. Unfortunately this damage cannot be diagnosed on a full thickness rectal biopsy as insufficient tissue is obtained and in any case the damage in some of these patients was in the transverse colon. Further tests of colonic function may have to be tried. It is possible that an examination of colonic responses to other drugs or to eating as well as bisacodyl stimulation might give better results.

Another interesting result of this study is that the patients with the longest history are more likely to have a flat motility trace after bisacodyl stimulation. This suggests the disorder is progressive and it seems most likely that it is some form of drug induced damage. One patient however had a normal plexus which indicates that a plexus disorder may not be the primary cause of slow transit constipation. It is probable that acquired plexus damage exacerbates the symptoms and leads to a failure of laxative treatment. The changes are not the same as those seen with anthraquinone type laxatives and it is possible that newer synthetic laxatives damage the plexus, though this has not yet been investigated.

CHAPTER 10

GUT HORMONE LOCALISATION IN THE COLON

INTRODUCTION

Though the first gut hormone was discovered by Bayliss and Starling in 1902, little progress was made in our understanding of the origin and function of such hormones until the introduction of immunological techniques. Two procedures, radioimmunoassay and immunocytochemistry, have provided most information. However there are considerable technical difficulties and much still to learn about the normal distribution of these hormones, some of which are still being discovered.

Further difficulties arose when it became apparent that some "gut hormones" were distributed all over the body, and other neuropeptides from the brain were also in the gut. The concept of a diffuse neuro-endocrine system has developed. Some peptides may have dual roles both as neurotransmitters, and as circulating hormones in the conventional sense.

Despite the fact that the physiology is not understood, there have nevertheless been some exciting discoveries. For example, the aganglionic segment of bowel in Hirschsprung's disease is depleted of Vasoactive intestinal polypeptide (VIP), enteroglucagon, and somatostatin (Bishop et al. 1981). Investigations like this in patients where there is a known neurological disturbance, when correlated with a disorder of gut function, may help us

to understand the purpose of these peptides found in the gut.

The human colon has a relatively poor peptide content. Only one circulating gut hormone, enteroglucagon, is found here. However, there are five peptides thought to have a purely local action. These are somatostatin, which may have a paracrine function, and the neurotransmitters VIP, substance P, bombesin, and enkephalin (Polak et al. 1980). The colectomies performed on the patients described in Chapter 14 offered a chance to study the tissue localisation of colonic peptides. This was of interest because it gave a chance to correlate the findings with a physiological abnormality (slow colonic transit time), as well as the disorder of the myenteric plexus found on silver staining (Chapter 9).

PATIENTS STUDIED

i) Slow transit constipation (7)

These were all women with severe constipation and are included in the 12 studied in Chapter 9. All had a normal barium enema and a prolonged gut transit time. The routine histopathology on the resected specimens was reported as normal.

ii) Idiopathic megacolon (7)

This group comprised 5 women and 2 men who had undergone bowel resection for megacolon. In all cases the recto-anal inhibitory reflex had been normal and no aganglionosis was demonstrated on routine histopathology.

iii) Controls (13)

Tissue for control studies was obtained from patients undergoing bowel resection for malignant colonic tumours. Tissue samples were taken as far away from the tumour as possible. Eight patients were male and 5 female. In no case did routine histopathology show any abnormality of the colon apart from the resected tumour.

METHODS

a) Rectal biopsy pilot study

Before the extraction from colectomy specimens was performed a pilot study to examine rectal biopsies was carried out. This compared tissue from the lower part of the rectum in patients with slow transit constipation, irritable bowel syndrome and megacolon. Samples were taken through a sigmoidoscope from patients attending outpatients or for control tisue from those attending for routine colonoscopy. The same biopsy forceps was used for all the patients to give approximately equal sized samples.

The results of this study were unsatisfactory because of a wide variation in the tissue content of the peptides. This could have been due to faulty handling or to the fact that the biopsies were of different depth. It is impossible to achieve the same depth in different patients and many of the neuropeptides are concentrated in the myenteric plexus which may not be sampled in all cases (Ferri et al. 1983). This method was therefore abandoned in favour of examination of resected specimens. The results are

tabulated in Appendix 3.

b) Study of resected tissue

Samples were collected from the operating theatres immediately on removal. The bowel was opened longitudinally where appropriate and rinsed in buffered saline. A strip of bowel wall 1 cm wide was cut along the whole length of the specimen. This sample was then transported on ice to the laboratories where it was divided for radioimmunoassay and histochemical study. In all cases the tissue was in the laboratory within one hour of removal.

i) Radioimmunoassay

Tissue for microscopy and assay was taken in matched pairs from different sites along the length of each sample. The samples for radioimmunoassay were cut into pieces of approximately 100 mg., blotted dry and weighed by addition to polypropylene boiling tubes of known weight. The samples were boiled at 100°C for 10 minutes in 0.5 M acetic acid in a water bath. The tubes were then weighed and frozen in liquid nitrogen. At the completion of the studies the tubes were thawed, the samples centrifuged and the supernatant withdrawn. This was than analysed for the following peptides using radioimmunoassay: VIP, Enteroglucagon and substance P.

ii) Histochemistry

Tissue samples were fixed in a 0.4% solution of benzoquinone in buffered saline for 2 hours. Samples were

then stored in phosphate buffered saline (PBS) containing 7% sucrose and 0.01% sodium azide until examination. The fixed tissue was then mounted on cork mats and orientated so that sections could be cut perpendicular to the gut wall. Samples were then snap frozen in Arcton (pre-cooled in liquid nitrogen) and 10 m sections cut in a cryostat at -20°C.

The localisation of peptide containing cells and nerves was done using indirect immunofluorescence. Fresh cryostat sections of the fixed tissue were picked up on dry slides and then placed in racks in covered petri dishes to create a damp chamber. A drop of commercially prepared antiserum diluted in 0.01 M PBS was applied to the section using a pipette and left for 1 hour at 4°C.

The sections were then rinsed in 3 changes of PBS for 5 minutes each and all the surface of the slide wiped dry apart from the section. A drop of the appropriate fluorescein labelled anti-globulin diluted in PBS was then placed on the section and left for 1 hour. Three washes in PBS were then performed as before and the sections mounted in buffered glycerin for viewing under ultra-violet light. Both positive and negative controls were used throughout.

The antisera used were raised to VIP, substance P, enteroglucagon, somatostatin, bombesin, met-enkephalin and neurotensin. Details of the antisera used and their specificity are given in Appendix 4.

RESULTS

a) Radioimmunoassay

No differences were found in the tissue levels of hormones in the three groups. The recorded values tended to be lower in the constipated patients, particularly those with a megacolon. However, there was a wide variation in the levels recorded and this together with the relatively small numbers of patients studied resulted in there being no statistically significant changes. Unfortunately, the somatostatin assay was not completed because of technical difficulties at the time these results were compiled. The mean values for all the samples were as follows:

	Substance P	Enterolucagon	VIP
CONTROLS	16.0 ± 3.1	54.3 ± 13.9	454 ± 126
SLOW-TRANSIT	13.6 ± 5.8	53.7 ± 24.2	340 ± 76
MEGACOLON	9.0 ± 1.9	24.8 ± 9.4	202 ± 52

All values in pMol/Gm. wet weight

Mean ± s.e.m. (all NS v controls)

b) Immunocytochemistry

All sections were examined by two independant observers for the presence of immunoreactive cells or nerves. The results were classified as follows:

+++ strongly positive
++ positive
+ weakly positive
-+ equivocal
- not seen

Normal tissue examined routinely and in the control tissue gave a varied response, presumably reflecting minor changes in the preparation of the tissue. Somatostatin and enteroglucagon were only seen in mucosal cells. The other peptides were only seen in nerve fibres. No neurotensin immunoreactivity was seen in the control tissue.The range of results seen in normals and the two groups of constipated patients are given in table 10a.

No significant abnormalities were seen in the patients with idiopathic megacolon. One patient with slow transit constipation had a generalised decrease in staining towards the rectum, with a particularly marked loss of VIP and substance P containing nerves. In the others the nerves and cells looked normal though in two there was a marked increase in the number of Schwann cells. Correlation with the peptide levels was good, in particular the patient with a diminution in staining distally had the following tissue levels:

	EG	VIP	Sub P
Proximal	13.4	164	6.3
Middle	0.8	6	9.7
Distal	5.3	5	0.3

All in pMol/gm. wet weight

TABLE 10a

Assessment of immunofluorescent nerves and cells in the constipated patients and controls.

SLOW TRANSIT CONSTIPATION

Case	BOM	EG	SOM	SubP	VIP	ENK	NT
1	-+	++	+	++	++	-	-
2	-+	++	+	++	++	-	-
3	-+	++	+	++	++	-	-
4	-+	+	-+	+	++	-	-
5	-	++	++	++	++	+	-
6	-	++	+	+	++	-	-
7	-	++	+	+	+++	-	-

IDIOPATHIC MEGACOLON

Case	BOM	EG	SOM	SubP	VIP	ENK	NT
1	-+	+	-+	+	+++	-	-
2	-+	++	+	++	++	-+	-
3	-+	+	-+	++	++	-+	-
4	-+	++	+	++	++	-+	-
5	-+	++	+	++	++	-	-
6	-+	++	+	++	++	-+	-
7	-+	++	+	++	++	-	-

CONTROL FINDINGS

Bombesin	- to -+
Enteroglucagon	all ++
Somatostatin	all +
Substance P	+ to ++
VIP	all ++
Met-enkephalin	- to -+
Neurotensin	all -

There appeared to be no correlation with the abnormalities reported on the silver staining (Chapter 9). For example, one patient (No.5 in table 9a - see page 167) who had a flat motility trace and a markedly abnormal myenteric plexus (Figure 9d) was reported as having no abnormality on microscopy. Mean values of extracted peptides concurred with the staining in her case being as follows: Enteroglucagon 75 pMol/gm. wet weight, VIP 559 pMol/gm., and substance P 18 pMol/gm.

DISCUSSION

The results presented here suggest that an abnormality of the peptide containing nerves is not responsible for the symptoms of patients with slow transit constipation. In addition there is no evidence of any disorder of these nerves in idiopathic megacolon. The findings are in contrast to those in Hirschsprung's disease and Chagas' disease (Bishop et al. 1981, Long et al. 1980), conditions which also result in chronic constipation. The diminution found on radioimmunoassay was not significant and can probably be accounted for by the dilatation of the bowel giving a relative reduction in cells and nerves per gm. wet weight. This is particularly likely in idiopathic megacolon where there was much muscle hypertrophy. The much milder trend in slow transit constipaion may be because the colon is longer than normal.

The morphology of the myenteric plexus was normal and this make it difficult to explain the findings on silver staining presented in Chapter 9. The increased numbers of

Schwann cells reported in 2 patients with slow transit does however correlate with evidence of axonal loss on silver staining. It is possible that the present techniques of immunocytochemistry are missing some nerve fibres as well as staining up the argyrophobe cells not well seen with the silver stain. More basic research clearly needs to be done on the relationship between the two techniques, and it is possible that immunocytochemical stains would show more interesting results if horizontal sections were used rather than the vertical samples in this study. It should be possible to define the biochemical characteristics of the argyrophil and argyrophobe cells using immunocytochemistry, and this might help our understanding of gut physiology and explain why a depletion of the former is associated with constipation.

The single patient who had a deficiency of peptides in the distal colon had been using regular phosphate enemas up to the time of surgery. It is therefore possible that the peptide containing cells and nerves were damaged by this local treatment. All the patients had used large doses of stimulant laxatives by mouth, and it is surprising that no changes were seen that might correspond with those reported on electron microscopy in laxative abusers (Reimann et al. 1980).

CHAPTER 11

A STUDY OF GUT HORMONE RELEASE

INTRODUCTION

The gut is thought to be the largest endocrine organ in man. Immunocytochemical techniques have shown peptide containing cells scattered throughout the body with particularly high concentrations in some parts of the intestine. Despite the explosion of interest in the past 15 years the exact role of many of these hormones is unknown. It is possible that some act locally rather than through systemic release. Animal experiments using massive doses of these hormones and the occasional hormone producing tumour in man have confirmed that they can have dramatic effects on gut motility and bowel function (Bloom 1977).

One method of examining the effects of circulating gut hormones in man is the use of a test meal. This has been applied to several disease states and shown, for example, that motilin levels are elevated in most conditions giving rise to severe diarrhoea. (Besterman et al. 1978a, 1978b, 1979, 1982). In a previous study of patients with functional bowel disease the same group claimed to have found no significant changes in circulating gut hormone levels. (Besterman et al. 1981). However it was felt that their study had failed to define the different sub-groups with constipation and diarrhoea adequately. More importantly, if there was really no difference in circulating hormone levels between patients with severe constipation or diarrhoea, then

it would suggest that these hormones do not have a regulatory role - at least through their systemic release. Because the different nutriments used in the previous studies have contradictory effects on the release of some gut hormones, a simple oral water load was used in the present study. This had previously been shown to be a reliable stimulus to motilin, pancreatic polypeptide, gastrin and vasoactive intestinal polypeptide release in man. (Christofides et al. 1979).

The main purpose of this study was to compare 12 girls with severe constipation and slow intestinal transit with a group of age and sex matched controls. But it was also thought important to see if there were any differences between this group and those who also complained of constipation but had a normal gut transit rate. A third group of constipated patients with idiopathic megacolon was also included. Finally a group with severe functional diarrhoea was studied to provide a comparison with the opposite extreme of bowel symptoms. Another criticism of the previous study (Besterman et al. 1981) was that their patients did not have a consistent pattern of symptoms. It is recognised that patients with functional disorders can have symptoms fluctuating from one extreme to the other on successive days (Connell 1961). All the patients included in this study had a consistent pattern of symptoms and those with constipation had no episodes of diarrhoea and vice versa.

PATIENTS STUDIED

(a) Slow-transit Constipation

This group comprised 12 women with severe constipation. They had been symptomatic for an average of 14 years before the study. All had a normal barium enema but evidence of delayed intestinal transit measured by using radio-opaque markers. The mean number of bowel actions per week in this group was 0.5. Mean age was 27 years and mean percentage ideal body weight 97 ± 2%.

(b) Idiopathic Megacolon

This group comprised 7 women and 3 men who were chronically constipated with evidence of colonic and rectal dilatation on barium enema. Hirschsprung's disease had been excluded by the presence of a normal recto-sphincteric reflex. All had rectal obstipation at the time of study. The mean number of bowel actions per week was 3.5. Mean age was 23 years and mean percentage ideal body weight 95 ± 3%.

(c) Irritable Bowel Syndrome (Pain and constipation)

This group comprised 8 women and one man who complained of abdominal pain and constipation. None experienced any episodes of diarrhoea. Barium enema and bowel transit studies were normal in all cases. The mean number of bowel actions per week was 4.3. Mean age was 45 years and mean percentage ideal body weight 102 ± 4%.

(d) Irritable Bowel Syndrome (Diarrhoea)

This group comprised 6 women and 3 men who complained of chronic diarrhoea and who had been fully investigated with no cause being found. All had a normal barium enema. The mean number of bowel actions per week was 78. Mean age was 46 years and mean percentage ideal body weight 112 ± 11%.

(e) Control Subjects.

The different age range in the disease groups presented a problem. A matched group was found of 12 women for the girls with slow transit constipation and a second group of both men and women with a higher mean age then selected for the groups with the irritable bowel syndrome. The control studies were performed on volunteers from the medical and ancillary staff of St. Mark's and St. Bartholomew's hospitals. None had sought medical advice for any bowel complaint and reported bowel function to direct questioning as "normal". The exact frequency of their bowel actions was not sought prior to the study to avoid bias in selection. Subsequent questioning showed that the mean number of bowel actions per week in these groups was 6. Group A comprised 12 women whose mean age was 29 years and mean percentage ideal body weight 98 ± 4%. Group B comprised 9 women and 3 men whose mean age was 42 years and mean percentage ideal body weight 101 ± 4%.

METHODS

The stimulus to release of gut hormones was 10ml/Kg. body weight of tap water drunk within five minutes following a 12 hour fast. Blood samples were taken from an indwelling catheter at -10, 0, +10, +20, +40, and +60 minutes from ingestion of water. The samples were taken into heparinized tubes and 400 KI units of aprotinin added. After separation, the plasma was stored at -20°C until assay.

Hormone radioimmunoassays were carried out at The Royal Postgraduate Medical School using conventional methods (Bloom et al. 1982). Antisera were raised to synthetic human gastrin 1, natural human pancreatic polypeptide, natural porcine vasoactive intestinal polypeptide, natural bovine neurotensin and natural porcine motilin. The gastrin assay saw both sulphated and non-sulphated forms of G-17 and G-34 and showed less than 2% cross-reactivity with CCK-8 and CCK-33. The other antisera showed no significant cross reaction with other known gut regulatory peptides. The assays could detect the following plasma changes with 95% confidence: Gastrin 1 pMol/L, pancreatic polypeptide 4 pMol/L, vasoactive intestinal polypeptide 1.5 pMol/L, neurotensin 5 pMol/L, motilin 3 pMol/L.

Statistical significance was assessed by use of the Students t test or the Wilcoxon test. The integrated incremental response (IIR) was calculated to give an approximation of the total release of each hormone over the hour, less the mean basal value. In the following example for hormone 'X' the values recorded are represented by the

letters a-e:

For hormone X.

Mean basal +10 +20 +40 +60 mins

a b c d e

$$\text{IIR for X} = \frac{a+b}{2}x10 + \frac{b+c}{2}x10 + \frac{c+d}{2}x20 + \frac{d+e}{2}x20 - ax60$$

In those groups where fasting levels were widely apart the total integrated response (TIR) is a more appropriate measure for comparing hormone release and this is calculated in the same way but without subtracting the basal value (ax60 in the example above).

RESULTS

Pilot studies showed no significant difference in the responses of neurotensin and vasoactive intestinal polypeptide for the girls with slow transit constipation and their controls. These hormones were therefore not studied further. The results of the pilot studies on these two hormones are shown in figures 11 d-e.

Basal (fasting) concentrations, peak rise after the water load, the integrated incremental response (IIR) and total integrated response (TIR) of motilin, pancreatic polypeptide and gastrin over one hour are shown in tables 11 a-c. The mean rise of these hormones in the patients with slow transit constipation is illustrated in Figure 11a, and compared with the responses of the patients with diarrhoea.

Figures 11 b-c demonstrate the rise in pancreatic polypeptide and gastrin in the other constipated patients.

a) Slow transit constipation

Fasting levels of both motilin and pancreatic polypeptide were normal but the peak rise and IIR of these hormones were significantly reduced ($p<0.01$ and $p<0.05$). Fasting levels and the peak response of gastrin were reduced ($p<0.05$) and there was also a marked decrease in the TIR ($p<0.01$).

b) Idiopathic Megacolon

Fasting levels of motilin were normal but there was a reduction in the peak rise and IIR ($p<0.02$ and $p<0.01$). No significant changes were seen in the pattern of pancreatic polypeptide release. Gastrin release tended to be reduced but the only significant difference was at +20 mins (controls 14.0 pmol/L ± 2.1 s.e.m.; megacolon 4.5 pmol/L ± 2.6; $p<0.05$). The TIR was however reduced ($p<0.01$).

c) Irritable bowel syndrome (pain and constipation)

No significant differences were seen in the pattern of motilin and pancreatic polypeptide release. Levels of gastrin tended to be reduced and there was a significant reduction in both the peak rise ($p<0.05$) and the TIR ($p<0.02$).

d) Irritable bowel syndrome (diarrhoea)

Fasting levels of motilin were raised ($p<0.05$) but

TABLE 11a
Plasma motilin levels after drinking water (10ml/Kg.) in control subjects and patients with constipation or diarrhoea. Basal and peak hormone levels are given as pMol/l. Integrated incremental response and Total integrated response are given in nMol/l over 60 minutes.

	Basal	Peak rise	IIR	TIR
Controls (a)	32.0 ± 6.9	38.4 ± 6.0 ***	1.38 ± 0.2 ***	3.30 ± 0.56
Constipation	34.9 ± 5.4	13.25 ± 4.6	0.29 ± 0.1	2.32 ± 0.41
Controls (b)	39.4 ± 8.3	41.2 ± 5.0 **	1.48 ± 0.2 ***	3.84 ± 0.6
Megacolon	47.8 ± 4.5	16.2 ± 8.4	0.38 ± 0.4	3.25 ± 0.37
IBS/Pain	64.3 ± 13.9 *	30.0 ± 8.0	0.98 + 0.2	4.55 ± 0.78
Diarrhoea	83.4 ± 15.1	33.0 ± 10.0	1.13 ± 0.4	6.13 ± 0.83

P values versus controls
* p<0.05
** p<0.02
*** p<0.01

TABLE 11b
Plasma pancreatic polypeptide levels after drinking water (10ml/Kg.) in control subjects and patients with constipation or diarrhoea. Basal and peak hormone levels are given as pMol/l. Integrated incremental response and Total integrated response are given in nMol/l over 60 minutes.

	Basal	Peak rise	IIR	TIR
Controls (a)	39.8 ± 10.0	109.7 ± 37.4	3.57 ± 1.3 *	6.11 ± 1.8 ***
Constipated	25.8 ± 5.1	40.7 ± 13.0	1.40 ± 0.4	2.94 ± 0.6
Controls (b)	37.7 ± 10.1	111.4 ± 36.7	38.4 ± 1.4	6.12 ± 1.9
Megacolon -	36.2 ± 11.1	77.2 ± 42.1	2.40 ± 1.1	5.61 ± 1.7
IBS/Pain	46.7 ± 10.4 **	99.1 ± 41.9 **	4.22 ± 1.4 ***	6.38 ± 1.9 ***
Diarrhoea	75.1 ± 17.0	228.0 ± 49.7	8.35 ± 1.9	12.89 ± 2.0

P values versus controls * $p<0.05$
** $p<0.02$
*** $p<0.01$

TABLE 11c
Plasma gastrin levels after drinking water (10ml/Kg.) in control subjects and patients with constipation or diarrhoea. Basal and peak hormone levels are given as pMol/l. Integrated incremental response and Total integrated response are given in nMol/l over 60 minutes.

	Basal	Peak rise	IIR	TIR
Controls (a)	7.5 ± 2.2	11.5 ± 2.6 *	220 ± 87	699 ± 113 ***
Constipated	2.5 ± 0.6	5.6 ± 1.8 *	88 ± 48	247 ± 47
Controls (b)	8.3 ± 2.3	12.0 ± 3.9	228 ± 97	729 ± 148 **
Megacolon	4.1 ± 0.5	5.7 ± 1.9 *	69 ± 34	323 ± 39 **
IBS/Pain	4.7 ± 0.7	4.4 ± 1.5	113 ± 40	297 ± 63
Diarrhoea	10.5 ± 6.6	11.5 ± 4.8	211 ± 69	843 ± 44

P values versus controls * $p<0.05$
** $p<0.02$
*** $p<0.01$

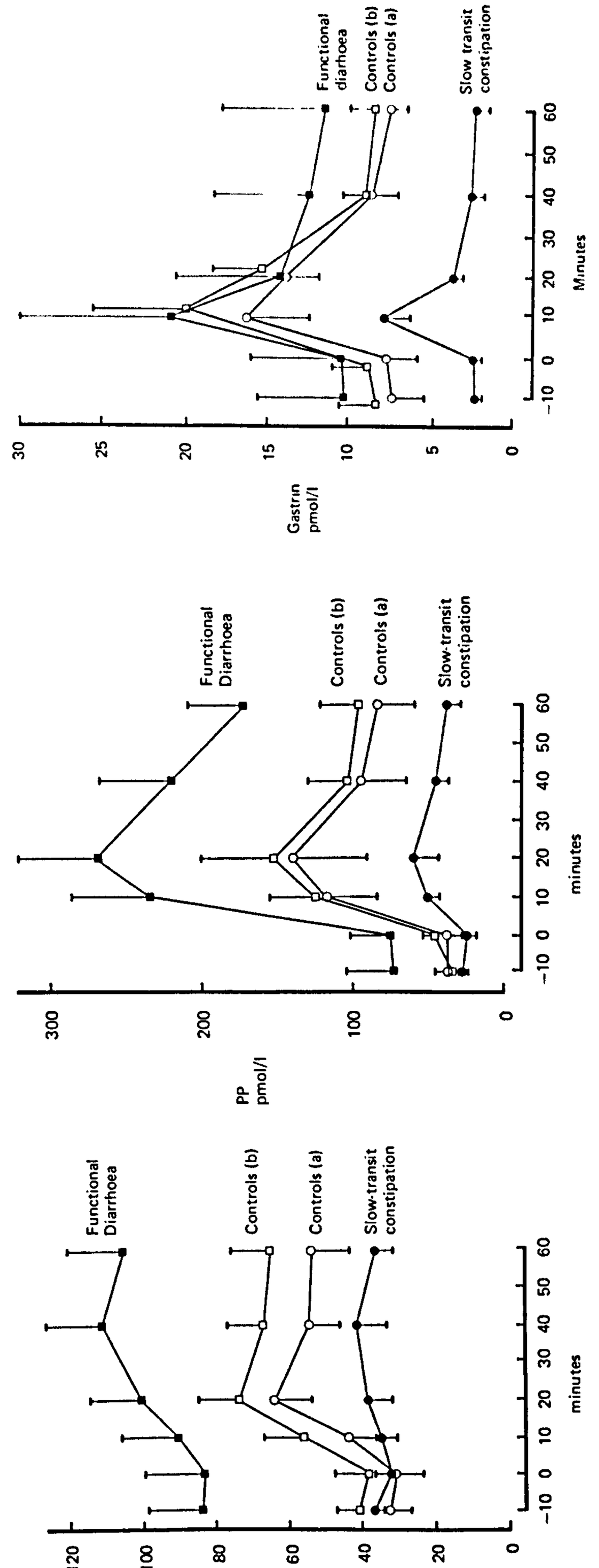


FIGURE 11a
Plasma levels of motilin, pancreatic polypeptide and gastrin before and after an oral water load in the patients with slow transit constipation and functional diarrhoea compared to control subjects. Control group (a) are matched to the constipated patients and control group (b) to those with diarrhoea.

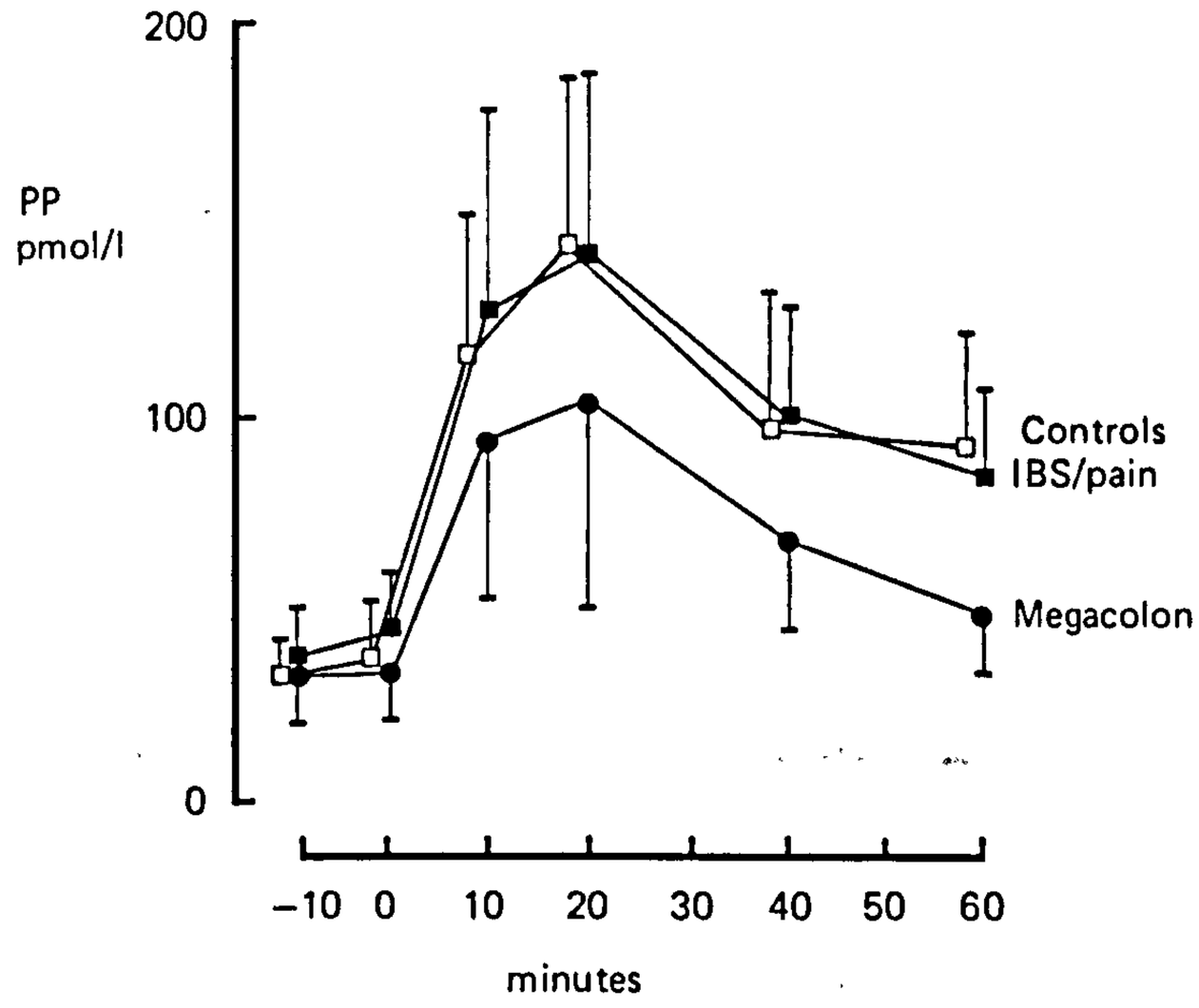


FIGURE 11b. PANCREATIC POLYPEPTIDE RESPONSES IN MEGACOLON AND IRRITABLE BOWEL.
This shows the response of the other two groups of constipated patients matched with the second control group. None of the differences for the group with megacolon were statistically significant.

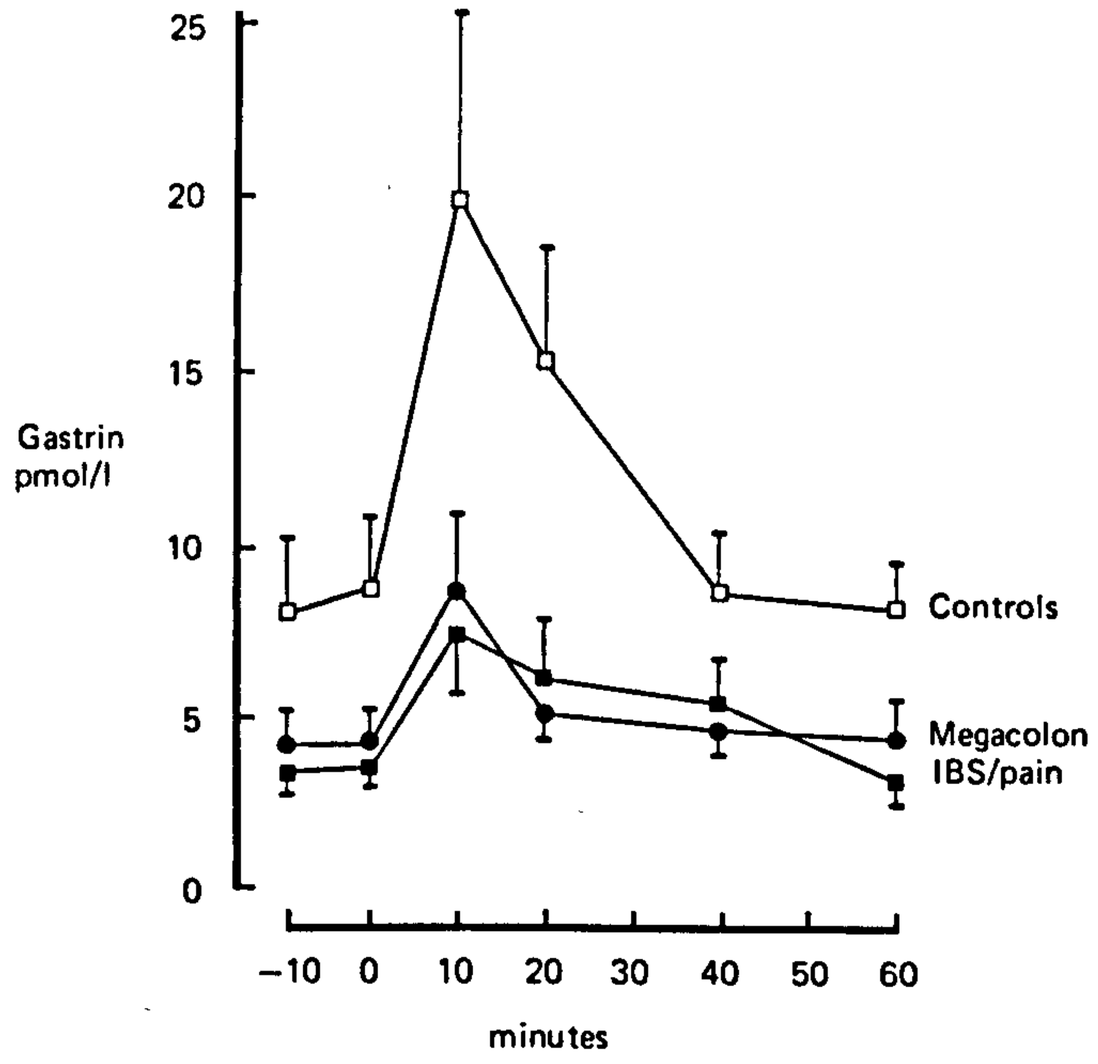


FIGURE 11c. GASTRIN RESPONSES IN MEGACOLON AND IRRITABLE BOWEL.
This shows the reduced gastrin response in both the other groups of constipated patients when compared with controls. The total integrated responses for both groups were significantly reduced.

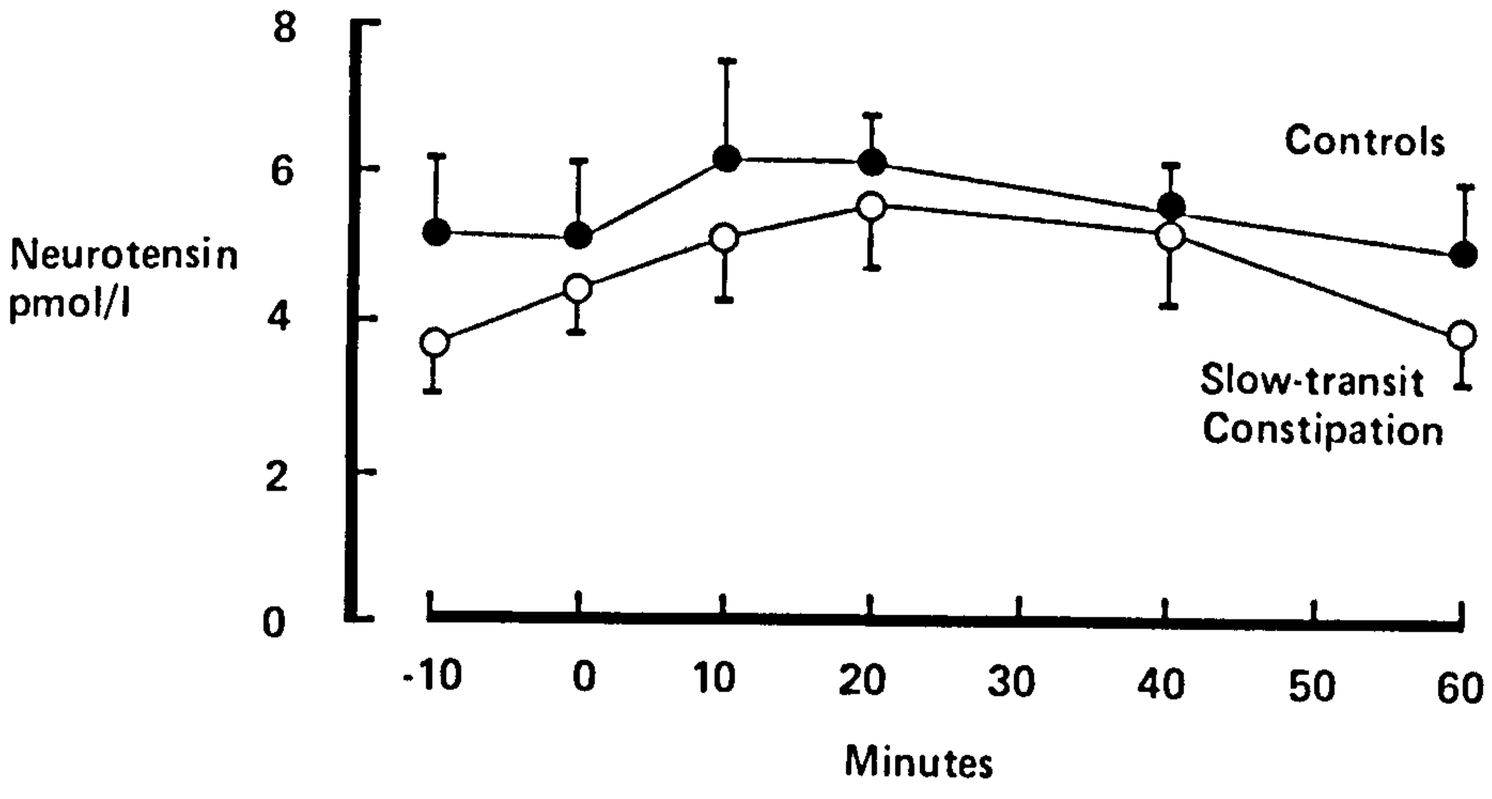


FIGURE 11d. PILOT STUDY: NEUROTENSIN LEVELS.
Response of circulating plasma neurotensin after an oral water load in 10 patients with slow transit constipation compared to control subjects (mean ± sem).

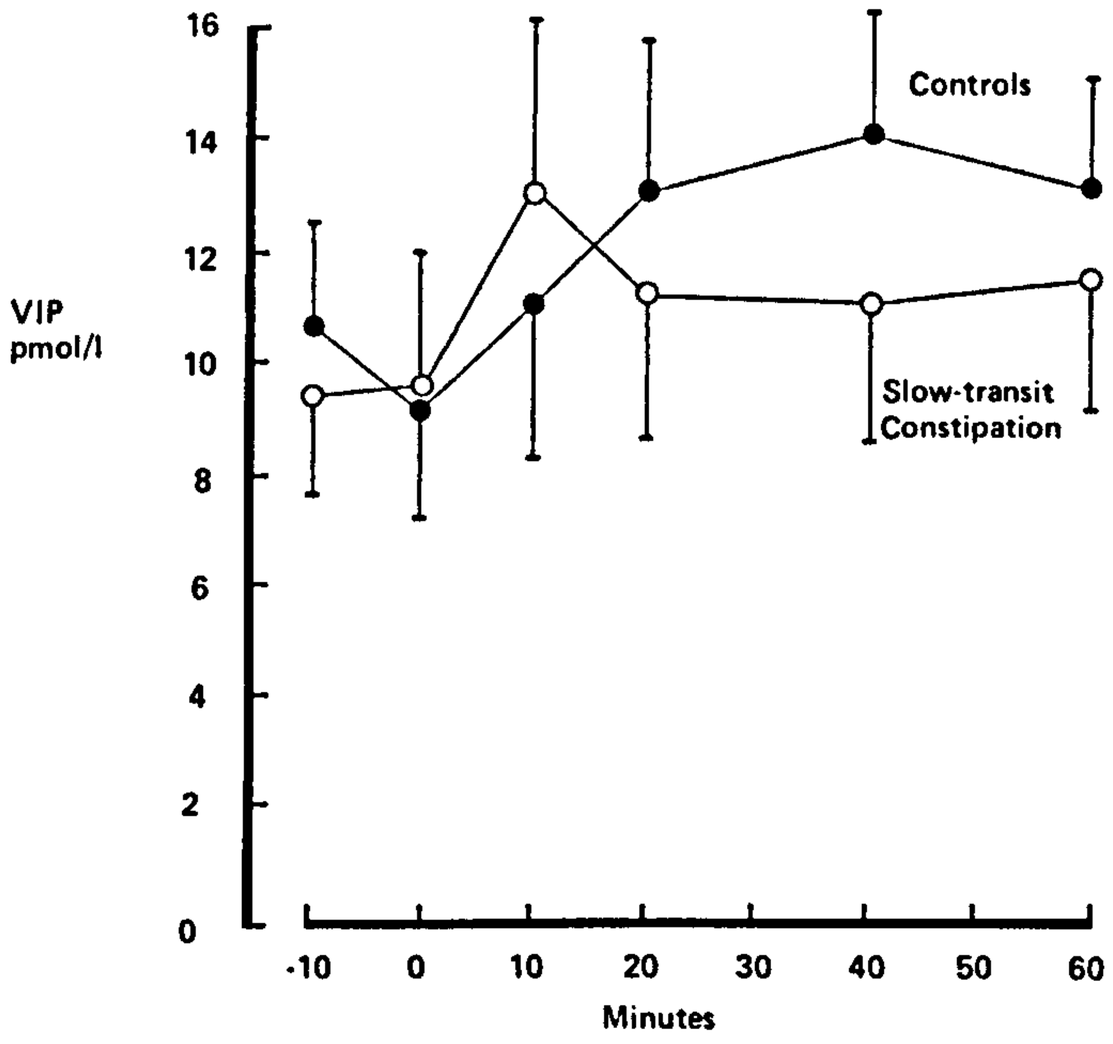


FIGURE 11e. PILOT STUDY: VIP LEVELS.
Response of circulating plasma vasoactive intestinal polypeptide to an oral water load in 10 patients with slow transit constipation compared to control subjects (mean ± sem).

the subsequent rise was within the normal range. Both fasting levels of pancreatic polypeptide and the peak rise were increased ($p<0.02$). There was a corresponding marked increase in both the IIR and TIR ($p<0.01$). There was no abnormality of gastrin release.

DISCUSSION

In a previous study of a group of patients with the irritable bowel syndrome Besterman et al. (1981) examined the effect of the Hammersmith test breakfast on circulating levels of gut hormones. The test meal they used included eggs and toast which delay gastric emptying and release a wide range of hormones including those that are thought to have an inhibitory effect on gut motility such as enteroglucagon. The water load was chosen for this study because it should pass rapidly through the stomach to the small intestine and because it is a good method of stimulating motilin release. The primary purpose of this study had been to look at motilin release in severe constipation and the discovery of abnormal gastrin release was a surprise. Though the water load does stimulate gastrin release, the levels are only about 25% of those obtained with the test breakfast.

Motilin is a 22 amino-acid peptide found principally in the duodenum and jejunum. It is released after a meal but the mechanism is complex, with fat stimulating and glucose inhibiting its release. Distension

of the stomach whether by a balloon or with water stimulates a large rise in plasma levels with values about twice those obtained by the test breakfast. It is likely though that the rise seen after drinking water is partly due to distension of the duodenum and jejunum as the stomach normally empties rapidly (Christofides et al. 1979, Christofides et al. 1981). The actions of motilin in man are still not clear. Studies in animals have suggested a relationship between circulating motilin levels and the peristaltic activity of the gut (Itoh 1981). Colonic pressure activity can be stimulated in humans by infusion of motilin in concentrations similar to those found after a meal (Rennie et al. 1980), and low motilin levels have been recorded in pregnancy where there is reduced smooth muscle tone in the gut and when constipation is a common problem (Christofides et al. 1982).

Raised motilin levels are found in patients with diarrhoea from a variety of causes (Besterman et al. 1978a, 1978b, 1979, 1982). Studies in man have shown that motilin can accelerate gastric emptying (Christofides et al. 1981) and initiate the interdigestive motor complex (Vantrappen et al. 1979). These actions may be important in patients with diarrhoea though the fact that all groups with diarrhoea have raised levels suggests this is a non-specific response.

The present study shows that fasting motilin levels are raised in patients with functional diarrhoea who have a consistent pattern of symptoms. This change was not seen by Besterman et al. but there was a trend in their study in the same direction and it it possible that the choice of test

meal has maximised the difference. A new finding in this study is that there is a reduction in motilin release in patients with idiopathic constipation, whether the colon is dilated or not. It is not possible to determine from these results whether this abnormal release contributes to their symptoms. The flat response seen in the patients with slow transit constipation might be due to a delay in gastric emptying. However in cases where there is such a delay gastrin levels are usually elevated and in these patients they were reduced.

Pancreatic polypeptide (PP) is a 36 amino acid peptide and is found mainly in the pancreas. It is released rapidly after a meal by a complicated and still incompletely understood mechanism. Part of this is neural but its release is also stimulated by other gut hormones including vasoactive intestinal polypeptide, gastric inhibitory peptide and cholecystokinin (Bloom et al. 1979). Its main actions are to relax the gall bladder and reduce pancreatic enzyme output - effects which are directly antagonised by cholecystokinin. Studies in humans show that it does not affect the rate of gastric emptying or the initiation of the interdigestive motor complex (Adrian et al. 1981, Janssens et al. 1982). In animals however high doses given intravenously result in defaecation, and a slow infusion causes an increase in the motility of the whole gut (Lin et al. 1978). Any possible effect on colonic motility in man has not yet been investigated. PP levels are unrecordable after pancreatectomy and considerably reduced in patients with chronic pancreatitis (Adrian et al 1979). Release of PP

after a meal is markedly increased in patients who have had intestinal resection but not in those with diarrhoea from other causes (Besterman et al. 1978a, 1978b, 1979, 1982).

The finding of impaired PP release in the patients with slow transit constipation was new and there does not seem to be an obvious explanation. Besterman et al. had found in their study an increased basal PP level in patients with the irritable bowel syndrome and diarrhoea. This is confirmed in the present study where basal levels, peak rise and integrated responses were increased. The response of PP does seem to be internally consistent and it is therefore possible that it acts as a regulator of gut motility. A furher possibility is that another hormone whose response is also related to bowel function is acting on PP release and the changes are just secondary. A study of the effects of PP on colonic motility in man would be worthwhile.

Gastrin was one of the first gut hormones to be isolated and has been extensively studied. It exists in several molecular forms, the principal ones being the 17 and 34 amino acid peptides. It is found mainly in the gastric antrum and duodenum and released into the circulation after a meal. The response is greatest to amino acids and peptides so that levels rise highest after a protein meal. The vagus stimulates gastrin release and this accounts for the rise seen in the cephalic phase of gastric secretion and after gastric distension. Amongst the disorders that have been associated with raised gastrin levels are: pernicious anaemia, chronic gastritis, renal failure, short bowel syndrome, hyperparathyroidism, gastinoma and post vagotomy

(Bloom 1979). The two principal effects of gastrin are the stimulation of gastric acid secretion and a trophic effect on gasto-intestinal mucosa. Interest has also been shown in its possible effects on gut motility and it has been suggested that an abnormal response to circulating gastrin levels might account for the symptoms of some patients with the irritable bowel syndrome (Harvey 1977). Gastrin in physiological doses does not appear to affect gastric emptying in man nor to interrupt the interdigestive motor complex (Ouyang 1981). Its role in stimulating the so called "gastro-colic" response after eating has been examined. It was found that though both gastrin levels and colonic activity rose after a meal they did not correlate and motor activity preceeded the rise in plasma gastrin (Kirwin et al. 1976). Recent studies suggest that the initial rise in colonic activity is neurogenic whilst there is a second response after a few minutes which cannot be blocked by anticholinergic drugs and may be hormonally mediated (Snape et al. 1979). Gastrin infused intravenously in physiological doses has been shown to increase colonic motor activity and may be involved in the second delayed response (Snape et al. 1978).

The finding of reduced fasting and stimulated gastrin levels in patients with severe constipation is therefore very interesting. Particularly because a hormone released from the stomach has been shown to be behaving abnormally in what was thought to be primarily a colonic disorder. This suggests that the disorder may be more widespread or that the secretion of gastrin is inhibited

when there is a hold up in the passage of colonic content. It is known that infusion of a hyperosmolar solution into the colon will inhibit gastric acid secretion (Jian et al. 1981) and this could be mediated by neural or hormonal mechanisms. The failure of gastrin release might therefore be an example of a "colo-gastric" reflex.

This study has shown a reduction in the release of three gut hormones in patients with slow transit constipation. However levels of one hormone were also reduced in the other groups of patients with constipation and as this abnormality is not confined to those with slow transit it is unlikely to be the sole cause of their symptoms. Hormone levels may be affected by another humoral agent which was not studied or has yet to be discovered. Cholecystokinin is thought to be important in stimulating gut motor activity. It was not studied because it is not released by the water load. A study of the response of cholecystokinin to a fatty meal in patients with slow transit constipation would be interesting.

One possible explanation for the findings in the constipated group is that peptide containing cells and nerves had been damaged by laxatives. The anthraquinone group are known to destroy intramural ganglion cells (Smith 1968) but the effect of these drugs on the peptidergic system has not yet been examined. The peptide containing cells of the colonic mucosa in some of the patients with slow transit constipation and megacolon has however been examined as part of the present study (Chapter 10).

CHAPTER 12

A STUDY OF SEX HORMONES

INTRODUCTION

As all the patients in this study were women it was decided to study their sex hormones. Some had indicated that their symptoms were relieved in pregnancy and others had spontaneous bowel actions during menstruation. In addition it was noticed that in many cases the symptoms had come on around the time of the menarche. These facts suggested that hormonal influences might be important though there had been no previous studies linking particular sex hormone abnormalities with severe constipation.

The constipation of pregnancy is stated in many textbooks to be due to raised progesterone levels and experimentally progesterone has been shown to inhibit the activity of muscle strips from the gut (Bruce et al. 1979). Small bowel transit in women is delayed in the luteal phase of the menstrual cycle when progesterone levels are highest, but there may be other hormone changes that cause this effect (Wald et al. 1981). Circulating motilin levels are reduced in pregnancy and this may contribute to the symptoms many women report (Christofides et al. 1982).

As there were no other clues linking constipation with known hormone disturbances it was decided to screen patients then attending the hospital. After consultation with a reproductive endocrinologist measurements of several ovarian and pituitary hormones were made.

PATIENTS STUDIED

Twenty-five women were recruited from those attending outpatients. In all cases a diagnosis of slow transit constipation had been made by exclusion of primary causes for their symptoms. All had a normal calibre barium enema and a delay in gut transit rate measured by means of polythene markers. No controls were studied for the majority of the hormones as the results were compared with previously established normal ranges in the biochemistry laboratory at St. Bartholomew's Hospital. However, following the results of a pilot study, control subjects were obtained for the measurements of Prolactin and B-endorphin. These were in two groups:

a) Normal subjects (15). These were volunteers from the nursing and secretarial staff of St Mark's Hospital. All were women and described their bowel function to direct questioning as "normal".

b) Irritable Bowel Syndrome (13). These were patients also attending outpatients who complained of severe abdominal pain and constipation. In each case however, full investigation had revealed no abnormality, and in addition a bowel transit study with polythene markers was normal.

METHODS

Blood samples were taken at 9 am through an indwelling catheter. Because of possible stress effects on prolactin secretion, this hormone was measured on 2 further samples taken at 10 am and 11 am and the mean value used. In addition, patients were asked to collect a 24 hour urine

sample before their next outpatient visit. Levels of the following hormones were measured:

Prolactin

Cortisol

Growth Hormone

Thyroxine

Tri-iodothyronine

Thyroid Stimulating Hormone

Follicle Stimulating Hormone

Luteinising Hormone

Testosterone

Oestradiol

Sex Hormone Binding Globulin

Progesterone (Day 21 of cycle if menstruating)

24 Hour Urinary Oestrogens

Met-enkephalin

N- and C-LPH (B-endorphin)

RESULTS

The results for each hormone measurement are presented seperately and compared with controls where appropriate. Not all 25 patients are represented in each group. Some samples were lost in the laboratory, and in other cases (e.g. Met-enkephalin) the biochemist only agreed to measure hormone levels on half the patients unless any abnormalities were detected. In addition, some results were invalid on those patients who were using the contraceptive pill.

a) Prolactin

This hormone gave the most consistently abnormal result. Excluding those girls who were taking the contraceptive pill (which can cause a raised prolactin) only 4 patients had a normal prolactin level. In 2 it was borderline, and in 14 raised. In contrast, all the patients with the irritable bowel syndrome and 13/15 control subjects had normal values (Figure 12a). The mean prolactin level in the patients with slow transit constipation was significantly greater than in the other groups. Controls 176 ± 23 mU/L (s.e.m.), Irritable bowel syndrome 189 ± 26 (NS v controls), Slow transit constipation 569 ± 78 ($p<0.01$ v controls and IBS).

b) Cortisol

All cortisol levels were normal. One patient had a high value of 2050 at 9 am (UL normal 600). This was presumed to be due to contamination in the laboratory as subsequent investigation of pituitary function and repeated values were normal.

c) Growth Hormone.

Eight of 23 patients studied had a raised growth hormone level. Normal values are less than 5 mU/L. The range of abnormal values recorded was from 5.2 to 23.0 mU/L (Figure 12c).

d) Thyroxine, tri-iodothyronine and thyroid stimulating hormone.

All values were within the normal range.

e) Follicle Stimulating Hormone

All values were normal apart from one patient in whom a value of >50 U/L. suggested ovarian failure. Examination of her records indicted that an ovarian cyst had previously been removed but the other ovary was present.

f) Luteinising Hormone

Apart from a very high value in the same patient who had an elevated FSH (see above) all levels were within normal limits.

g) Testosterone

Five of 20 patients on whom results were obtained had an abnormally high level. In these patients the values ranged from 3.2 to 7.0 nmol/L. (Figure 12d).

h) Oestradiol

Fifteen of 25 patients had a low plasma oestradiol level, but in some cases this was probably due to the effects of the contraceptive pill which interferes with ovarian function. Of the 15 not using such medication 8 had a low level. One of these was the patient with high FSH and LH values who probably had ovarian failure (Figure 12e).

i) Sex Hormone Binding Globulin

All values were within normal limits.

j) Progesterone

Fourteen patients who were menstruating had progesterone levels measured in both the follicular and luteal phase of the cycle. Three had no rise in the luteal phase (levels <1, 2.0 and 7.5) suggesting that they had not ovulated that month at least. All the values in both phases in the other patients were within the range seen in normal women.

k) Urinary Oestrogens

The results mirrored those of the plasma oestradiol with 5/11 samples below the range of normal in those not taking the contraceptive pill (Figure 12c).

l) Met-enkephalin

Only 10 samples were assayed, all of which were within the normal range (Figure 12f).

m) B-endorphin

All but three of 16 samples analysed were above the normal range. Because of the interest this aroused further samples on other constipated patients were included, and many of these were abnormal too. However as measurements of endogenous opiates can be technically difficult and blood levels affected by minor stress it was decided to include some samples from normal subjects without informing the laboratory. These gave similar results suggesting that there was no significant difference between constipated patients and controls. (Figure 12g)

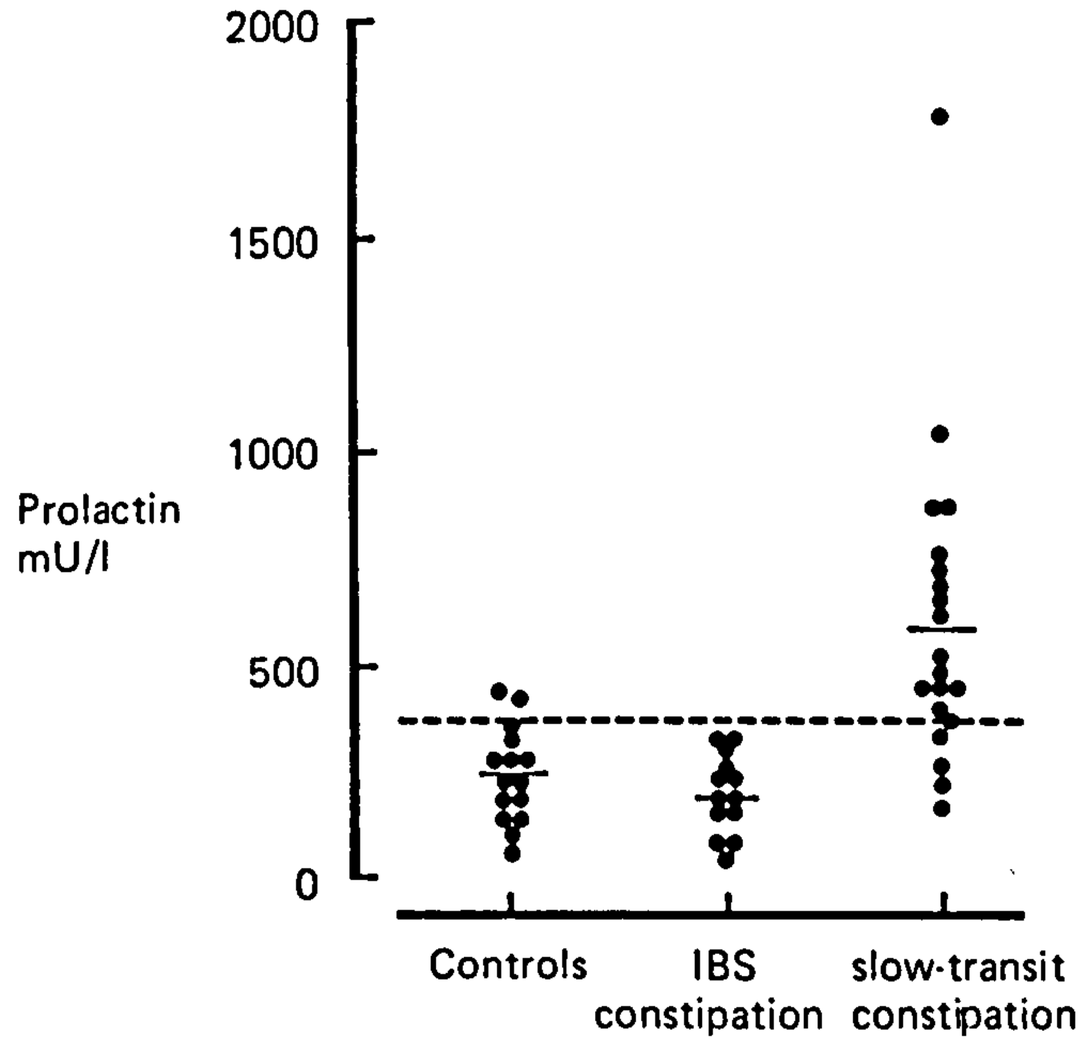


FIGURE 12a PROLACTIN LEVELS.
Mean of three recordings taken at 9am, 10am, and 11am on the same day through an indwelling catheter. This compares the values in constipated patients with normal or prolonged gut transit time and controls. The dotted line indicates the upper limit of normal.

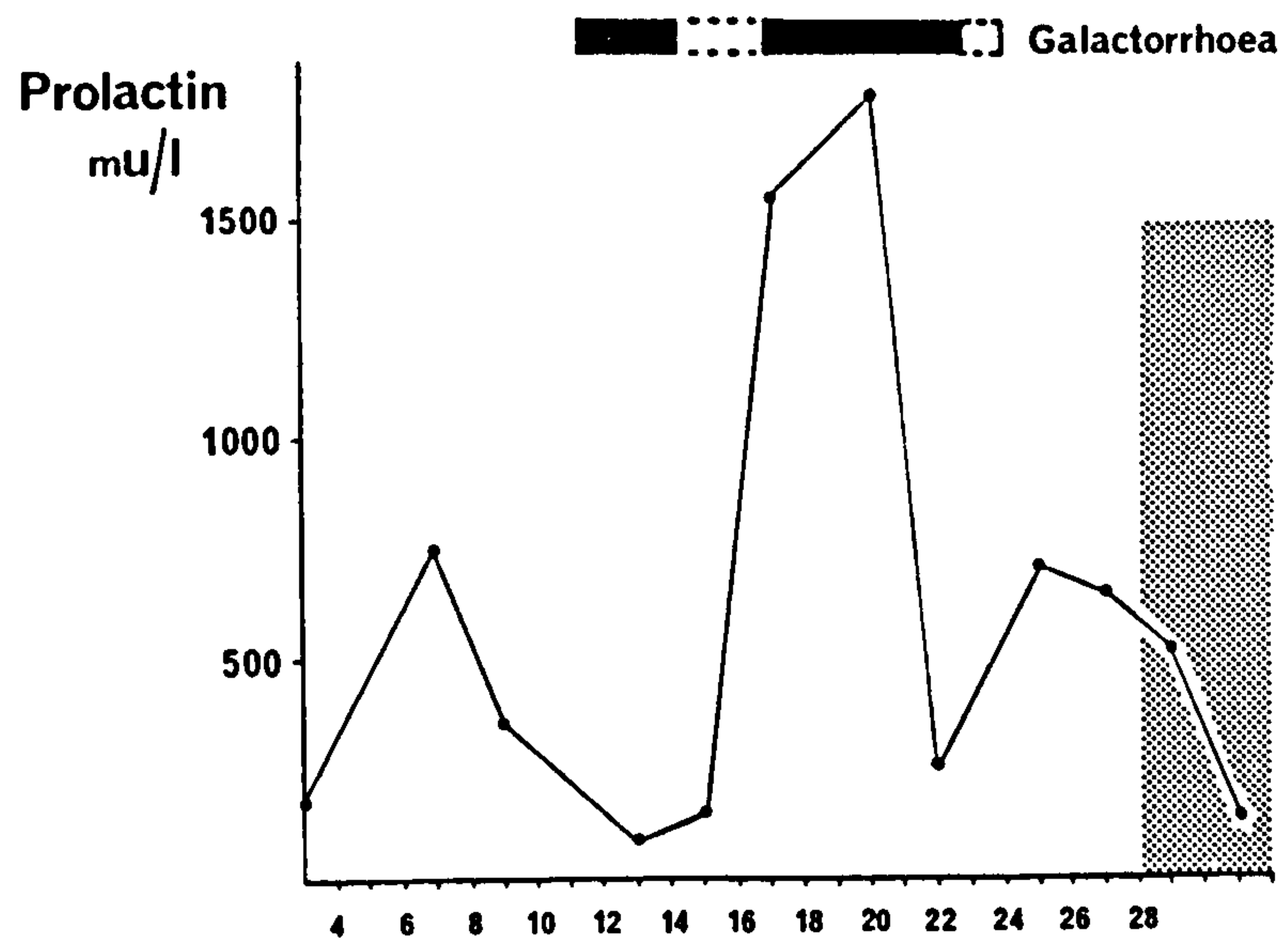


FIGURE 12b. PROLACTIN CYCLE
This illustrates the serum prolactin level recorded in one patient through a complete menstrual cycle. The bar at the top indicates periods of mild or severe galactorrhoea and the shaded area at day 28 the onset of menstruation. (Upper limit of normal 360 mU/l).

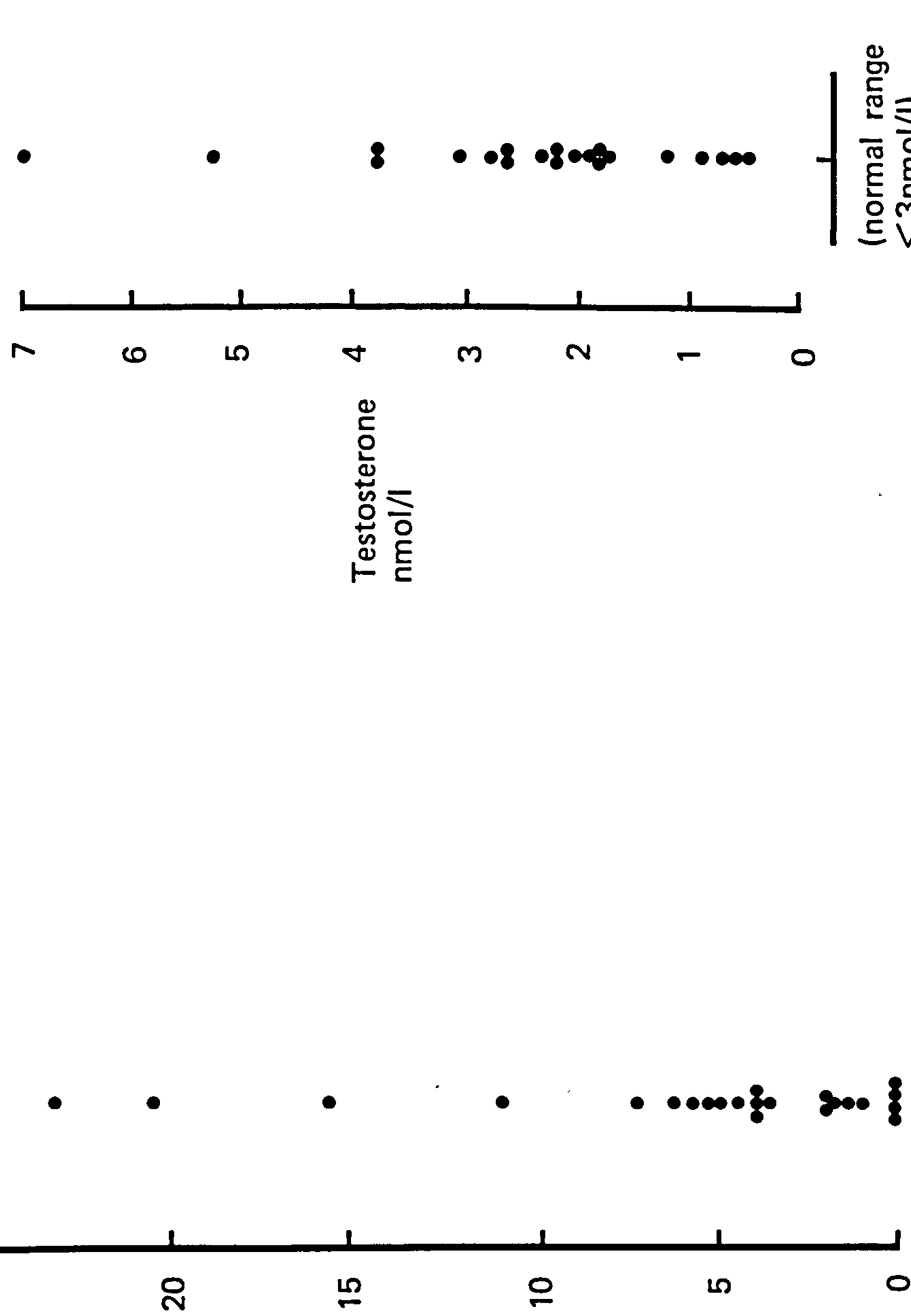


Figure 12d. TESTOSTERONE LEVELS
Results from 21 patients with
slow transit constipation. None
of the 5 with raised values had
evidence of virilism.

Figure 12c. GROWTH HORMONE LEVELS
Fasting blood levels of growth
hormone in 23 patients with
slow transit constipation.
Samples were taken at 9am.

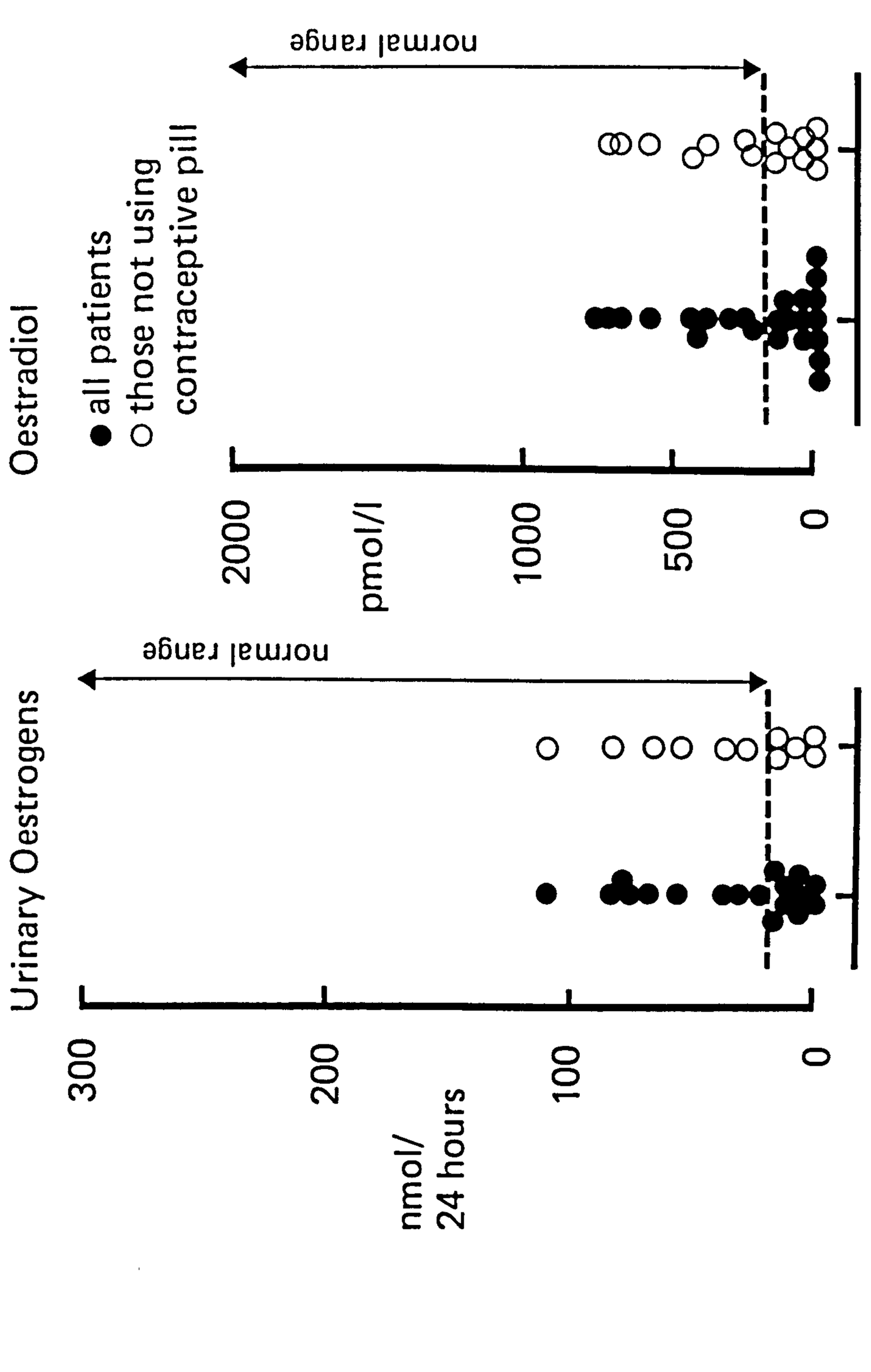


Figure 12e. OESTROGENS
Results of the available 24 hour urinary oestradiols in patients who were not taking the contraceptive pill at the time of the study. Normal ranges are above the dotted lines.

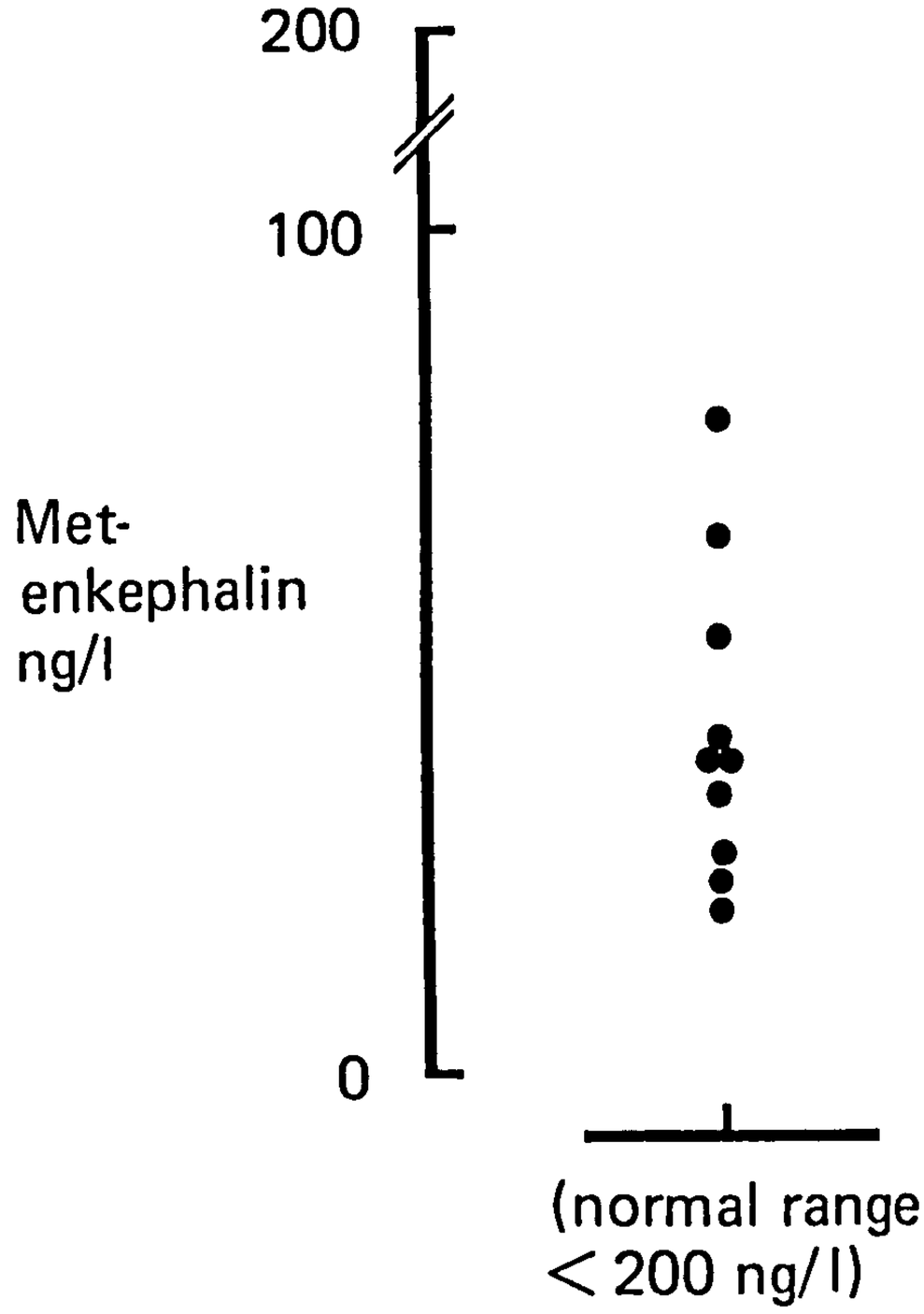


FIGURE 12f MET-ENKEPHALIN LEVELS.
Results in 10 patients with slow transit constipation of the fasting 9 am. serum met-enkephalin. All values were well within the normal range and no further patients were therefore studied.

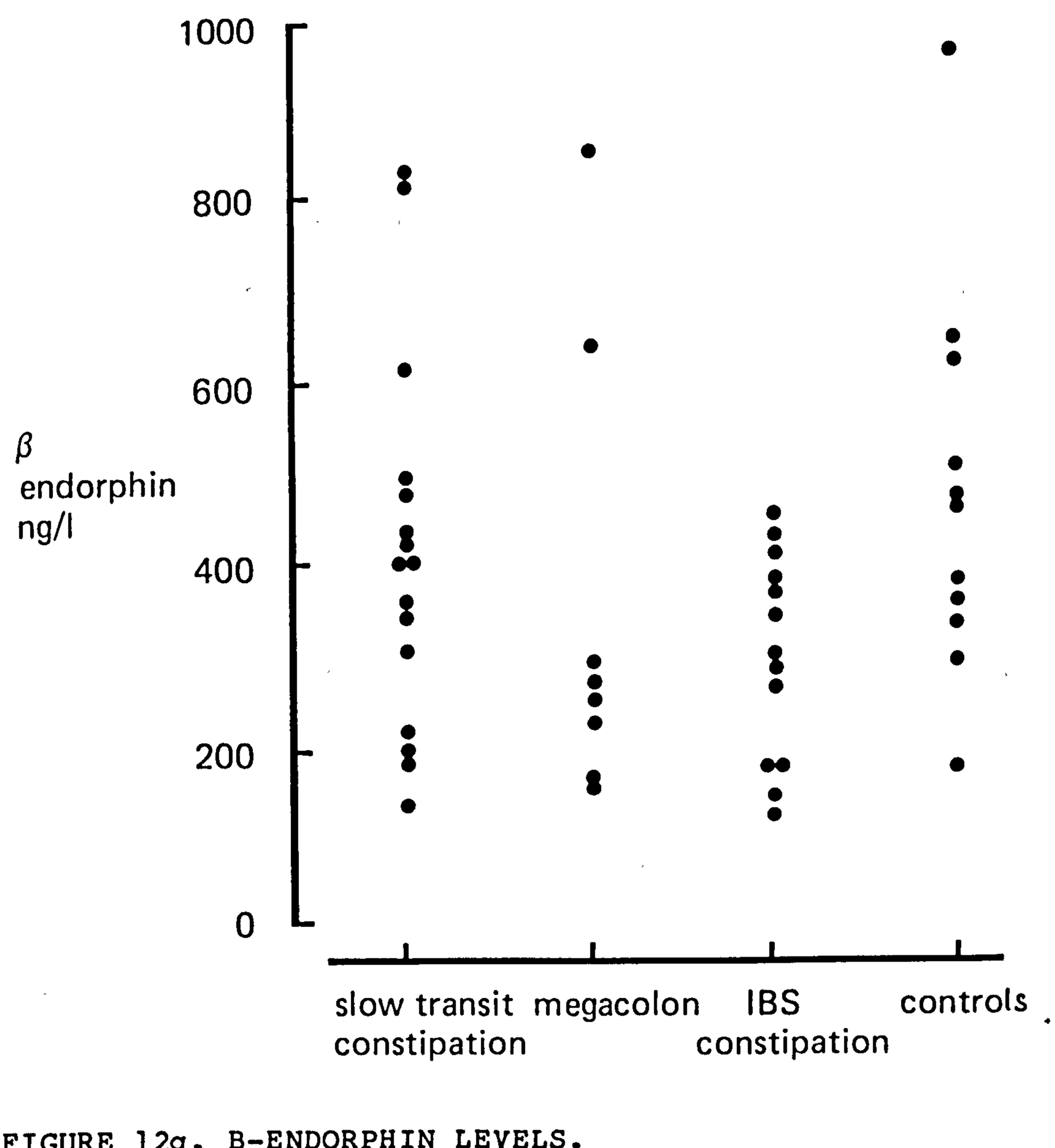


FIGURE 12g. B-ENDORPHIN LEVELS.
Comparison of the endorphin levels at 9am in patients with different types of constipation and controls. The upper limit of normal was considered to be 200 ng/l., but the majority of patients and all but one control had values higher than this. There was no significant difference betweeen any of the groups.

FURTHER STUDIES

i) Naloxone administration.

Because of the initial results suggesting abnormal levels of endogenous opiates as well as hyperprolactinaemia, some more detailed studies were done on 5 patients with raised serum prolactins. These included an assessment of the effects of Naloxone (an opiate antagonist) on pituitary function and colonic motility. These results which were essentially negative and of doubtful interest in view of the later endorphin results in normals, have been included in appendix 5.

ii) Prolactin cycle.

To find if the raised prolactins were due to a stress effect, perhaps resulting from the visit to hospital, it was decided to study the values at home. Only one patient lived near enough to have her blood taken at home. This patient who had galactorrhoea before each menstruation agreed to have blood samples taken at 8.30 am every 3 days throughout one menstrual cycle. The values fluctuated widely (Figure 12b) but in a manner that suggested a cyclical phenomenon rather than a response to stress, or secretion by a prolactinoma. An autonomous tumour would be likely to give consistemtly high values as well as figures in excess of 2000 mU/L. Following treatment with bromocriptine, the prolactin levels in this patient returned to normal, but there was no change in bowel function.

DISCUSSION

The most consistent finding was that of raised prolactin levels in the majority of patients with constipation not taking the contraceptive pill. The function of prolactin in non-pregnant women (and indeed in men) is not known. Prolactin is secreted by the anterior pituitary, and levels are known to be raised in pregnacy (when it stimulates lactation), in liver failure and in hypothyroidism (Horrobin 1973). All these possibilities had been excluded in the patients studied. Prolactin secreting tumours are relatively common, but levels in patients with microadenomas are consistently greater than 2000 U/L and such tumours are not associated with constipation (Rees 1983).

Raised prolactin levels are known to be associated with stress, whether physical or psychological (Noel et al. 1971, 1972). Few studies have performed serial measurements such as were done here to exclude this effect. Levels will rise after venepuncture and simple proceedures such as sigmoidoscopy, but should fall again within an hour. The indwelling needle used for these studies should have avoided artificially elevated values and the pattern of release in the patient studied in detail (Figure 12b) suggests a physiological response.

The possibility that the abnormalities are secondary to drugs was considered, but none of the patients were taking drugs known to cause this effect, such as metoclopramide, tricyclic antidepressants or opiates. Chronic use of laxatives might cause hyperprolactinaemia,

but there is no information in the literature on this point. Many of the patients had been using magnesium sulphate as a regular treatment before the studies.

Raised prolactin levels go some way to explaining the ovarian dysfunction recorded in some patients in the rest of this study. In addition these high levels might account for the galactorrhoea reported by a few patients in the questionnaire (Chapter 3). Excessive prolactin secretion is known to cause amenorrhoea and inhibit ovulation (McNeilly 1979). Women with prolactinomas are usually infertile and have very low oestradiol excretion. It is thought that prolactin interferes with the release of gonadotrophin releasing hormone (GnRH) which in turn regulates luteinising hormone (LH) release. LH is required to stimulate ovulation, and with FSH; oestrogen and progesterone secretion. GnRH can also be inhibited by opiates and there is evidence that endogenous opiates are involved in the supression of GnRH in patients with prolactinomas (Grossman et al. 1982).

The possibility then arises that the hyperprolactinaemia and constipation in these patients might be due to an increased level of endogenous opiates. As well as the effects on pituitary and ovarian function indicated above, opiates also affect gut motility and constipation is an almost invariable side effect of treatment with morphine. There are opiate receptors (Sun et al. 1982), and enkephalin containing nerves in the colon (Polak et al. 1977). Constipation secondary to excess opiates could be caused in a variety of ways, either by increasing colonic segmentation

(Sun et al. 1982) or by increasing anal sphincter tone (Sundler et al. 1980). Central effects may also reduce the urge to defaecate (Jaffe et al. 1975).

There is doubt however whether endogenous opiates can cause the same effects as morphine on gut motility. The results of naloxone administration on colonic motility and pulsatile LH release in a few patients detailed in Appendix do not support the hypothesis that excess production of endogenous opiates is involved in the genesis of these patients symptoms. In any case the studies of colonic motility in Chapter 8 indicate that this form of constipation is not associated with colonic hypersegmentation.

The fact that the one patient treated with bromocriptine had her prolactin levels lowered but without any change in bowel function suggests the endocrine changes are secondary. However abnormal prolactin secretion might account for some of the other symptoms reported by patients on the questionnaire. Abdominal swelling is a common feature in these patients and can be so severe as to resemble pregnacy. A case of pseudocyesis has been recorded in which the patient developed breast enlargement, galactorrhoea, weight gain, morning sickness, abdominal distension and amenorrhoea; all in association with a raised prolactin level. When confronted with the true diagnosis by a psychiatrist, the abdominal distension disappeared within 30 minutes. Prolactin levels fell soon afterwards and menstruation occurred in 2 weeks (Yen et al. 1976). Similar abdominal distension can also occur with a prolactinoma

(Lennard-Jones 1984).

Prolactin may potentiate the effcts of pressor agents and there is a case report of one patient with acrocyanosis and galactorrhoea associated with hyperprolactinaemia. All the abnormalities were reversed by giving bromocriptine (Morrish et al. 1976). This may posibly explain the high incidence of digital vasospasm reported in the questionnaire by the constipated patients.

Though not specifically sought in the questionnaire, idiopathic oedema has been a problem in some of the patients. This is interesting because prolactin is intimately associated with fluid balance in lower animals. Secretion of prolactin controls osmoregulation in fish such as the salmon enabling them to make the transition from salt to fresh water. Experimentally, prolactin enhances salt and water absorption from the small intestine of the rat though no studies have yet been done on intestinal absorption in man. Prolactin is found in human amniotic fluid, and levels are very low in cases of hydramnios (Ramsay et al. 1972, Horrobin 1973). In addition levels of prolatin have been shown to rise in the luteal phase of the menstrual cycle in girls with pre-menstrual tension. Salt and water retention occur in this condition, which may respond to pyridoxine (Brush 1979). Pyridoxine is a co-factor in the conversion of L-dopa to dopamine, and dopamine supresses prolactin secretion. The finding of prolactin containing cells in the mucosa of the small intestine suggests it may be another "brain-gut" peptide though the rise in prolactin after eating is apparently due to pituitary secretion (Stevens et

al. 1982, Quigley et al. 1982).

Another possibile explanation for the low oestradiols and urinary oestrogens is that the women were eating an unusual diet. Vegetarian women have been shown to have increased faecal excretion of oestrogens with correspondingly reduced plasma levels (Goldin et al. 1982). The dietary findings in Chapter 4 suggest that the intake of fat and fibre in the constipated patients is normal and this is unlikely therefore to be the cause. A more likely alternative explanation is that severe constipation leads to an alteration in the intestinal microflora. Sex steroid hormones are involved in an entero-hepatic circulation that requires bacterial deconjugation before reabsorption. When the faecal flora are reduced, conjugated faecal oestrogens are markedly increased and this accounts for the failure of oral contraceptives in some girls who use drugs such as ampicillin (Simon et al. 1984).

A few patients had raised growth hormone levels. These rise in response to stress, like prolactin, and may have been stimulated in these patients by the venepuncture. There does not seem to be any other explanation for these findings. Again a few patients had a raised testosterone level. High testosterones are a feature of the Stein-Leventhal syndrome in which ovarian cysts are also found. Though a significant proportion of the patients who had answered the questionnaire had undergone ovarian cystectomy, none in whom a raised testosterone was recorded had any other features of this syndrome. These findings therefore are also unexplained.

CHAPTER 13

PSYCHIATRIC INVESTIGATION

INTRODUCTION

Bowel function provides a fertile field in which behavioural psychiatrists can exercise their imagination. Freud's observations on the relationship between lavatory training and subsequent disorders of bowel function were made retrospectively and in an age when rigid methods of lavatory training were used (Freud 1924). Attempts have since been made to establish a causal relationship though no-one has been able to explain why boys should be affected more often than girls (Huschka 1942, Prugh 1954, Pinkerton 1958). It has been suggested that constipation results from a conflict between rigid, obsessional, perfectionist parents and an aggressive child. These parental characteristics are those of the "anal character" outlined by Freud (1916) who speculated that girls were not so commonly affected as they were "less aggressive and defiant" than boys (Freud 1946).

Constipation in young children, which has been the subject of most psychiatric investigation, is associated with megarectum. It also is of limited duration, often responding to short term laxatives and anal stretch or sphincterotomy (Clayden et al. 1976). The young women involved in this study seem to have an entirely separate disorder, though a few reported symptoms going back to the first few years of life. Clinical impressions had suggested that some of these women were emotionally disturbed, though

it is difficult to assess whether this is cause or effect.

Studies on adults with functional bowel symptoms have suggested that a disturbed childhood is more common in patients with the irritable bowel syndrome (Mendeloff et al. 1970, Hislop 1979, Macdonald et al. 1980). Most agree that patients with the irritable bowel syndrome are emotionally disturbed (Chaudhary et al. 1962, Hislop 1971, Esler et al. 1973, Palmer et al. 1974, Young et al. 1976) but there are apparently no psychological differences between those with constipation and others with diarrhoea (Whitehead et al. 1980). There is no doubt however that disturbances of gut physiology can occur secondary to psychological disorders or stress (Almy et al. 1947, Latimer et al. 1981)

A study of the mental state of the women with slow transit constipation seemed appropriate, especially as the defaecatory disorder described in Chapter 6 suggested a possible functional disorder of the voluntary anal sphincters. In view of previous studies linking gut disorders with abnormal psychological profiles (Paulley 1959) it was decided to study in parallel a group of women with Crohn's disease. This was in the hope of excluding the possibility that any abnormality might be secondary to the presence of a severe gut disorder rather than a primary psychological problem.

PATIENTS STUDIED

A consecutive series of 20 patients (Mean age 24.5 years) seen either in the outpatients or admitted for investigation were studied. All but one agreed to be seen by

a consultant psychiatrist, on the understanding that the interview was for the purposes of research only. All had idiopathic slow transit constipation, defined by the exclusion of primary causes for their symptoms. All had a normal calibre rectum and colon and a delay in whole gut transit rate.

An age and sex matched control group was selected from patients with Crohn's disease attending the hospital outpatients. Each was selected to have a similar length of history and the same number of hospital admissions as the constipated patient with whom they were matched.

METHODS

a) Interview

Nineteen patients were seen by a consultant psychiatrist. They had agreed to this on the understanding that the results would not be placed in the general hospital records and that the interview was to help in research. However, individual patients were at liberty to seek further psychiatric advice from the same doctor if they wished, and 3 subsequently had psychosexual counselling. The interview was semi-structured along the lines adopted in routine psychiatric outpatients. It was thought unjustifiable to subject the Crohn's disease patients to a long and penetrating interview, and they were not included in this part of the study.

b) Questionnaires

Four questionnaires were used:

i) The General health questionnaire (GHQ) is used to try and detect psychiatric disorders in the general population. It does not define the disorder, but indicates which patients merit further investigation. For this study the shortened 30 question version was used (Goldberg et al. 1970).

ii) The Crown-Crisp experiential index (CCEI) was formerly known as the Middlesex Hospital questionnaire. It assesses personality and symptoms on 6 parameters: depression, anxiety - somatic, phobic or free-floating, obsessionality, and hysteria (Crown et al. 1970).

iii) The hostility and direction of hostility questionnaire makes an assessment of personality from the aspect of anger. It shows the degreee of anger and indicates whether this is directed outwards or inwards (Caine et al. 1967).

iv) Finally a simple quality of life questionnaire was devised using an analogue scale. This compared the 2 groups in four areas: home life, work, social leisure activities and private leisure activities.

Patients were invited to answer the questionnaires at a single sitting during an outpatient visit or on the ward. No help was given in selecting the answers. Patients were reassured that the results of the questionnaires would not be placed in the hospital notes and that they would be sent for analysis anonymously. They were asked to fill in the forms as quickly as possible and to answer all

questions. Examples of the forms provided are included in appendix 6.

RESULTS

a) Interviews with psychiatrist

Fourteen of the nineteen patients interviewed (74%) showed evidence of a disturbed family background. In 5 one parent died before the age of 16 and in 4 the parents were divorced or separated. In one of the latter group, the patient was made a ward of court. Three patients had suffered because of gross parental disharmony, one patient being taken into care and the other 2 affected by their fathers alcoholism. In 2 cases one parent had been very ill during the patients childhood.

Twelve (63%) had psychosexual problems, and 5 a past psychiatric history. Of these, 2 had taken overdoses, one had a phobic illness, one had been put on tranquillisers in adolescence and the other suffered from depression. All but 3 described their personalities as either anxious, obsessional or conscientious, contemplative or moody and all complained of being unhappy, fed-up or anxious at the time of the interview. It was difficult to ascertain how these complaints were related to the bowel symptoms however.

b) Questionnaires

All were scored blind and the results compared with known standards or the Crohn's disease group using the students t test or Wilcoxon test where appropriate.

i) General health questionnaire.

Both groups of patients showed a large number of possible psychiatric problems with 12 of the constipated and 10 of the Crohn's group scoring high enough to require further attention. However when the mean scores were compared with data from a control population neither group differed significantly from normal.

ii) Crown-Crisp experiential index.

The results of the six parameters for the two disease groups compared with normal young women and psychoneurotic subjects are given in Figure 13a. There were significant differences in the constipated group who showed less phobic anxiety ($p<0.01$) but more somatic anxiety ($p<0.001$) than normals. In contrast the Crohn's disease group showed more free floating anxiety ($p<0.05$), phobic anxiety ($p<0.01$) and somatic anxiety ($p<0.01$) than normals. The two disease groups were compared (Figure 13b) and the Crohn's disease group had significantly more phobic anxiety ($p<0.005$) and obsessionality ($p<0.02$) than the constipated patients.

iii) Hostility and direction of hostility questionnaire.

Established data (Caine et al. 1967) has shown that patients with psychological problems tend to show an abnormal degree of inwardly directed hostility (Figure 13c). When placed on the same scale (Figure 13d) both groups of patients showed a large scatter but the mean value for the constipated patients was within the normal range. The

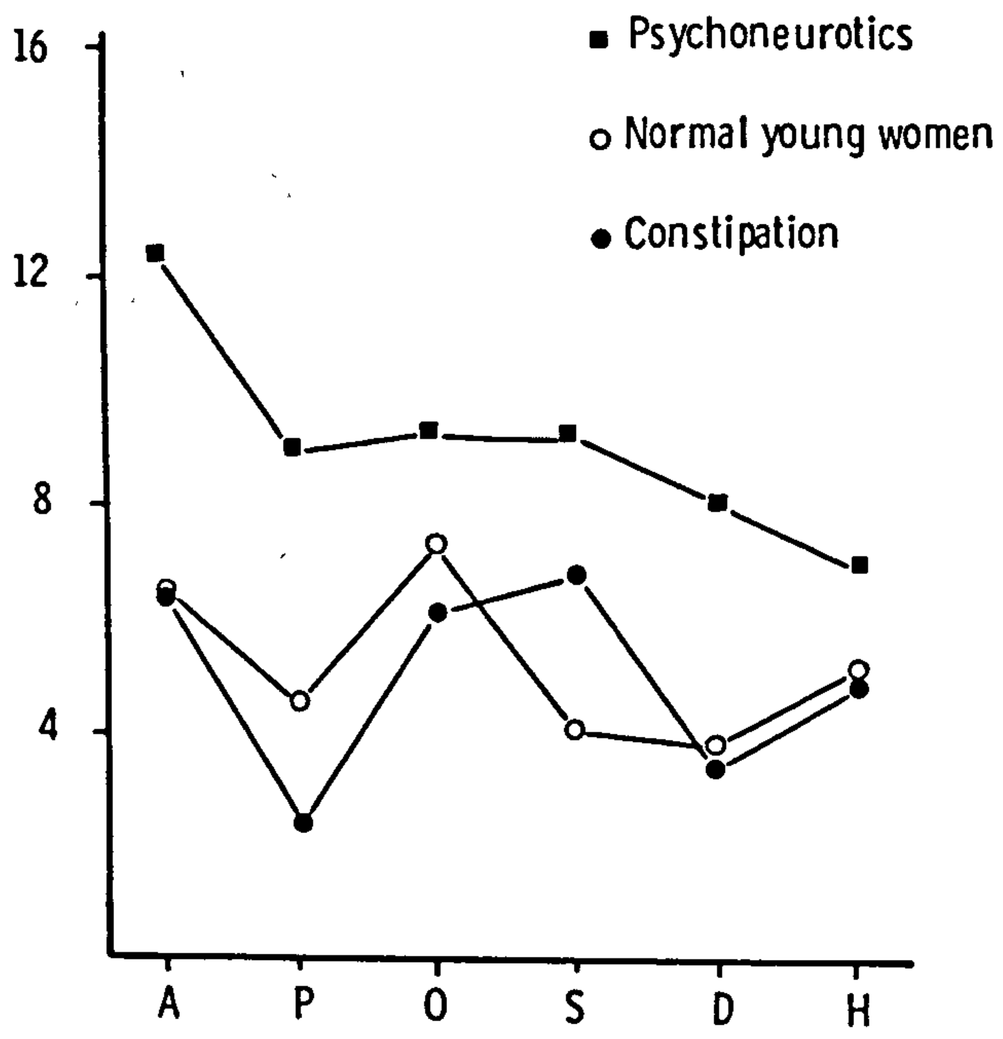


Figure 13a. CROWN-CRISP INDEX SCORES 1. Mean scores on 6 parameters for a group of psychoneurotic patients and normal young women (Data from Crisp et al. 1978) compared with that obtained from the constipated patients.

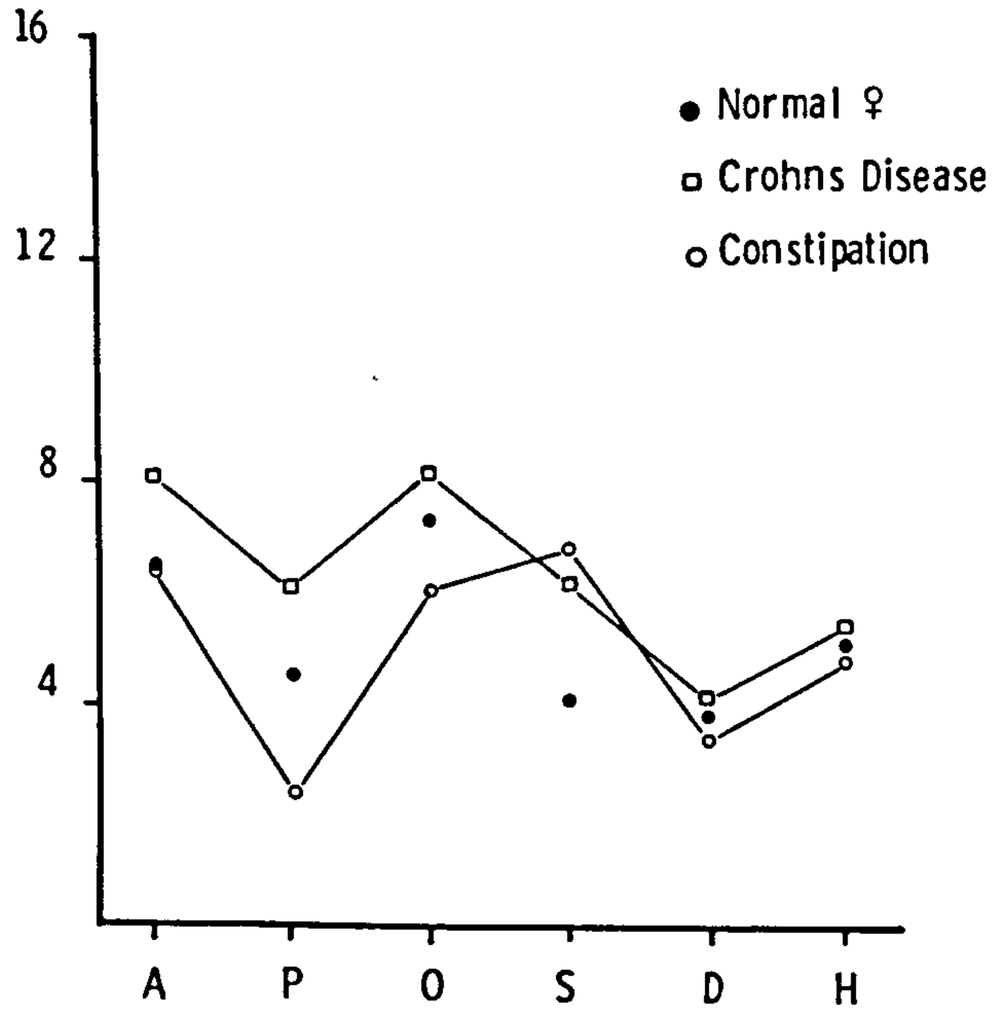


Figure 13b. CROWN-CRISP INDEX SCORES 2. A comparison between the patients with slow transit constipation and those with Crohn's disease for the 6 parameters. The data on normal young women is the same as Fig. 13a.

(For both digrams: A=Free floating anxiety, P=Phobic anxiety, O=Obsessionality, S=Somatic anxiety, D=Depression and H=Hysteria)

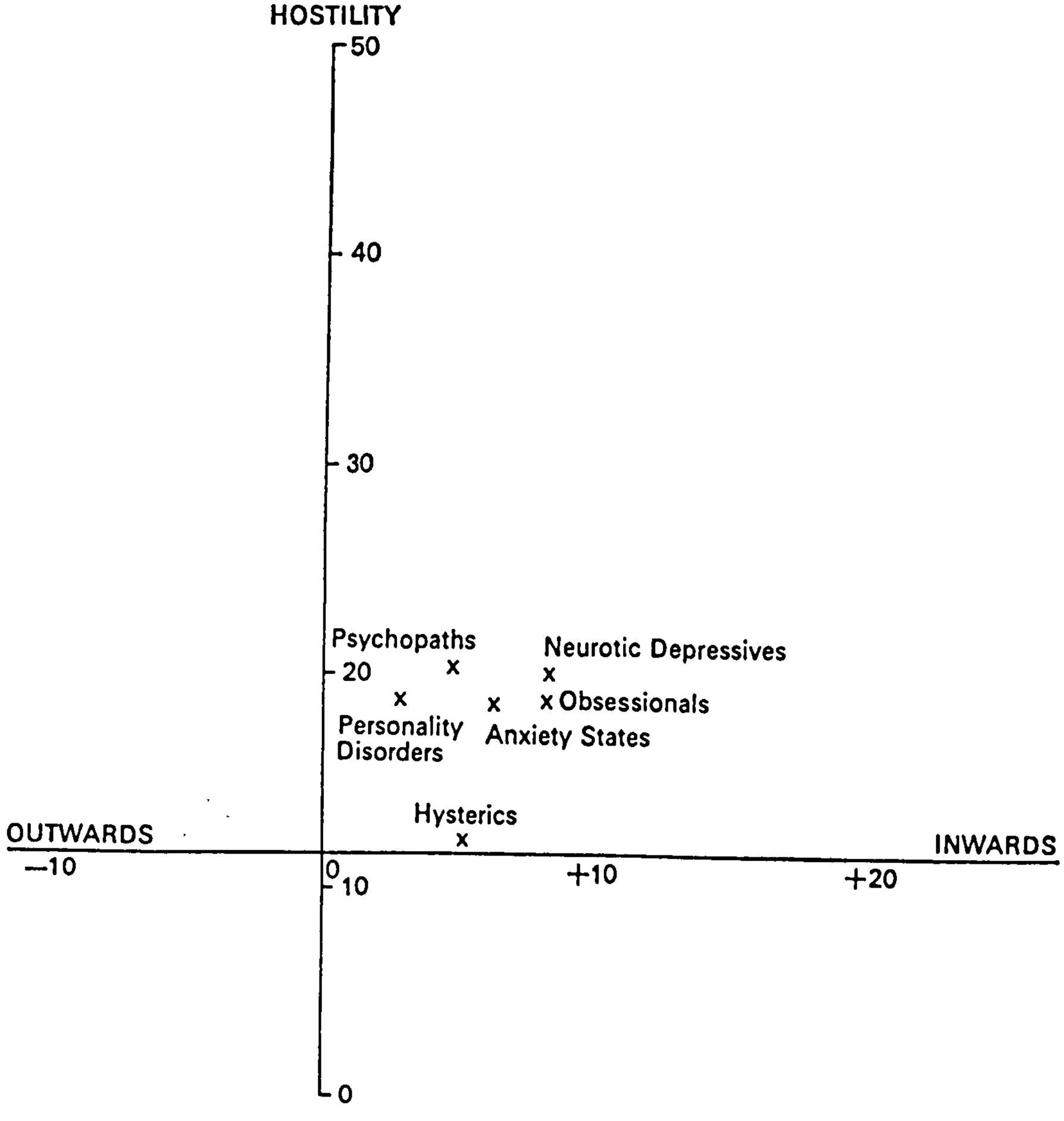


FIGURE 13c. HDHQ: PSYCHIATRIC SCORES.
Data from Caine et al. (1967) giving the degree of inwardly directed hostility recorded in different groups of psychiatric patients. The meeting point of the ordinate and axis was the mean value obtained in the normal population.

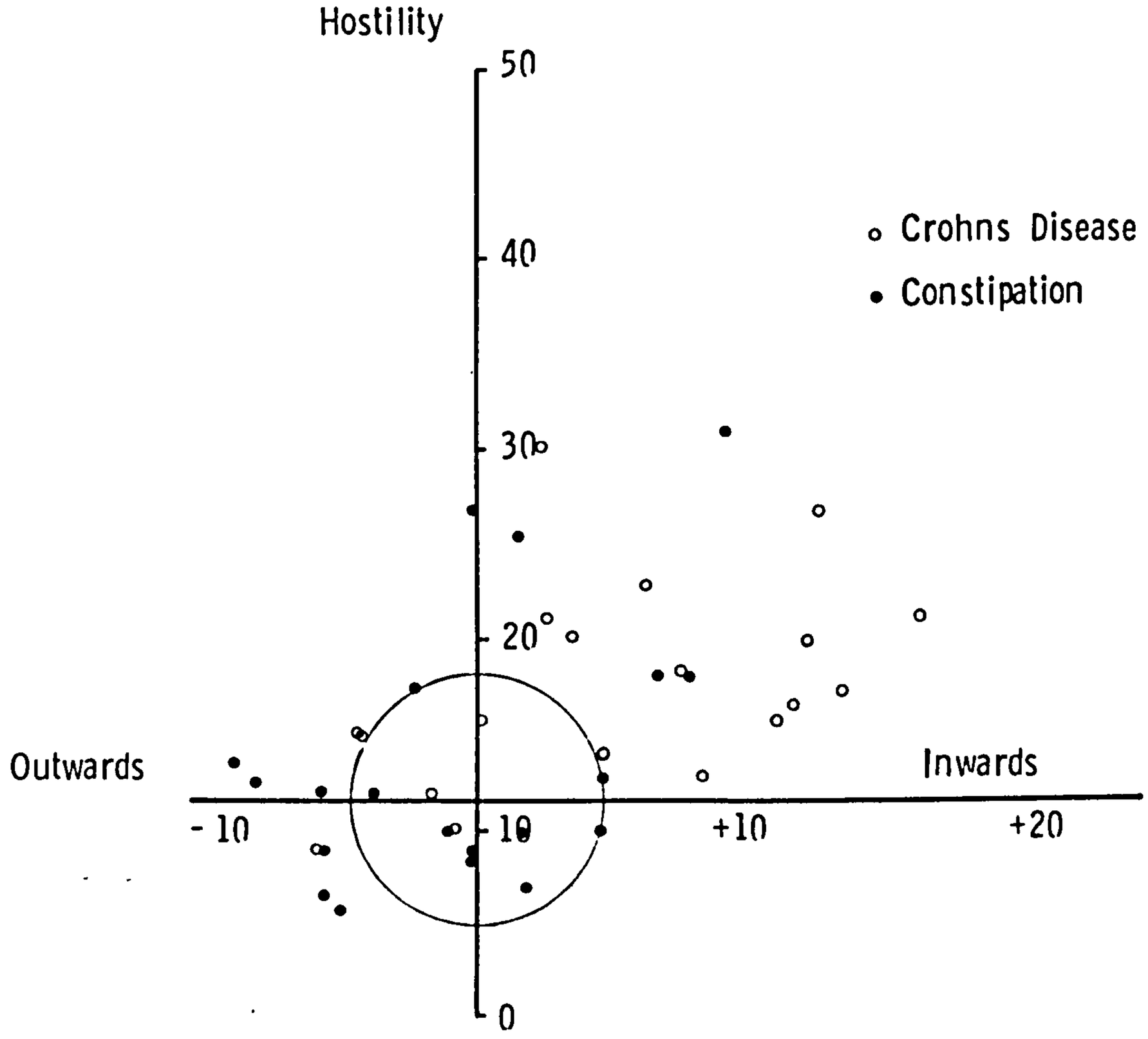


FIGURE 13d. HDHQ: RESULTS (1).
Hostility scores for each of the patients with slow transit constipation or Crohn's disease. The circle indicates the accepted normal range.

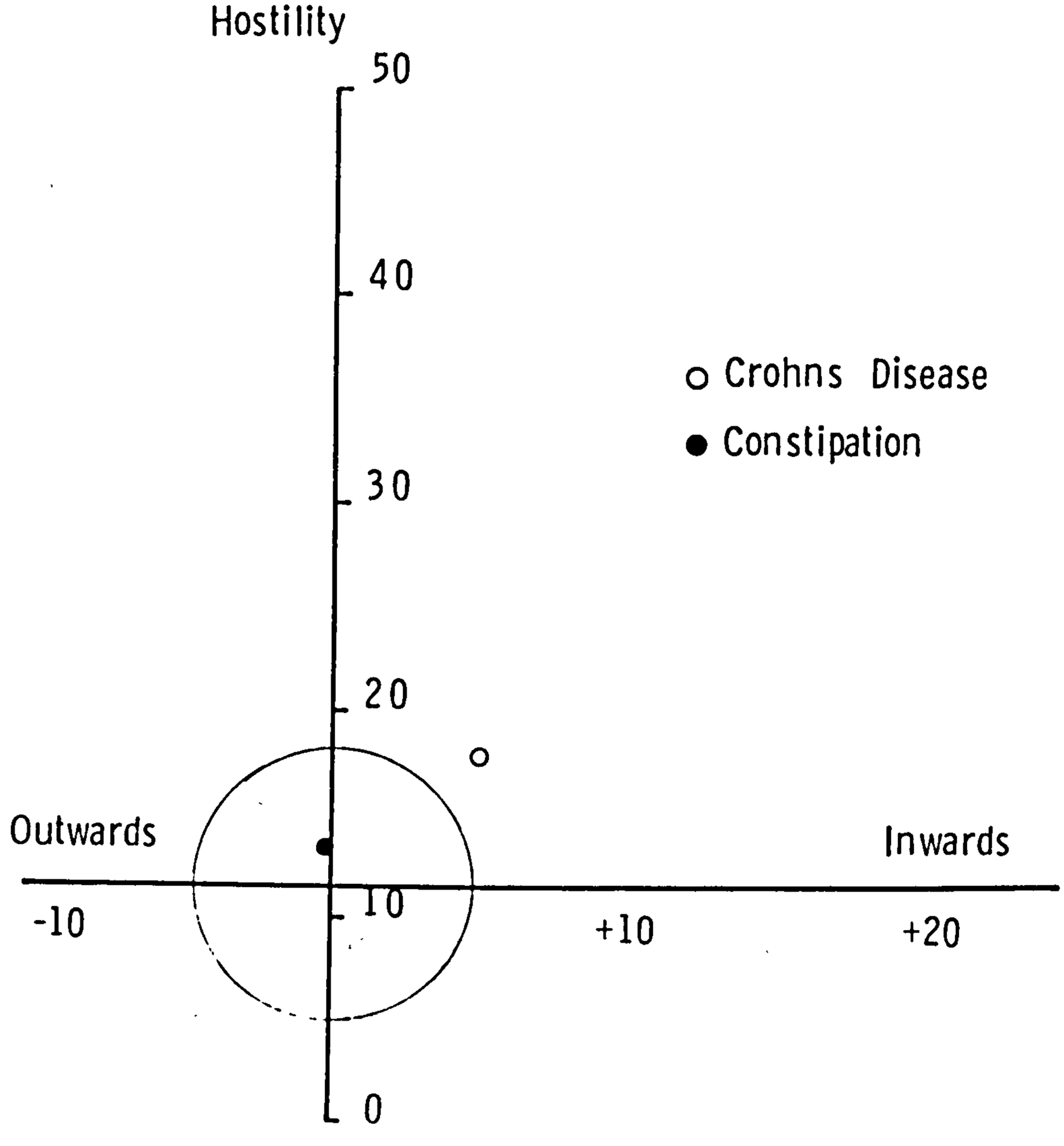


FIGURE 13e. HDHQ: RESULTS (2).
The mean values of the results presented in Figure 13d. The results for the constipated patients as a group are within the normal range indicated by the circle. However the Crohn's disease group are in an area corresponding to psychiatric pathology in Figure 13c.

Crohn's disease group however showed a mean value approximating to that recorded in patients with recognised psychiatric disorders (Figure 13e).

iv) Quality of life questionnaire.

The degree of disabilty recorded by both groups varied widely and there were no significant differences between them. The constipated patients tended to score more highly however. The results were as follows:

	CONSTIPATED	CROHNS
WORK	4.0 ± 2.4	2.7 ± 1.9
HOME	2.5 ± 1.9	1.9 ± 1.6
SOCIAL	3.8 ± 2.3	2.2 ± 2.2
PRIVATE	2.6 ± 2.5	1.5 ± 1.6

Table 13a.
Results of the quality of life questionnaire comparing the women with slow transit constipation with those suffering from Crohn's disease. The scores are given as Mean + 1 standard deviation. For each group (Work, Home management, Social leisure activities and Private leisure activities) a score was given on a simple analogue scale ranging from 0=not at all to 8=very severe disturbance.

DISCUSSION

The principal findings in the constipated parients are the high proportion of possible psychiatric abnormalities on the General health questionnaire, a suggestion of a high level of family problems and the heightened level of somatic anxiety on the Crown-Crisp questionnaire. These findings have some similarity to those reported previously in patients with functional bowel

disease. For example McDonald et al (1980) have shown loss of parents during childhood to be more common in patients with non-organic illness and Mendeloff (1970) that life stresses - such as loss of a parent before the age of 16 - to be more common in patients with an irritable colon. Hislop (1979) produced similar findings in a study of the irritable bowel syndrome. Somatic anxiety in the irritable bowel syndrome is also considerably increased compared with normals on the Crown-Crisp index (Palmer et al. 1974).

However the Crohn's disease group deviated more from normal in many parameters on the questionnaires and scored higher for anxiety than the constipated group for all except somatic anxiety. In retrospect it is perhaps unfortunate that the Crohn's disease group did not take part in the interview as it would have been interesting to find out how many of them had problems in childhood. It appears that the questionnaires do not support the idea that there is a significant psychological problem in the constipated patients. A discrepancy has therefore emerged in this study between the psychiatrists opinion and the other results.

In other studies a discrepancy between interview and questionnaire was noted (McDonald et al. 1980) though the same authors confirmed previous reports (Hill et al. 1967) that patients with non organic illness have more obsessional traits. This study showed patients with slow transit constipation to have less obsessionality than normals (a fact disputed by the interviewer) and this must cast doubt on the usefulness of these questionnaires in clinical research.

The high incidence of psychosexual problems discovered at interview is interesting as the symptoms of constipation in most subjects started or became worse during adolescence. In a few the onset of constipation was related to a traumatic psychosexual event. This would suggest the concept of an anal version of vaginismus - anismus - as suggested in Chapter 6 could be correct. Biofeedback relaxation techniques already used in children with success (Olness et al. 1980) might be applicable here. However the children reported in the paper by Olness et al. suffered from megarectum and were trained to increase abdominal pressure in order to expel a stool. It has yet to be discovered whether adults can be trained to relax the voluntary anal sphincters on attempted defaecation.

Where constipation has been associated with psychiatric disease in the past the problem has been that of gross faecal retention with overflow incontinence or soiling (Pinkerton 1958, Haward et al. 1962, Watkins et al. 1965, Tobon et al. 1974). If such patients ignore the call to stool or resist defaecation it is easy to envisage how a megacolon might develop and to understand the possible role of the voluntary anal sphincters in assisting faecal retention. But if such a mechanism operates in the women with slow transit constipation, why do they not also have a megabowel? A fuller study including patients with idiopathic megacolon would be interesting, but the value of psychiatric questionnaires needs to be reassesed before further research is done.

CHAPTER 14

RESULTS OF TREATMENT

A) COLECTOMY

INTRODUCTION

The surgical treatment of constipation has been controversial since Arbuthnot Lane developed the operation of colectomy and ileo-rectal anastamosis at the beginning of this century. Other surgeons at the time carried out rather more bizarre procedures such as gastropexy or nephropexy for abdominal symptoms (McWhinnie et al. 1984) but as doctors came to realise that many complaints were functional in origin these were abandoned. The undoubted success of Lane's early surgery was forgotten and if some surgeons still performed colectomy for idiopathic constipation they did not write up their results.

Analysis of the St Mark's Hospital records since the introduction of the transit studies (which defined slow transit constipation), showed that treatment of constipation by colectomy is now relatively common. From 1969-1982 99 patients had undergone partial or sub-total colectomy for chronic constipation (Table 14a). In 43 a diagnosis of Hirschsprung's disease was made based on physiological studies and a full thickness rectal biopsy. This diagnosis was confirmed in all cases by pathological examination of the resected specimen. Another 35 patients had an enlarged colon without evidence of aganglionosis and this group was

	Male	Female	Total
HIRSCHSPRUNG'S DISEASE	28	15	43
IDIOPATHIC MEGACOLON	18	17	35
SLOW-TRANSIT CONSTIPATION	0	21	21
Total	46	53	99

Table 14a.
Patients treated by sub-total or partial colectomy for chronic constipation at St. Mark's Hospital from 1969-1982.

diagnosed as having idiopathic megacolon. The remaining 21 patients had a normal calibre colon but an abnormal gut transit time. The results of surgery in these patients which are part of the group studied in Chapter 3 will now be discussed.

CLINICAL DETAILS

This group of patients comprised 21 women with a mean age of 27.8 ± 2.3 years (s.e.m.). The details of previous surgery and the results of colectomy are given in Table 14b for the 16 who had sub-total colectomy, and in Table 14c for those with a more limited resection. In 16 patients the constipation was of gradual onset. Of the remaining 5, two developed symptoms after appendicectomy, one after hysterectomy and another after a fall leading to a vulval haematoma. The symptoms had usually begun in the teenage years though 3 had been symptomatic before the age of 10. The reported bowel frequency ranged from once weekly to once every 10 weeks. None of the patients had been helped by a high residue diet. Bowel transit studies were abnormal by definition. Only 2 patients had passed any of the shapes during the studies, the rest still had all 20 remaining after 5 days.

A striking feature was the amount of previous surgery undergone by the patients; Seven having had exploratory laparotomy, twelve appendicectomy and 9 major gynaecological surgery. Two patients undergoing sub-total colectomy had previously had a sigmoid colectomy without benefit. Nine patients had undergone anal proceedures and

these will be discussed later.

OPERATIONS PERFORMED

Sixteen patients had sub-total colectomy, eight with caeco-rectal and eight with ileo-rectal anastomosis. The anastomosis in these cases was at the level of the pelvic brim apart from one patient who had a caeco-sigmoid anastomosis. Five patients had partial resections; two having a left hemicolectomy and three sigmoid colectomy, one with a Duhamel proceedure.

RESULTS

a) Sub-total colectomies.

The functional results were assessed by interview and questionnaire. Ten of 16 patients are now opening their bowels 5 times weekly or more. One of these patients subsequently complained of diarrhoea and presumptive evidence of laxative abuse was obtained. However she had been well with a normal bowel action for the first two years after surgery. Four others were improved though bowel frequency was below the normal range and they still needed to take occasional laxatives. Two patients were no better. Both had complicated previous histories with multiple operations to the pelvic floor and both had previously undergone hysterectomy. One of them could not urinate either and a permanant urostomy with ileal conduit had been performed elsewhere.

During interviews a discrepancy was observed between the records and the patients comments. For example,

one girl was faecally incontinent at night but had not told the surgeon concerned "as he was so nice and I didn't want to upset him". For this reason it was decided to send all the patients a questionnaire so that they could record further details about the effects of surgery. The results of this are given in table 14d. The marked increase in bowel frequency is confirmed though 6 patients admitted to still using laxatives. Over half were still straining for more than 5 minutes at stool and other symptoms such as bloating, pain and a poor appetite were still common. Seven reported attacks of diarrhoea (defined as the passage of frequent watery stools) and 6 had been incontinent of faeces at some time. In only one was this a major problem; she was continent by day, but incontinent nearly every night if a large evening meal was taken.

b) Partial colectomies.

Five patients underwent partial colectomy in addition to two who had this proceedure at other hospitals. None were helped by a limited resection, the mean weekly bowel frequency for this group (reported by questionnaire) rising from 0.23 ± 0.01 (s.e.m.) to 0.5 ± 0.07 (NS). One patient eventually asked for another opinion elsewhere and a colostomy was performed. One has been given an ileostomy and two others are under consideration for further resection.

COMPLICATIONS

There were no deaths or serious complications in these patients. Seven were however readmitted with attacks

CASE	AGE Onset	AGE Opn	BOWEL FREQ.	TRANSIT STUDY	PREVIOUS SURGERY	MEDICAL PROBLEMS	ANASTO-MOSIS	RESULT	PROBLEMS
1)	16	19	4 Wks	20	Appendicectomy	Menorrhagia Raised prolactin	CRA	BA 1-2xWeekly	Nil
2)	18	23	2 Wks	14	-	-	CRA	BA 1xDaily	Nil
3)	8	53	4 Wks	20	Hysterectomy	'Fits'	CRA	No change	Ano-rectal myectomy (failed)
4)	12	18	6 Wks	20	FT Rectal biopsy	Epilepsy Amenorrhoea Raised prolactin	CSA	BA 2-3xWeekly	SBO (settled)
5)	11	20	1 Wk	20	Anal stretch	Idiopathic oedema Amenorrhoea	CRA	BA 5xDaily	SBO x3 (settled)
6)	4	21	4 Wks	20	Appendicectomy	-	CRA	BA 2xDaily	SBO (settled)
7)	15	21	10 Wks	20	FT Rectal biopsy Laparotomy Myectomy, D&C Sigmoid colectomy	Epilepsy	CRA	BA 2xWeekly	SBO (settled)
8)	17	28	4 Wks	20	-	Raised prolactin	CRA	BA 1xWeekly	Uses laxatives
9)	17	42	2 Wks	20	Appendicectomy Sphincterotomy Anal stretch Hysterectomy	Raised prolactin Migraine Idiopathic Oedema Solitary ulcer	IRA	BA 2xDaily	Nil
10)	20	22	3 Wks	20	Appendicectomy Laparotomy Ov. cystectomy	Amenorrhoea Myocarditis Renal stones	IRA	BA 3xDaily	Anal fissure (Laxative addict)

11)	24	34	6 Wks	20	FT Rectal biopsy Laparotomy Appendicectomy Hyst/Ov.cyst Mammoplasty Rectopexy	Idiopathic oedema Solitary ulcer	IRA	No change but diarrhoea with laxatives	SBO (laparotomy)
12)	4	23	6 Wks	20	-	Raised prolactin Amenorrhoea Blackouts	IRA	BA 1xDaily	Nil
13)	12	22	1 Wk	20	Appendicectomy Sigmoid colectomy	-	IRA	BA 2xDaily	Nil
14)	18	23	6 Wks	20	Appendicectomy	Raised prolactin	IRA	BA 10xDaily	Incontinent SBO (laparotomy)
15)	11	16	6 Wks	20	Appendicectomy Laparotomy (2) Ileostomy Anal stretch	Amenorrhoea	IRA	BA 2xDaily	SBO (laparotomy)
16)	16	27	4 Wks	17	-	Idiopathic oedema	IRA	BA 5x Weekly	Nil

Table 14b. Clinical details of patients undergoing sub-total colectomy for slow transit constipation. Ages at onset of symptoms and at operation are given. Bowel frequency is the reported interval between spontaneous bowel movements. Transit study gives the number of polythene markers present after 5 days (normal: less than 5). Abbreviations: CRA=caeco-rectal anastomosis, IRA=ileo-rectal anastomosis, CSA=caeco-sigmoid anastomosis, BA=bowel actions, SBO=small bowel obstruction, FT=full thickness.

CASE	AGE Onset	AGE Opn	BOWEL FREQ.	TRANSIT STUDY	PREVIOUS SURGERY	MEDICAL PROBLEMS	OPERATION	RESULT
1)	14	18	6 Wks	20	Appendicectomy Ov. cystectomy D&C	Blackouts	Sigmoid colectomy	No change
2)	35	41	4 Wks	20	Caesarian Secn. Hysterectomy Colporrhaphy Laparotomy (2) Appendicectomy Cholecystectomy Ov. cystectomy	Angina	L Hemicolectomy	No change
3)	12	48	4 Wks	20	Thyroidectomy Laparotomy Hysterectomy Appendicectomy	Graves dis. Bronchitis	Sigmoid colectomy	BA every 2/52
4)	14	26	4 Wks	20	FT Rectal biopsy Appendicectomy	-	Sigmoid colectomy	No change Colostomy
5)	13	40	4 Wks	20	Hysterectomy Rectopexy D&C (2)	Blackouts	L Hemicolectomy	No change SBO (laparotomy) Ileostomy

Table 14c. Clinical details of patients undergoing segmental colonic resection for slow transit constipation. Ages at onset of symptoms and at operation are given. Bowel frequency is the reported interval between spontaneous bowel movements. Transit study gives the number of polythene markers present after 5 days (normal: less than 5). Abbreviations: BA=bowel actions, SBO=small bowel obstruction, FT=full thickness.

PATIENTS ASSESSMENT OF THE RESULT OF COLECTOMY

	Before	After	P
*			
Weekly bowel frequency (Spontaneous)	0.3	21.7	<0.001
Using laxatives	16	6	<0.01
Abdominal pain	16	8	<0.01
Abdominal bloating	16	10	<0.05
Good appetite	7	11	NS
Urge to defaecate	2	13	<0.001
Straining at stool (>5 mins)	16	9	<0.05
Any rectal bleeding (3 mnths)	9	3	NS
Attacks of diarrhoea	0	7	-
Any faecal incontinence	0	6	-

Table 14d.

This table gives the results of the questionnaire sent to the 16 patients who had undergone sub-total colectomy asking them to record the effect of the operation. The weekly bowel frequency was that reported without the use of laxatives. Positive answers to the last 3 questions were asked if the patients had noted any of those symptoms in the 3 months prior to operation, or in the 3 months before the survey. Statistical analysis was made using the students t test for bowel frequency* and the $\chi 2$ test with Yates correction for the others.

of apparent small bowel obstruction. Three underwent laparotomy with division of adhesions but the others settled conservatively. The latter group had all undergone caecorectal anastamosis. Examination of their plain abdominal radiographs on admission and a comparison with later films suggested that a ball of faeces had impacted the caeco-rectum (Figure 14a).

The presentation of one patient after surgery allowed some observations to be made on the nature of the abdominal swelling commonly encountered in this group of patients. Since she had undergone colectomy the swelling could clearly not result from colonic distension with stool or gas. Comparison of the clinical pictures before and after surgery (Figures 14b-c) showed a disturbance of posture on both occasions with a marked lumbar lordosis. This abdominal protrusion disappeared under anaesthesia prior to surgery suggesting a muscular disorder. At her presentation after operation, surface electromyography was carried out showing sustained abnormal electrical activity in the erector spinae muscles (Figure 14d). If this observation is confirmed in others it suggests the possibility of a widespread abnormality of striated muscle function affecting the spine as well as the pelvic floor and possibly other muscles. This may help to explain the difficulty these patients have in defaecating since apart from any pelvic floor problem, it is impossible to strain at stool with the abdomen held in the position illustrated in these photographs.

The recurrance of constipation in some may be due to changes in the anatomy of the rectum. Later examination

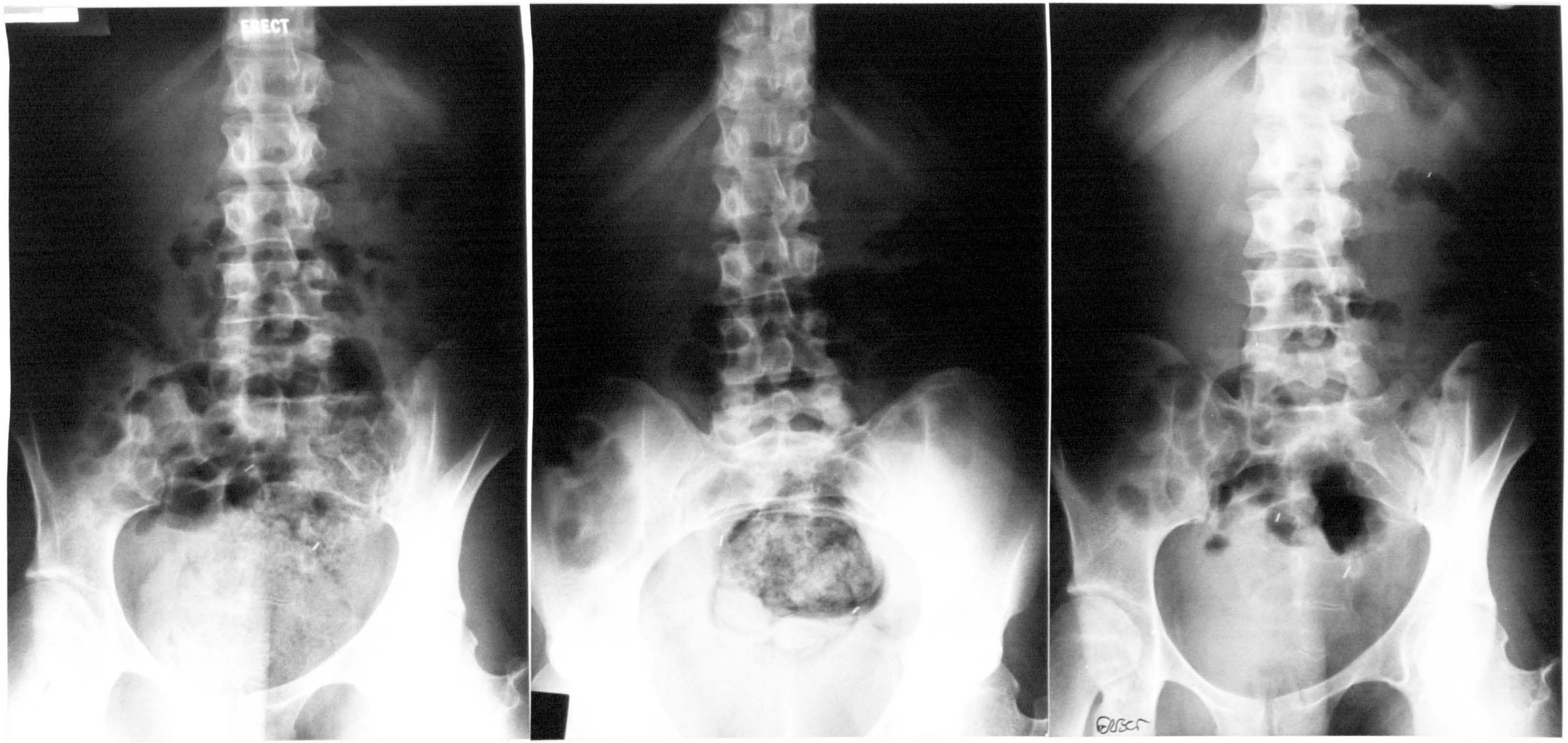


Figure 14a. RECTAL IMPACTION AFTER COLECTOMY.
This patient presented at another hospital three months after colectomy and caeco-rectal anastomosis with suspected small bowel obstruction. The initial film on the left showed a ball of faeces impacting the rectum and some dilated loops of small bowel above. There were however no significant fluid levels on the erect film. She was managed conservatively by repeated rectal washouts and the rectum gradually emptied (centre and right).

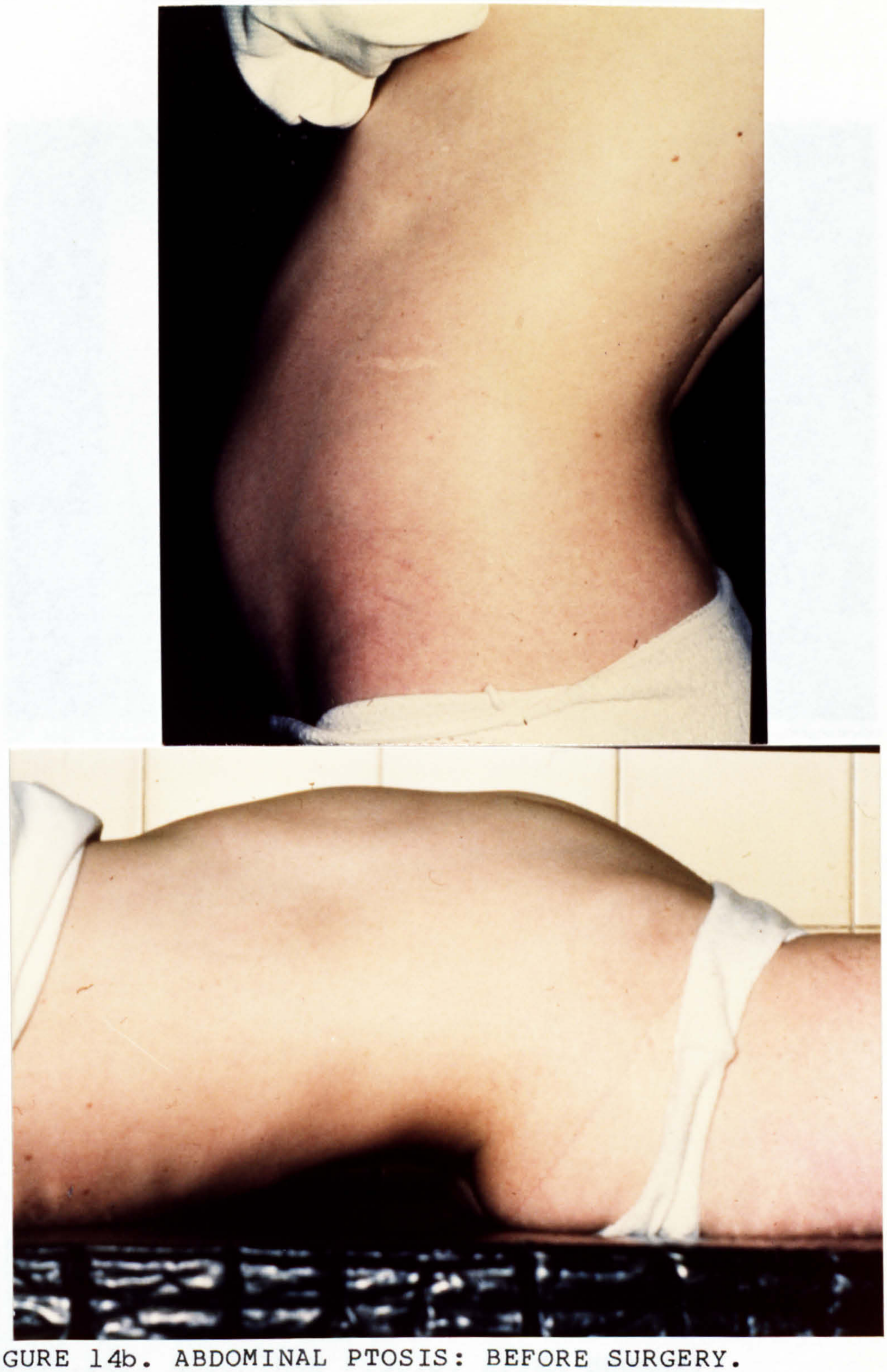


FIGURE 14b. ABDOMINAL PTOSIS: BEFORE SURGERY.
These photographs demonstrate the extreme "swelling" of the abdomen found in patients with slow transit constipation. In many cases it enlarges so as to resemble a 6 month pregnancy. However on lying down, the cause is revealed as a marked lumbar lordosis. The muscle spasm appears to be involuntary and in this patient was maintained for 2 weeks. No faecal masses were felt and the abdomen became flat again under anasthesia.

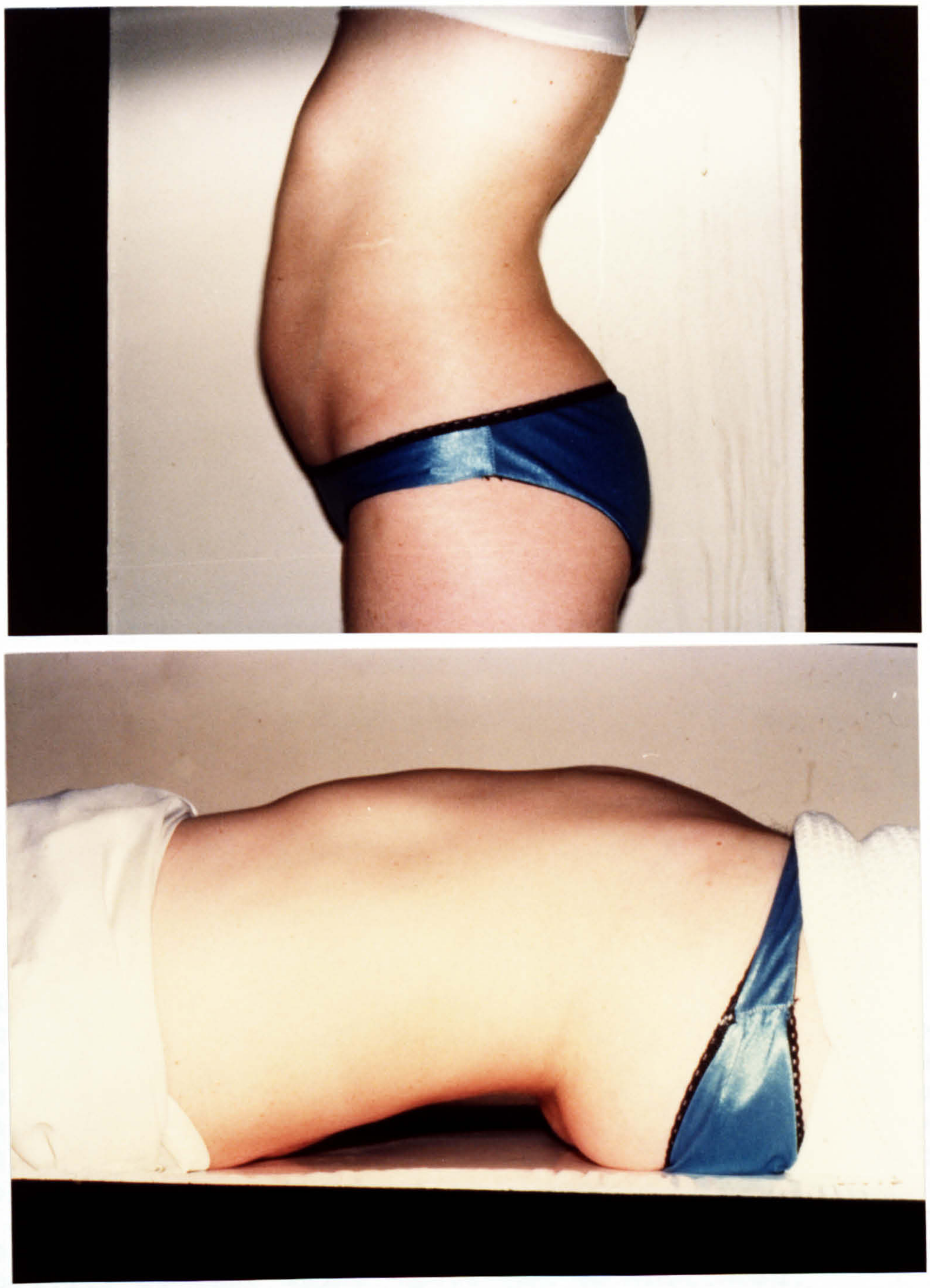


FIGURE 14c. ABDOMINAL PTOSIS: AFTER SURGERY.
These photographs were taken of the same patient in Figure 14b after colectomy and at the time of her presentation with suspected small bowel obstruction (see Figure 14a). Since her colon has been removed the apparent swelling can clearly not be caused by faecal impaction in that organ. Again, the apparent swelling is seen to be secondary to a lumbar lordosis possibly as a reflex response to the rectal distension.

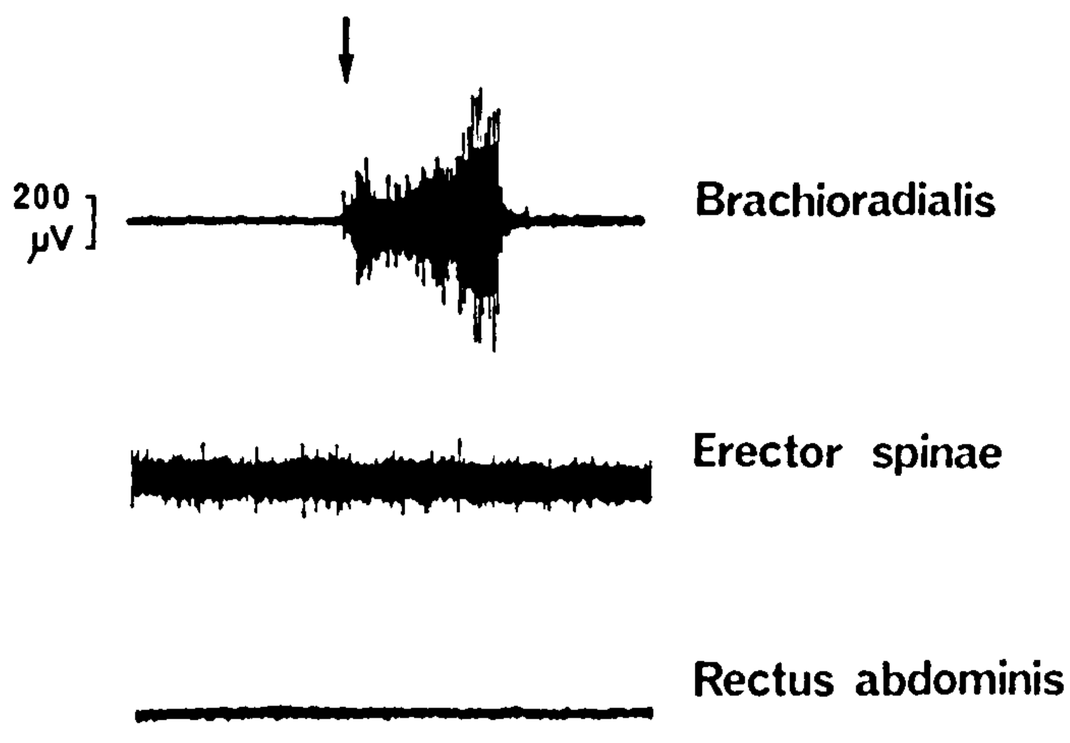


FIGURE 14d. ABDOMINAL PTOSIS: ELECTROMYOGRAPHY.
Surface recordings using bipolar electrodes over selected muscles on the arm, leg, back and abdomen. These were obtained from the patient illustrated in Figure 14c on the same day the photograph was taken. Normally at rest all the striated muscles of the body, apart from those making up the pelvic floor, are electrically silent. Any movement produces a sharp increase in activity (as in the arm muscle arrowed). In this patient the erector spinae muscles showed sustained activity at rest which could not be abolished.

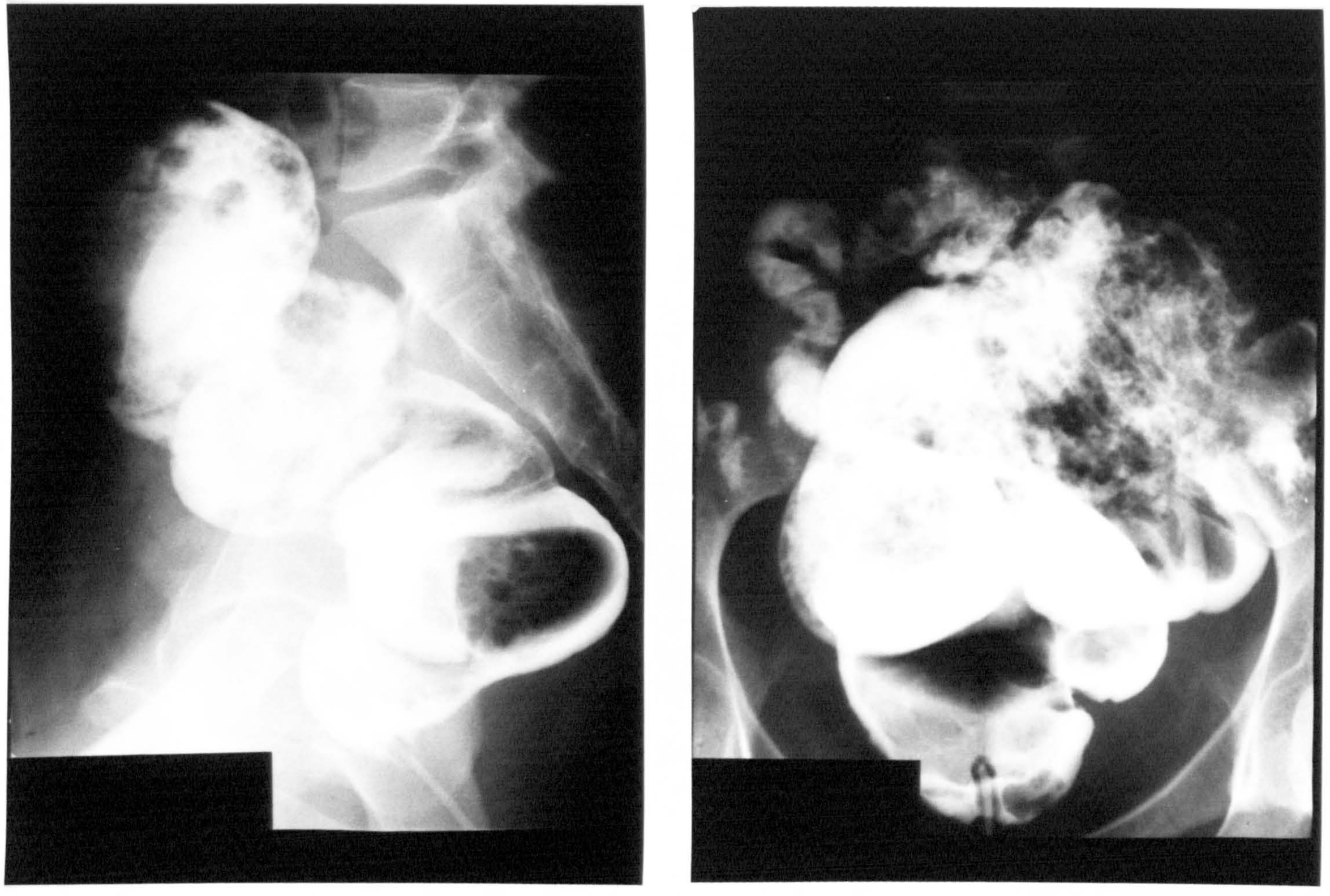


Figure 14e. GASTROGRAFFIN ENEMA AFTER CAECO-RECTAL ANASTOMOSIS.
This examination was performed on a young girl of 19 who had become constipated again some months after colectomy. The cause of this was found to be a dilatation of the caeco-rectum which was filled with soft faeces. On the AP view (right) a loop of small bowel is seen entering the top of the dilated caecal remnant.

by gastro-graffin enema in one patient showed the caecal remnant had enlarged and was possibly acting as a terminal reservoir (Figure 14e). This observation only re-emphasises the mystery of why these patients did not have colonic or rectal enlargement secondary to their severe constipation. It is possible that pelvic nerves are damaged during colectomy that allow subsequent rectal dilatation.

B) ANAL SPHINCTER PROCEDURES

INTRODUCTION

The physiology of the anal sphincters has been discussed in Chapter 6. Previous treatment has been directed at the internal anal sphincters and disruption of their activity by stretch or sphincterotomy is widely practiced for the treatment of constipation with megacolon. A more extensive sphincterotomy was developed for the treatment of short segment Hirschsprung's disease (Bentley 1966) which involved removal of a strip of the internal sphincter extending up into the rectum. This was later applied to other groups with constipation and a success rate of over 60% claimed (Martelli et al. 1978b).

The concept of constipation secondary to overactivity of the striated muscles of the anal sphincter was first suggested by Beddard (1910). Others seem to have recognised anal spasm leading to constipation, but as secondary to local inflammatory processes (Gant 1923, Buie et al. 1938). Wasserman (1963) was the first to define striated muscle overactivity as a primary phenomenon causing

constipation. He described the results of partial division of the puborectalis muscle for what he termed the puborectalis syndrome. Later authors reported a series of 46 patients treated in this way, including 13 children with megarectum, but few clinical details are given (Wallace et al. 1969). It is perhaps significant that no further papers were published by these authors and the long term results of this treatment are therefore not known.

Several of the patients in this series have had local anal procedures. Following the reports by Martelli et al. (1978b) a number underwent ano-rectal myectomy. After demonstration of abnormal striated muscle activity as discussed in Chapter 6, a few patients with the most severe symptoms were treated by posterior puborectalis division.

RESULTS

i) Anal stretch or sphincterotomy.

The majority of cases treated were the most severely affected and had also undergone colectomy. Of the 64 patients who were surveyed in detail 4 had been treated by internal sphincterotomy. This involved division of the internal sphincter on its lateral aspect along the length of the anal canal. None of these patients benefited from the procedure. A further 6 patients had undergone anal stretch. Two having this done more than once. Patients reported a transient benefit, lasting no longer than 2 weeks, after which their symptoms returned. Since these operations had all been performed before the research studies were

initiated no objective tests were done to assess the affect of surgery.

ii) Ano-rectal myectomy.

Three patients underwent ano-rectal myectomy with removal of a 1 cm. strip of muscle 6 cm. long. This included the whole length of the internal sphincter and extended into the muscle of the rectal wall. None reported any benefit. One patient operated on during the time of these studies returned for further investigation after the operation and the balloon expulsion test was repeated. This showed that she was still unable to expel a water filled balloon from the rectum. The force applied to extract the balloon when straining had however fallen slightly from 650 to 500 gms.

iii) Puborectalis division.

Division of the puborectalis muscle in its posterior aspect was carried out on six patients. Three were included in the survey and three had been referred later. The muscle was exposed via an intersphincteric approach. The striated muscles were identified and the top portion behind the anus completely divided. This involved a cut of 1.0 to 1.5 cm. Following this the separation of the puborectalis could be felt on rectal examination.

All the patients claimed some improvement immediately after operation but only one had sustained benefit after 3 months. This patient said that defaecation was much easier after surgery. All the patients underwent a balloon expulsion test and defaecating balloon proctogram.

None could expel either balloon before the operation and only the one patient who reported a clinical improvement was able to expel the balloons afterwards. The mean resting ano-rectal angle on the balloon proctograms taken before and after sphincter division showed no significant change. Before: 90 ± 6° (SD), After: 95 ± 8° (N.S.).

C) BEHAVIOURAL RETRAINING

Early in the studies when the results of elecromyography became available it was thought that the disturbance possibly represented a habit disorder and that psychiatric treatment might therefore have a role. One patient with an aversion to defaecation and a huge megacolon had previously been referred for treatment to a psychiatrist specialising in behavioural treatment with encouraging results (Marks 1982). The same regime was therefore suggested for the patients with slow transit constipation.

Three patients eventually accepted an offer of behavioural therapy. One took exeption to being placed in the company of highly disturbed obsessional patients and discharged herself after 2 weeks. One patient adhered to the program for 3 months both as an inpatient and outpatient and the other for 1 year. The treatment included regular magnesium sulphate, which was their conventional medical regimen, accompanied by a program of bowel retraining. The psychiatrists were enthusistic about the response but there was no objective benefit. The two patients who completed treatment were still unable to defaecate and balloon

expulsion could still not take place. Referral for this treatment had been as a last resort in severely affected patients and all three eventually underwent colectomy.

D) DRUG TREATMENT

INTRODUCTION

The medical treatment of constipation has changed little in recent years. The main groups available are stimulants such as senna and bulking agents. Newer synthetic stimulants have been introduced but probably act in the same way as senna. A wider variety of synthetic and natural bulking agents are now available but these do not help patients with slow transit constipation. Dioctyl sodium did not seem to be helpful and liquid paraffin is no longer used for regular treatment because of the risk of inhalation lipoid pneumonitis. Epsom salts (magnesium sulphate), which produce an osmotic purge by holding water in the lumen of the bowel, was the commonest outpatient treatment used.

Review of the notes and the questionnaire showed that most had tried nearly every agent in the pharmacopoea. Before referral it was usual for patients to have tried a variety of proprietary agents, mainly those containing senna, cascara and phenolpthalein, either alone or in combination. Whatever the severity of the illness, a big enough dose of tablets would often provide some sort of bowel movement, though at the expense of one or two days in pain.

In outpatients these patients were usually given

magnesium sulphate crystals which they could mix into fruit juice and dilute to drink. This was given three times daily and the dose subsequantly adjusted until a satisfactory bowel action was achieved. Though this treatment was successful in milder cases it did not help all the patients and most complained that it was unpleasant to use. The main complaints were of bloating and nausea. Some patients had to abandon the treatment because of vomiting. Alternative treatments were therefore needed but it is difficult to plan rational treatment for a condition whose aetiology is not known.

Whilst studying the writings of Arbuthnot Lane it was noted that he treated many patients medically in his outpatients at Guy's Hospital. He was the first to introduce liquid paraffin, but he also gave young women with severe constipation an extract from the prostate gland of rams. This suggested the idea of examining the effect of prostaglandins on colonic motility in patients with slow transit constipation. Later when the results of the sex hormone studies were known (Chapter 12), a similarity was noted between the symptoms of patients with constipation who had hyperprolactinaemia and those with severe pre-menstrual tension with the same hormonal abnormality. Both had pre-menstrual exacerbations of their symptoms and many in both groups had idiopathic oedema. Success had been claimed initially for treating some of the latter group with pyridoxine (Vitamin B6), which has also been used for treating constipation and paralytic ileus (Jaques 1951, Hanck et al. 1982).

In other studies, the patients with pre-menstrual tension and hyperprolactinaemia responded to treatment with Gamma-linoleic acid (Brush et al. 1981). Again this was of interest because GLA, an essential fatty acid, is a prostaglandin precursor. If there was a block in the conversion of linoleic acid to GLA as postulated by Brush et al. then this might have offered an explanation for the gut symptoms. Prostaglandins being known to have important effects on gut secretion and motility.

Another possible treatment was suggested by one patient (excluded from the series) who presented with severe constipation and was found to have slow colonic transit time. However in her case the primary cause of constipation was discovered to be congenital bile salt deficiency. Gallstone dissolution with chenodeoxycholic acid is frequently complicated by diarrhoea and bile salts are included in some proprietary laxatives. For these reasons a trial of Chenodeoxycholic acid in slow transit constipation seemed worthwhile.

i) Study of rectally administered Prostaglandin E2

This study was initiated before it was realised that many patients with slow transit constipation have no spontaneous colonic segmenting activity. The rationale for the treatment was that many authors had reported increased colonic segmenting activity in constipation. Colonic activity in normal subjects had been shown to be reduced by intravenous PGE2 (Hunt et al. 1975) and it was hoped the symptoms of patients with slow transit constipation would be

relieved. This would then confirm that it was primarily a metabolic disorder. Also it might explain why some patients noticed their bowels move freely during menstruation, when there is an increased release of prostaglandins from the endometrium (Downie et al. 1974).

Unfortunately there was no effect. Prostaglandin E2 was administered as a suppository in 6 patients, none of whom defaecated afterwards. Positive results were however found in another group of patients with constipation associated with normal gut transit time. The details of this study are given in appendix 7.

ii) Trial of Gamma Linoleic Acid

The main dietary intake of essential fatty acids (EFA) is through vegetable oils and meats. Linoleic acid is the main EFA in the diet and is converted first to Gamma linoleic acid (GLA) and then eventually to the prostaglandins (Table 14e). The enzyme delta-6-desaturase is required to convert linoleic acid to GLA and it has been postulated that some groups of patients have a deficiency of this enzyme (Mead et al. 1976). Alternatively, it has been suggested that vitamin deficiency could block one of the stages lower down the metabolic pathway. Pyridoxine is required to convert GLA to Dihomo-GLA; and zinc, niacin, biotin and ascorbic acid to convert DGLA to prostaglandin E1. It is of interest that volunteers taking large doses of ascorbic acid to try and prevent viral infections developed diarrhoea (Horrobin 1982).

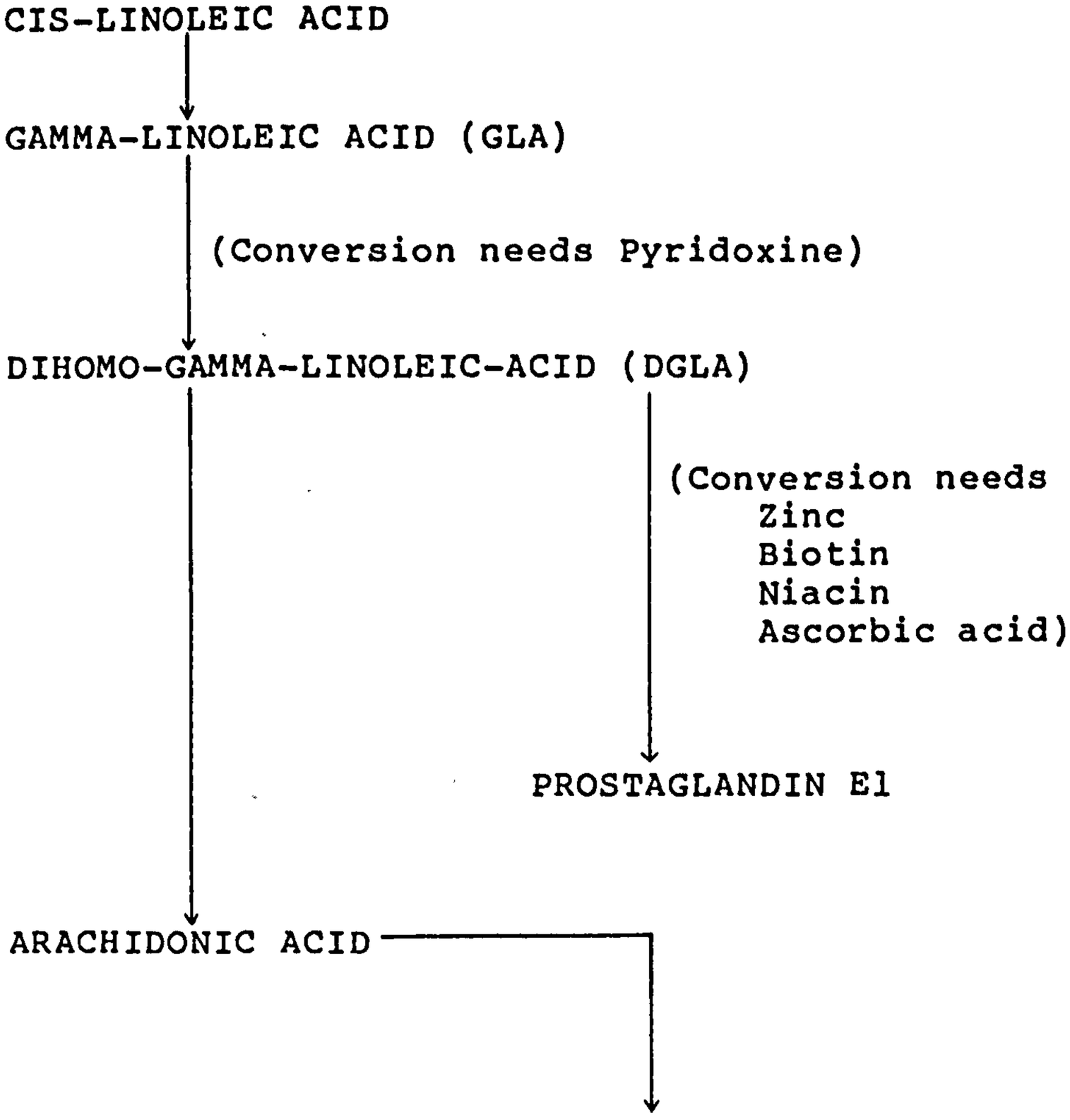


Table 14e.
STAGES IN THE CONVERSION OF CIS-LINOLEIC ACID TO THE PROSTAGLANDINS E1 AND E2 IN MAN. It has been postulated that a defisiency of the enzyme delta-6-desaturase needed to convert linoleic acid to GLA results in a deficiency of the latter which can only be overcome by supplements. Other vitamin deficiencies may retard later stages in its conversion.

Study design.

The trial was an open uncontrolled assessment of the effect of GLA on the symptoms of 6 patients with slow transit constipation. The only sources of GLA are human breast milk and the oil extracted from the evening primrose (Oenothera biennis). Capsules containing 250 mg. of evening primrose oil were obtained from Efamol Ltd. and the patients took 6 capsules daily for 3 months in addition to their normal treatment. They were asked to try and discontinue laxatives if possible. After this the same treatment was continued for a further 3 months together with daily supplements of zinc, biotin, niacin, pyridoxine and ascorbic acid. Patients were seen at monthly intervals throughout the study.

Results.

There was no effect on bowel function in 5 patients. The other patient was a lady of 28 who had been constipated since the age of 17. She attributed the onset of her illness to a diet but it is possible that this only exacerbated a pre-existing tendency. Without large doses of laxatives she would open her bowels only once every 10 days. Whilst taking the evening primrose oil capsules she noticed a marked improvement in bowel function although she continued to use laxatives. In the second part of the study she was persuaded to abandon the laxatives and found that with the oil and vitamin supplements she had a spontaneous daily bowel movement. At the conclusion of the study the oil was stopped and her constipation returned. On restarting it

her bowels once again returned to normal.

iii) Assessment of Chenodeoxycholic acid

The commercially available preparation for gallstone dissolution was given to 3 older patients who had finished having children (as it may have a teratogenic effect on the unborn child). They each received a dose of 15 mg./Kg.body weight as three divided doses daily for 2 weeks. There was no effect in any of the patients on bowel function. This method of treatment was therefore not pursued.

DISCUSSION

The treatment of severe idiopathic constipation whether associated with a megacolon or not has always been unsatisfactory. These problems are uncommon and the general physician or surgeon may be perplexed by a handful of patients who seem resistant to all medication. As there is no faecal impaction and the rectum may be empty it is often assumed that the patient has a psychological disorder and rapport breaks down if the patient feels their complaint is not being taken seriously. At specialist hospitals such as St. Marks, the worst cases tend to congregate and an answer has to be found for what can be extremely disabling conditions. Inevitably it is the most intelligent and articulate who will press for a definitive treatment and the selection if patients was consequently not based on strict criteria.

The first surgeon to suggest and to practice

colectomy as a treatment for chronic constipation was Arbuthnot Lane. There are three published reports of his work in which the case histories of 93 patients treated for constipation by colectomy or by-pass are given (Lane 1908, Chapple 1911, Lane 1913). These early papers are of particular interest as only 8 of the patients were men and the majority of women were under 35. In view of the sex ratios shown in Table 14a and assuming that the incidence of these disorders has not changed during the present century, it seems possible that he was operating on similar cases to those described in this thesis. In contemporary case reports he always recorded the presence of a megacolon but in the patients described in his early papers he did not. There is no doubt that many of his operations were a great success though no long term follow up reports are available. Anecdotal reports pay tribute to the effects of his treatment and Thompson (1964) records the case of a 44 year old lady who survived colectomy, and lived another 50 years with no further bowel trouble.

Lane's contemporaries also reported the results of colectomy for constipation, but after his ideas fell into disrepute there was no record of this being done for nearly 30 years. Surgery was however still performed for Hirschsprung's disease and megasigmoid (with or without volvulus). Thompson (1964) in his Lettsomian lecture was one of the first to come out of the closet and admit "with a sense of shame and guilt" that he had been operating on difficult cases. It appears however that the majority of the 15 cases he described had idiopathic megacolon.

Over the next few years colectomy for constipation began to regain acceptance. Henley (1967) described sigmoid colectomy in 4 patients who seem to have had an elongated sigmoid colon rather than a megacolon, and claimed good results. However the surgery of idiopathic megacolon at that time was not very successful (Jennings 1967). In America surgeons began to report the results of colectomy for megacolon and one report at least included some cases in which there was a "long redundant colon" (Mahorner 1970).

A review of the results of colectomy for idiopathic megacolon at the Mayo Clinic over 30 years showed many successes (McCready et al. 1979). The results at St. Mark's Hospital were variable, but sub-total colectomy was often helpful (Lane et al. 1977). Hughes et al. (1981) reported a series from Australia which included 10 women with functional constipation and 7 with idiopathic megacolon. The 10 with functional constipation seem to correspond with those described in this thesis. They all underwent sub-total colectomy with ileo-rectal anastamosis and 8 had a satisfactory result, the others eventually needing an ileostomy. A recent review from Minneapolis showed a series of 48 colectomies over 10 years (Belliveau et al. 1982). This suggests that surgical treatment for constipation is now gaining wider acceptance. In some of their cases the colon was of normal diameter though megacolon was not defined and bowel transit studies had not been performed. Taking all groups together, 80% of patients seemed satisfied with the result.

Colectomy for the patients described here was

apparently only undertaken with great reluctance. The surgeons concerned naturally feeling unhappy at removing what was to the naked eye a normal colon with a major surgical procedure that must of necessity carry a risk to the life of the patient. Constipation in these cases was not life threatening, as there was no stercoral ulceration with heamorrhage nor volvulus with intestinal obstruction. Neverthless, the quality of life in these patients was as poor as that of some patients who undergo colectomy for chronic ulcerative colitis, and the relief expressed afterwards as great.

These results show that a satisfactory result was achieved in the majority of patients who underwent sub-total colectomy. A more limited resection was of no help in the 7 patients on whom it had been tried and this contradicts the earlier paper describing pelvic colectomy for constipation (Henley 1967). More limited resections are also of no value in idiopathic megacolon (Jennings 1967, Lane et al. 1977) though sigmoid colectomy is helpful in patients with recurrent sigmoid volvulus (Ryan et al. 1982).

The functional results of ileo-rectal anastamosis seem to have been slightly better than for caeco-rectal. Comparison of the results for the two groups in their replies to the questionnaire showed that 5/8 of the former had a normal bowel frequency after operation compared with 3/8 in the latter group. This is if the range of "normal" is taken as 3 stools per day to 3 per week (Connell et al. 1965). This does not take account of the fact that some with caeco-rectal anastamosis were able to achieve a satisfactory

bowel action by using occasional small doses of laxatives. In addition 2 of the ileo-rectal group had excessive bowel frequency, though one of these turned out to be a laxative addict. Analysis of the other results showed that 4/6 patients who had experienced incontinence and 5/6 who complained of recurrent attacks of diarrhoea were in the ileo-rectal group. However only 1 of these patients still needed laxatives. The number of patients who still strained excessively were evenly divided and there was one complete failure in each group.

No useful medical treatment has been found for these patients apart from magnesium sulphate. This is harmless in the small doses used and not absorbed from the gut. It seems preferable to stimulant laxatives which in any case are reported by the patients to lose their effect and may cause the neuropathological changes recorded in Chapter 9. Future thereaputic avenues seem limited if the myenteric plexus changes are confirmed in all patients. The single success with gamma linoleic acid may not be of relevance to this group of patients, but rather to those with the irritable bowel syndrome. As the studies in Appendix 7 have demonstrated a reduction in the excess colonic segmenting pressures of these patients with prostaglandin E2, it may be they who would benefit from an increased supply of prostaglandin precursors.

From the evidence presented here it seems that clinicians should be advised to use magnesium sulphate for the less serious cases, but that colectomy should be considered in those worst affected, particularly for young

patients in order to prevent a lifetime of ill health and drug use. Hopefully, if recurrent straining is thus prevented, damage to the pelvic floor and possibly the development of rectal prolapse or a descending perineum in later life may be avoided. Local anal operations have not so far proved helpful and at present should be avoided. However as a defaecatory disorder seems to play a significant part in the development or continuance of symptoms, this possibility should not be completely discounted for the future. Further physiology studies will be needed to define more exactly which muscles are at fault. Though behavioural therapy has not proved useful, different techniques may be worth trying in the future, but there is obviously no point in applying these to patients whose myenteric plexus has been damaged.

CHAPTER 15

FINAL DISCUSSION

1) Why is this form of severe constipation only found in women?

Though the condition of idiopathic slow transit constipation had been recorded, the fact that all patients so defined are female had not previously been noted. It must therefore either be an inherited sex linked disorder, or occur as a result of some special anatomical arrangement or hormonal change peculiar to women. It might arise secondary to a psychological problem, but it seems unusual that no men become susceptible to the same influences.

The possibility of an inherited disorder is extremely remote. Diseases confined to women, apart from those of the organs of reproduction, are very rare. In addition, two pairs of identical twins were fortunately included in this series. The twin sister of one was interviewed and is entirely normal. The other twin could not be seen, but her general practitioner reported that she had never suffered with constipation.

Hormonal changes have been investigated, but the mild hyperprolactinaemia found in some of the women is almost certainly a consequence rather than a cause of their symptoms. Though some patients found bowel movements easier during menstruation, this is a finding in the same percentage of normal women. None of the hormonal changes in the normal menstrual cycle are sufficient to account for the gross disturbance of ano-rectal or colonic physiology that

results in the monthly bowel movement reported by many of the patients in this series.

The pelvic floor of women contains some differences from men that could predispose to constipation. Probably the most important is the absence of the prostate gland. This may buttress the front of the rectum in men preventing the development of a rectocoele during straining at stool. This possibility has not been investigated, but the balloon proctogram could be used for such a study. This might explain why constipation is much commoner in women, and any weakness anteriorly could be worsened after childbirth so exacerbating the symptoms. However, it is difficult to explain in an evolutionary sense why women would have developed an inadequate defaecatory mechanism, and if the anatomy is at fault why are all women not constipated?

Amongst children, it is boys who suffer most with constipation secondary to psychological problems. Both in childhood and when constipation occurs secondary to psychological disturbance in later life, it is nearly always associated with megabowel. It is possible that functional spasm of the anal sphincters occurs mainly in women because of psychosexual problems and a fear of intercourse. But it is not easy to understand why this should result in a long or redundant colon rather than a megabowel.

2) Are the symptoms due to a disorder of defaecation or of colonic function?

This question is probably the most important arising from the study because is has implications for future treatment. At present it cannot be answered, but it

seems possible a combination of the two is responsible. Anismus may be a feature of many types of constipation as the patients with megacolon and two with normal colonic transit time also had difficulty expelling a small rectal balloon. Colonic pressure wave activity might become reduced as a reflex phenomenon if defaecation is resisted (and it seems a sensible physiological response) but the failure of a few patients to respond to topical bisacodyl and the neuropathological findings suggest a definite colonic problem. This might of course be secondary to prolonged laxative use and until further studies are performed this must be the most likely hypothesis.

3) Is this condition a separate disorder from the irritable bowel syndrome?

Most patients with the irritable bowel syndrome have a variety of complaints that fluctuate in severity from day to day. Alternating constipation and diarrhoea is the most common symptom. It is possible to distinguish a group whose complaint is of painless diarrhoea and another with constipation alone, though most of the latter group have other symptoms such as bloating, pain and nausea. As previously explained, the bowel transit study will divide the group with chronic constipation into two, but are they different disorders?

The evidence that they are is that constipation with normal transit time affects both men and women, that most with normal transit can expel a rectal balloon and have a different pattern of colonic motility. Colectomy is of course not performed in this group so it is not known if

some of them also have a myenteric plexus abnormality. In addition none of the women in the normal transit group had hyperprolactinaemia, and their motilin and pancreatic polypeptide responses to an oral stimulus were greater.

In favour of their being one group is the similar reduction of gastrin release and the fact that there is overlap in the balloon expulsion and colonic motility findings. It could be argued that all patients start off with an irritable bowel and perhaps those who abuse laxatives develop a hypomotile colon secondary to myenteric plexus damage. This damage may interfere with the reflex control of external sphincter function (the mechanism by which external sphincter relaxation on straining occurs not yet being known). It is sometimes difficult to separate the two groups clinically but this does not nescessarily imply they are the same. Many medical disorders present with identical or non-specific symptoms and it is subsequent investigation that defines the disorder and allows rational treatment.

4) Is this condition separate from idiopathic megacolon?

There seems no doubt on the evidence presented here that this is the case. Colonic transit studies specifically on patients with megacolon have not been reported, but in some cases are abnormal. It seems likely that transit will be prolonged unless spurious diarrhoea occurs.
Differentiation from the patients in this study was made by barium enema and this resulted in complete separation and showed the sex ratio to be equal in idiopathic megacolon.

Rectal elasticity studies could be used to give confirmatory evidence and it is possible a combination of the two will give a firm definition of megabowel for future research studies.

Hormonal changes were seen in patients with megacolon including failure of motilin and gastrin release and in a few female patients (not reported here), hyperprolactinaemia. In addition previous work has demonstrated myenteric plexus damage in a minority of patients with megacolon. These findings could be argued two ways, either that the conditions are the same, or more likely that hormonal and neuropathological changes are secondary to the disease or its treatment.

5) How should this condition be managed?

If colonic damage is secondary, then attention should be given to treating the ano-rectal problem earlier and avoiding stimulant laxatives. This seems impossible as patients can obtain a variety of drugs without prescription and will probably only consult a doctor when these have failed. Physicians need to be educated about the condition and encouraged to prescribe saline laxatives. For those with severe symptoms who do not respond to laxatives sub-total colectomy with ileo-rectal anastamosis is probably the best treatment to give a reasonable chance of a return to normality. Full investigation in a specialist centre should ideally be carried out to exclude primary causes for the symptoms. Non-specialist surgeons should be discouraged at present from interfering with the anal sphincters until

further studies are complete.

6) Suggestions for further study

a) Ano-rectal physiology studies are needed to confirm that anal spasm prevents normal defaecation and to try and determine how the normal reflex inhibition of the external sphinter and puborectalis muscles occurs. The role of the internal sphincter needs critical reassessment, in particular to discover if earlier reported abnormalities of anal canal pressure were due to external sphincter activity rather than attenuated internal sphincter relaxation.

b) More detailed psychological assessment is needed perhaps including a comparison of the groups with megabowel, slow colonic transit and normal transit. If anismus is primarily a psychological problem then relaxation training might be reassessed, probably using different methods.

c) The neuropathological findings were unsatisfactory and did not correlate with function. Progress in this field is rapid and when immunocytochemical techniques have been refined a new study should be done. Ideally colonic motility should be studied at rest and in response to food and drugs, including stimulant laxatives. Hopefully it will be possible to combine this information with details of the anatomy of the whole myenteric plexus, rather than only the argyrophophill cells, and to find if cell numbers and fibres are genuinely depleted. Even if normal in number, it may be possible than there are

biochemical or ultrastructural changes in the neurones. Any new study should include electron microscopy and be strictly blinded - the pathologist not being aware of whether tissue sent is from constipated or control subjects.

d) As the myenteric plexus changes might be secondary to laxatives, futher studies of the effect of commonly used drugs on the myenteric plexus are needed. Initially it would be interesting to find out if bisacodyl and phenolpthalein cause similar myenteric plexus changes in animals to those reported following administration of senna.

e) Despite the failure of anal sphincter procedures, further assessment in specialised hands of division of the puborectalis muscle is indicated. Some of the patients who underwent colectomy remained constipated. It would be ideal if ano-rectal physiology studies could identify this group brfore surgery (so far they do not appear to have any particular characteristics). For those who have failed to respond and are about to have an ileostomy or colostomy performed, further attempts at muscle division would be ethical and the information gained might help future sufferers.

f) A controlled trial of a high fibre diet has never been done in slow transit constipation (and nor for that matter in idiopathic megacolon). It would be useful to have this information if only to educate other doctors and prevent unecessary suffering on the part of the patients.

g) The proctometrogram could have other applications. Its normal range should be defined in controls and then it would be interesting to find if it could be used as a diagnostic tool in gastroenterology outpatients in the assessment of patients who might have an irritable bowel. Other possible uses include assessment of rectal capacity in patients with inflammatory bowel disease before ileo-rectal anastamosis. As previously mentioned it will be useful in defining megabowel.

h) The defaecating balloon proctogram has already been used by several other workers to study disorders of defaecation. Its use could be as a screening test in outpatients to find if constipated patients have a disorder of defaecation. It might also have a use in the assessment of patients with descending perineum syndrome, rectocoele and, as demonstrated, in faecal incontinence.

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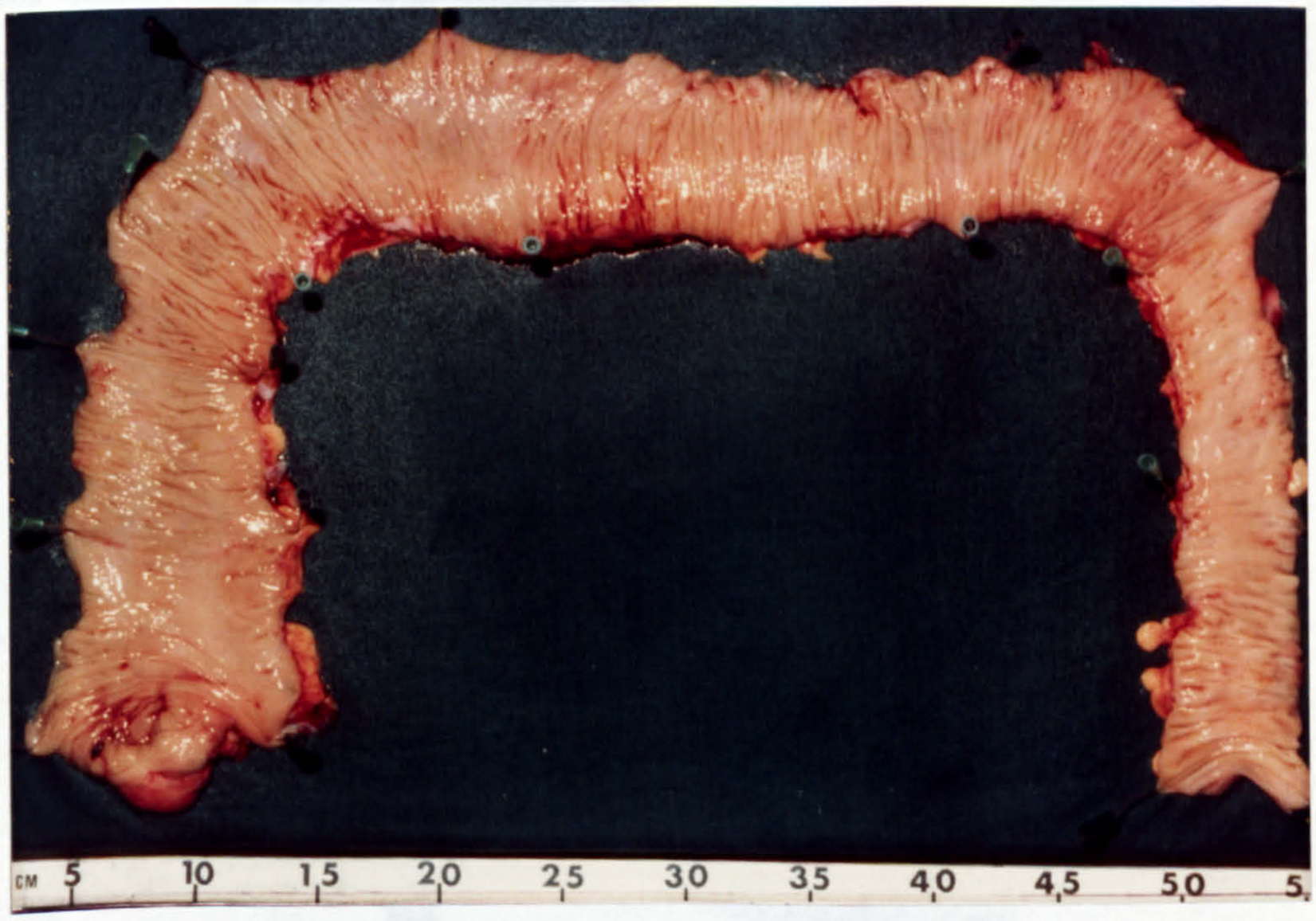
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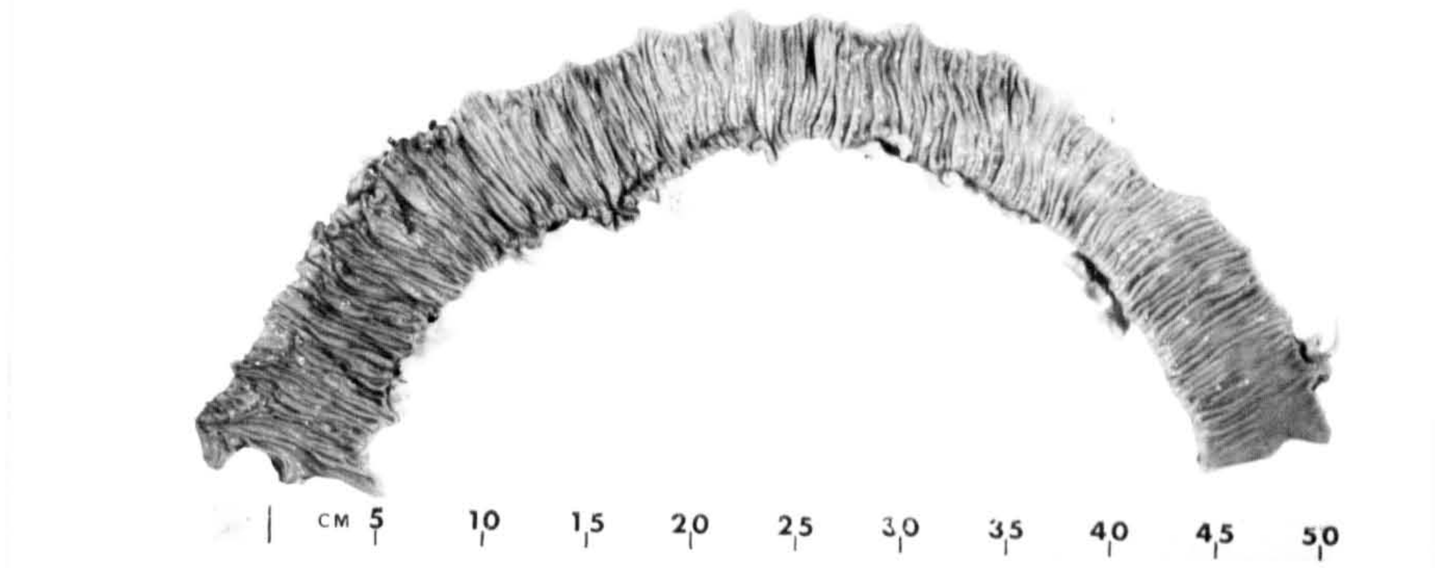
APPENDIX 1

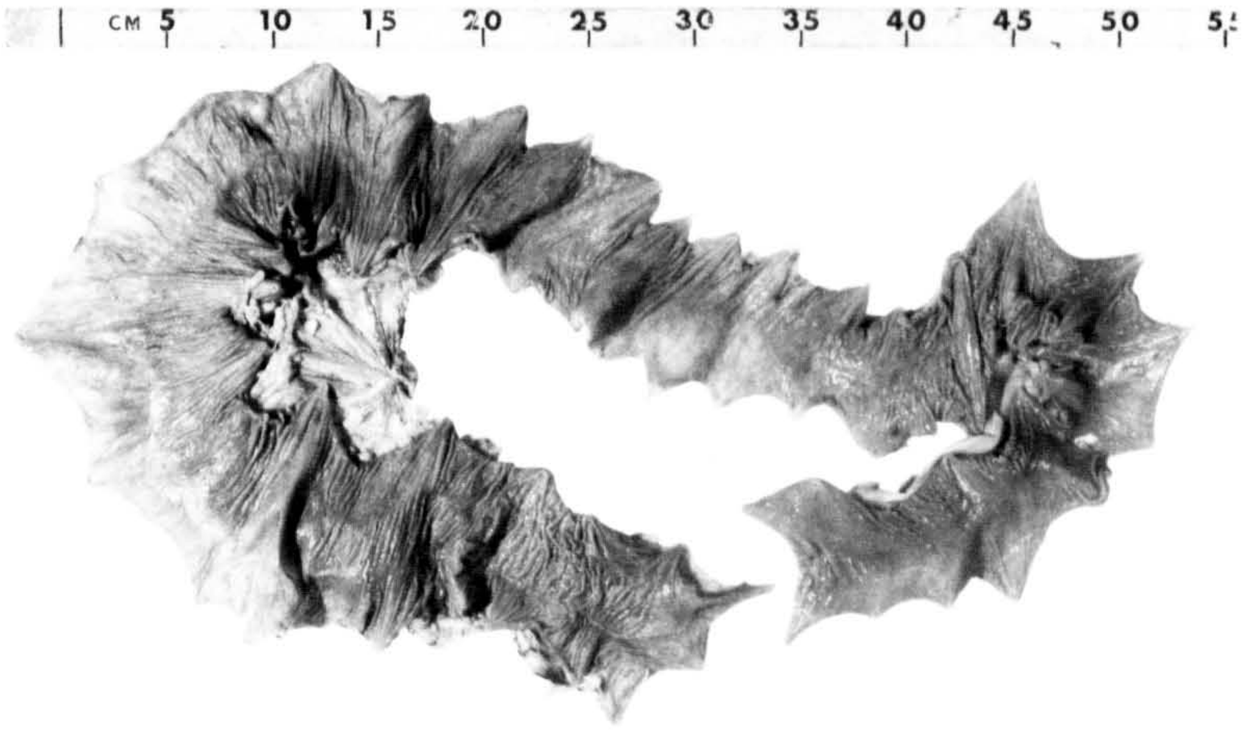
RESECTED COLONS

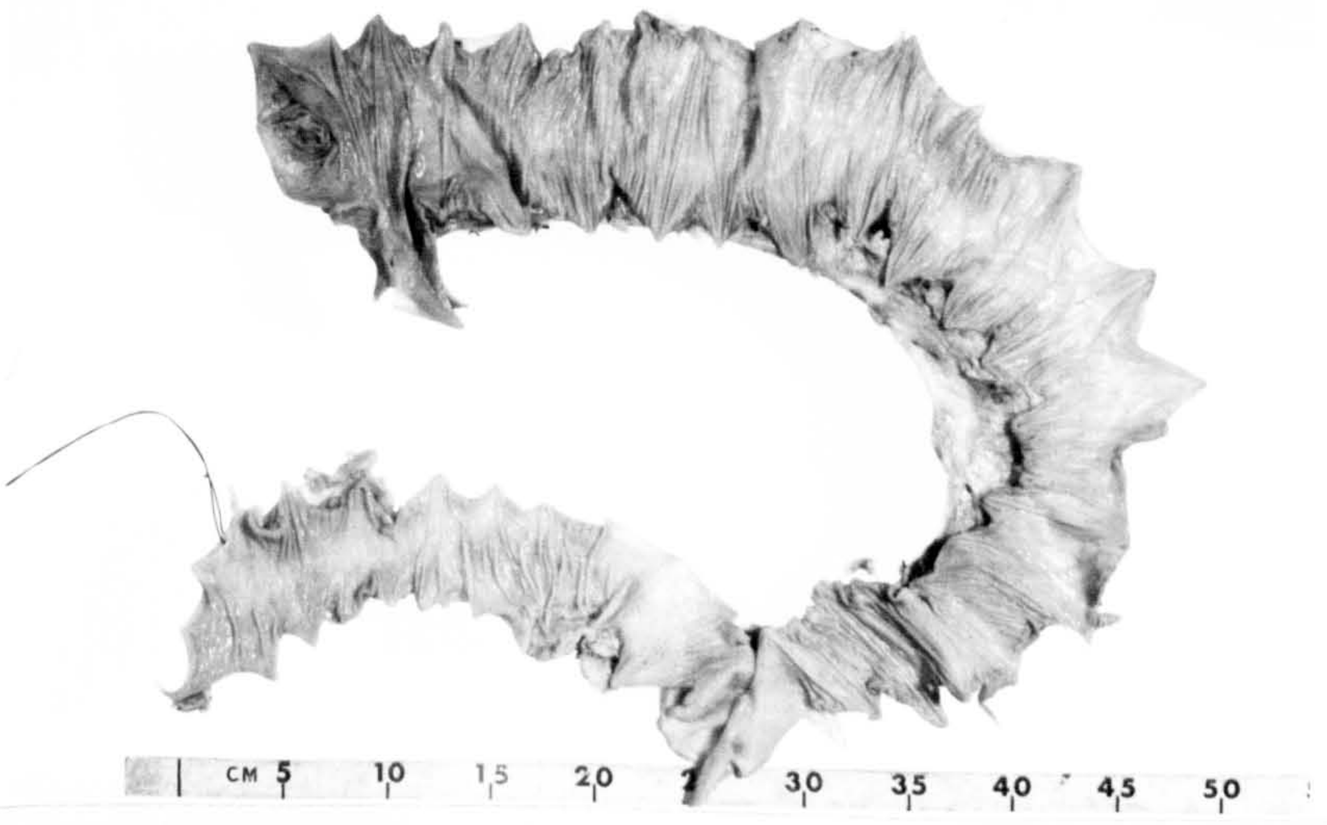
The routine practice of the pathology department at St Mark's Hospital is to open all specimens whilst fresh, to pin them out, and then fix in formalin. Apart from the first example below (also illustrated in Chapter 9) which was photographed in colour when fresh, all have been photographed after fixation. Five of the colons (Nos 1-5) had a 1 cm strip of tissue along their whole length removed before fixing for histochemical studies and are therefore slightly narrowed.

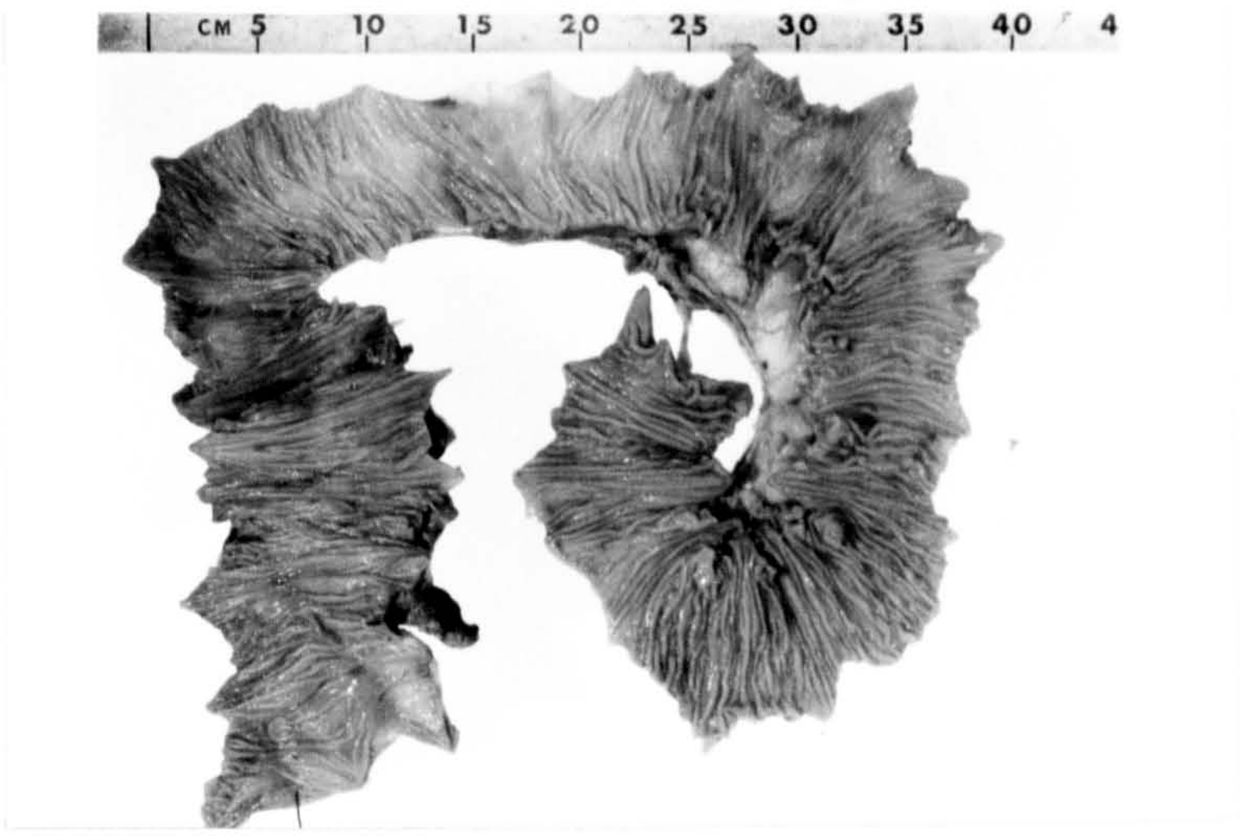


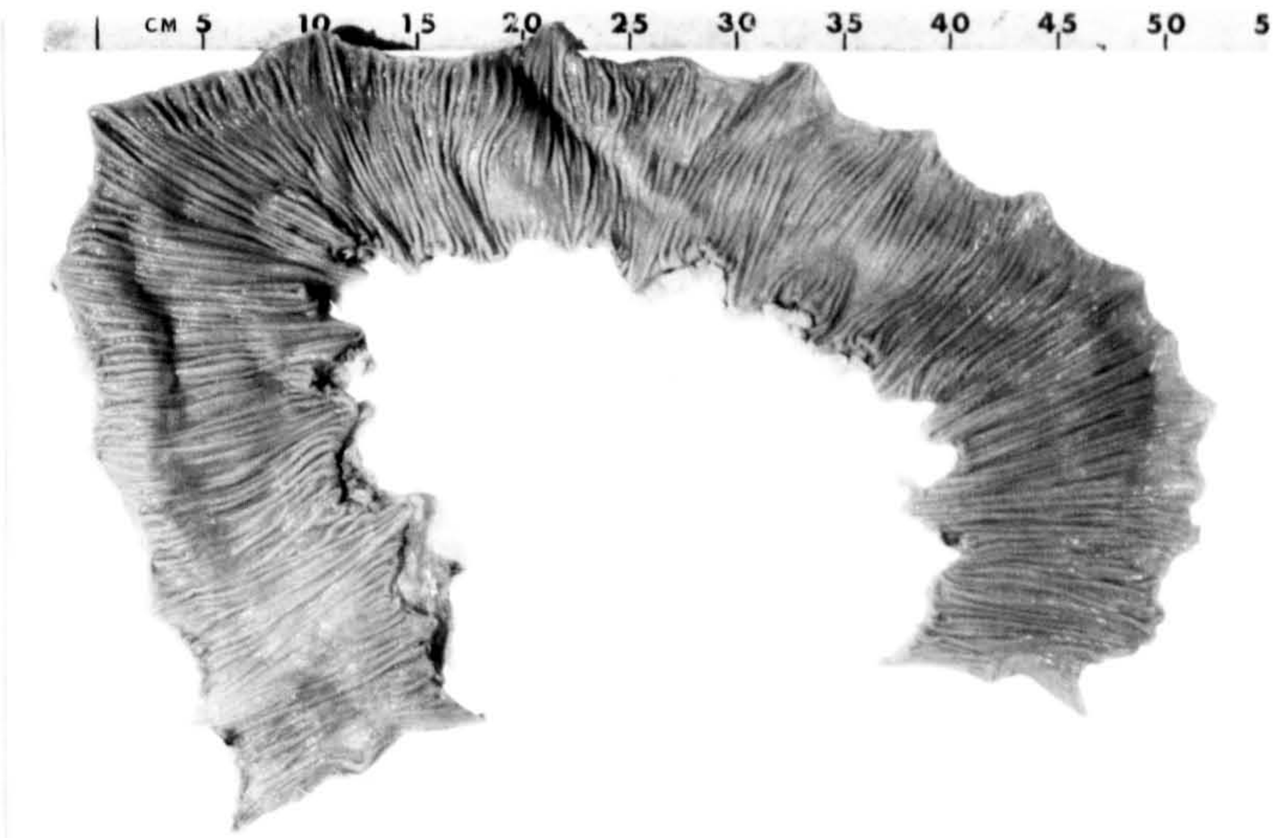


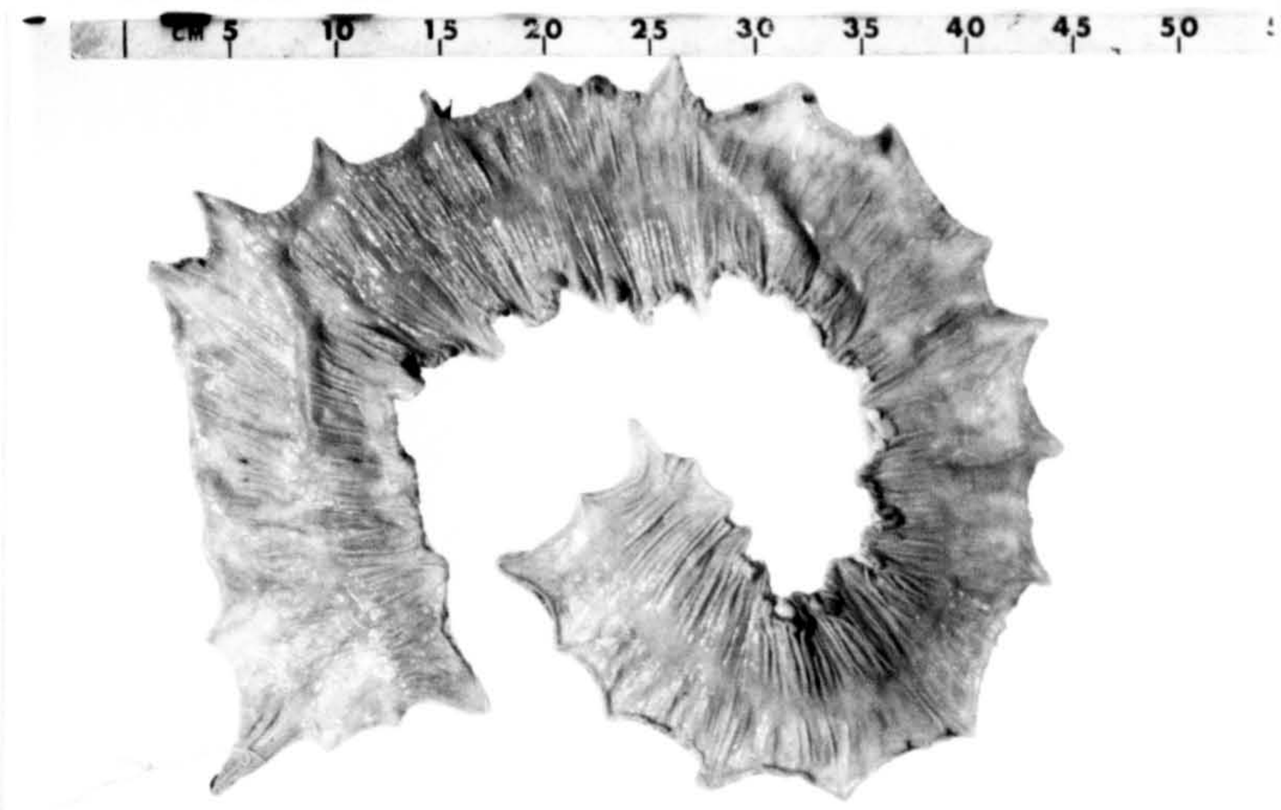

CM 5 10 15 20 25 30 35 40 45 50


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CM 5 10 15 20 25 30 35 40 45 50

APPENDIX 2

SILVER STAINING METHOD

1) Tissue fixed flat in unbuffered formal saline for 7 days.

2) Sample approximately 2 x 2 cm cut from colon.

3) Tissue sample placed mucosal surface down on stage of freezing dissecting microtome and set to cut at 50u. Tissue cut away until junction of longitudinal and circular muscle is visible. Sections with largest area of junction selected.

4) Fixed in Cajal's formol ammonium bromide for 24 hours.

5) Rinsed in 2 changes of distilled water and transfered to 50% alcohol with 10% pyridine for 1 hour at 37°C.

6) Rinsed again in 2 changes of distilled water and transfered to 20% silver nitrate solution (fresh) at 37°C for 25-45 minutes.

7) Rinsed through 3 changes of 10% formol (containing 2.7 mmol/L of calcium salts).

8) Rinsed in 2% formol for 30 seconds.

9) Rinsed with 2 changes of distilled water.

10) Placed in ammoniacal silver solution for 25-45 seconds and agitated. (Solution made by adding ammonium hydroxide to 20% silver nitrate and agitating until the first formed precipitate has dissolved)

11) Rinsed in 3 changes of 1% formol with constant agitation.

12) Section collected in distilled water.

13) Washed in sodium thiosulphate for 5 minutes.

14) Washed in distilled water, then dried and mounted.

APPENDIX 3

TISSUE PEPTIDE BIOPSY STUDY

Rectal biopsies were taken through a sigmoidoscope using rounded forceps (Officer type with smaller cups) from patients attending outpatients with different types of severe constipation. Control tissue was taken from subjects attending for colonoscopic removal of polyps. The tissue was then handled according to the following protocol:

1) Empty poypropylene boiling tube weighed.

2) Tube placed in boiling water bath.

3) 1 ml of 0.5 M acetic acid added.

4) Excess liquid removed from tissue sample by blotting and sample then weighed.

5) Sample added to boiling acetic acid at 100°C for 10 min.

6) Tube capped and reweighed.

7) Tube frozen in liquid nitrogen until assay.

At the conclusion of the study the samples were transferred to the Hammersmith Hospital for assay. The tubes

were then thawed and peptide levels assayed.

The results showed no significant differences between the groups and a wide variation in tissue levels. In addition there was no correlation between these results and the microscopic examination of paired biopsies examined using histochemical techniques. Furthermore it was realised that the values were different from those obtained in the laboratory using fresh tissue. Eventually the fault was traced to the methods used for disrupting tissue samples ultrasonically before assay. The results of this pilot study were therefore useless, but it did enable a fault in the methodology to be recognised which will be of help in future work.

RESULTS (All values in pMol/L extracted fluid)

	EG	SubP	SOM	VIP
Controls				
	306	10.2	85	95
	405	11.2	100	327
	217	5.2	111	120
	835	10.4	179	268
	70	0.2	25	95
	550	6.8	66	130
	523	9.3	128	174
	280	14.6	48	425
Slow transit constipation				
	810	14.2	342	258
	284	14.6	91	216
	297	8.7	77	151
	161	4.4	67	88
	283	7.4	86	142
	156	10.1	104	143
	188	18.9	131	159
	182	4.6	69	99
Irritable bowel syndrome / constipation				
	335	8.1	70	198
	188	11.7	96	179
	293	10.3	63	185
	266	11.0	47	116
	370	15.6	111	189
	876	11.0	123	664
	316	15.5	-	217
	239	4.9	375	177
	86	5.3	26	87

EG = Enteroglucagon
SubP = Substance P
SOM = Somatostatin
VIP = Vasoactive intestinal polypeptide

APPENDIX 4

ANTISERA FOR HISTOCHEMICAL STUDIES

The following table gives the various antisera used for indirect immunofluorescence with the optimal dilutions for maximum absorption.

Peptide antiserum raised against	Optimal dilution	Region specificity	Peptide concentration for absorption (nmol/ml diluted antiserum)
VIP	1:2000	C-terminal	0.1
Substance P	1:2000	C-terminal	10
Enteroglucagon	1:1000	C-terminal	10
Somtostatin	1:400	Mid-portion	10
Bombesin	1:200	C-terminal	10
Met-enkephalin	1:400	C-terminal	10
Neurotensin	1:400	C-terminal	0.1

APPENDIX 5

NALOXONE STUDY

Introduction

Initial studies on the group of patients with slow transit constipation had shown that many had raised prolactins. One possible explanation for this was that there were raised levels of circulating endogenous opiates. As well as hormonal changes opiates could have been contributing to the symptoms by increasing colonic segmenting activity or by affecting the action of the anal sphincters. If this were the case it should have been possible to block the effects of these opiates with Naloxone.

Study design

Five patients with slow transit constipation who had persistent hyperprolactinaemia were studied. After an overnight fast and without bowel preparation colonic pressure recorders as desribed in Chapter 8 were introduced into the rectum amd sigmoid colon. Two intravenous cannulae were then inserted, one for infusion and the other for blood sampling.

At 9.00 am an infusion (active or placebo) was started and the patient given a test meal of toast, eggs, marmalade, orange juice and coffee (530 Kcal). At 1.00 pm an identical meal was given and the infusion changed. The infusions were either:

a) Naloxone 4 mg. as a bolus followed by 2.8 mg/Hour in normal saline.

or

b) Equivolume normal saline as bolus and infusion.

Continuous recordings were made of colonic pressures and blood samples were taken at 15 minute intervals for lutenising hormone (LH) and follicle stimulating hormone levels. It was hoped that the inhibition of LH release by the supposed high level of circulating opiates would be abolished by naloxone and that an immediate increase in circulating LH would follow. This has previously been demonstrated in patients with hyperprolactinaemia from other causes.

RESULTS

The two figures demonstrate the failure of this study. In figure a the rise in LH is shown to be in the normal range when compared to data obtained in patients with prolactin secreting tumours. (Other data courtesy of Dr A. Grossman, St Bartholomew's Hospital). When the motility indices for each 4 hour period including the response to each meal were compared there was no significant difference (figure b). These results concur with the finding that circulating endogenous opiate levels in these patients were in fact normal (see Chapter 12). A motility index as described in Chapter 8 was used to assess colonic activity for the two parts of the study.

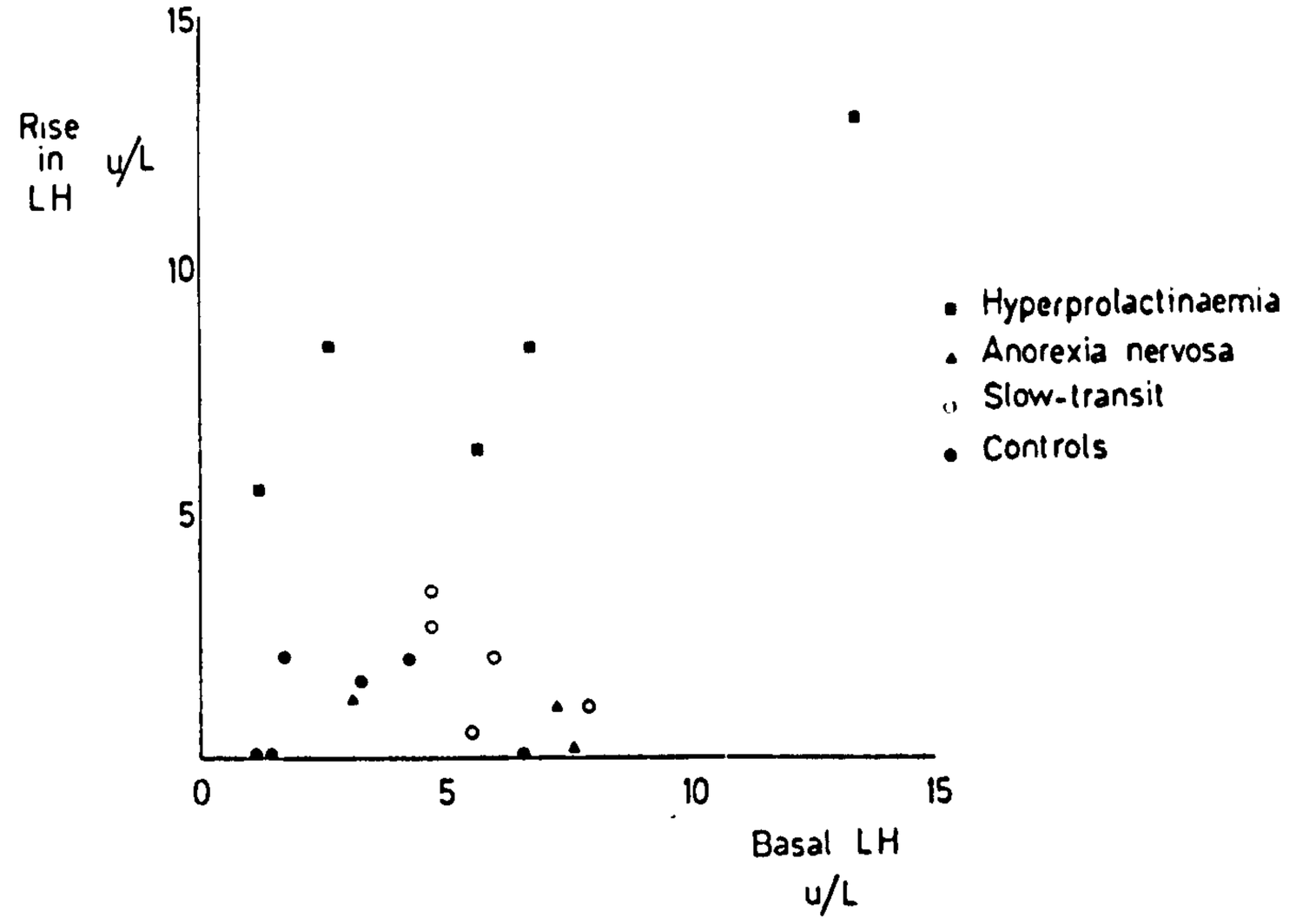


FIGURE a. LH RISE AFTER NALOXONE.
This figure plots basal LH level against the rise following the bolus and infusion of naloxone. The values for slow transit constipation were very small and correspond to those of control subjects.

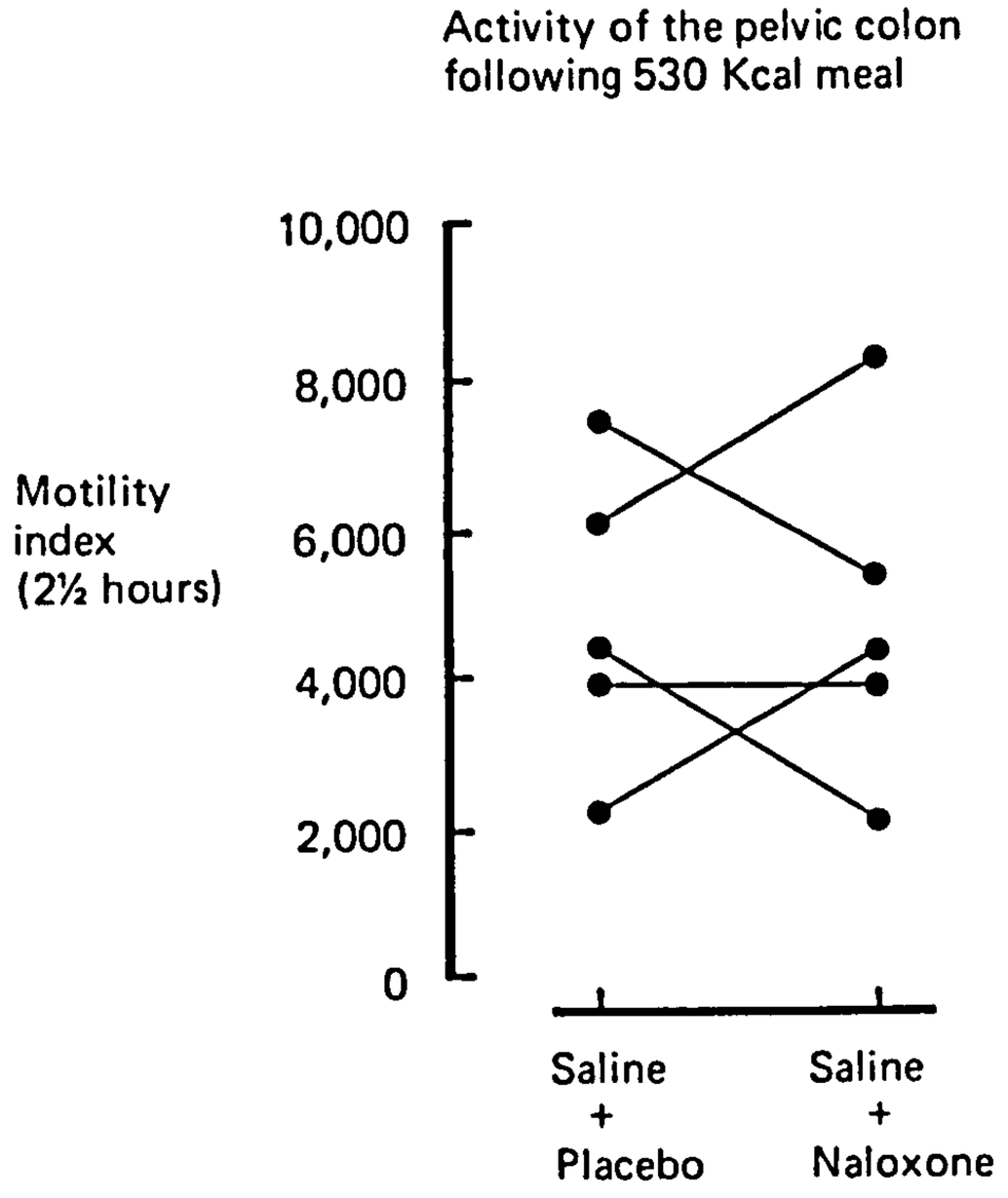


FIGURE b. COLONIC MOTILITY BEFORE AND AFTER NALOXONE.
The activity of the pelvic colon for 2 1/2 hours after each meal is given as a motility index. Two patients had slightly increased and two reduced activity with naloxone. There was therefore no difference between the infusions.

APPENDIX 6

PSYCHIATRIC QUESTIONNAIRES

Copies of the 4 questionnaires answered by 20 patients as part of the psychiatric study (Chapter 13) are given below.

CROWN-CRISP EXPERIENTIAL INDEX

1. Do you often feel upset for no obvious reason? *Yes*..... *No*..... .....
2. Do you have an unreasonable fear of being in enclosed spaces such as shops, lifts, etc? *Often*..... *Sometimes*..... *Never*..... .....
3. Do people ever say you are too conscientious? *No*..... *Yes*..... .....
4. Are you troubled by dizzyness or shortness of breath? *Never*..... *Often*..... *Sometimes*..... .....
5. Can you think as quickly as you used to? *Yes*..... *No*..... .....
6. Are your opinions easily influenced? *Yes*..... *No*..... .....
7. Have you felt as though you might faint? *Frequently*..... *Occasionally*..... *Never*..... .....
8. Do you find yourself worrying about getting some incurable illness? *Never*..... *Sometimes*..... *Often*..... .....
9. Do you think that 'cleanliness is next to godliness'? *No*..... *Yes*..... .....
10. Do you often feel sick or have indigestion? *Yes*..... *No*..... .....
11. Do you feel that life is too much effort? *At times*..... *Often*..... *Never*..... .....
12. Have you, at any time in your life, enjoyed acting? *Yes*..... *No*..... .....
13. Do you feel uneasy and restless? *Frequently*..... *Sometimes*..... *Never*..... .....
14. Do you feel more relaxed indoors? *Definitely*..... *Sometimes*..... *Not particularly*..... .....
15. Do you find that silly or unreasonable thoughts keep recurring in your mind? *Frequently*..... *Sometimes*..... *Never*..... .....
16. Do you sometimes feel tingling or pricking sensations in your body, arms or legs? *Rarely*..... *Frequently*..... *Never*..... .....
17. Do you regret much of your past behaviour? *Yes*..... *No*..... .....
18. Are you normally an excessively emotional person? *Yes*..... *No*..... .....
19. Do you sometimes feel really panicky? *No*..... *Yes*..... .....
20. Do you feel uneasy travelling on buses or the Underground even if they are not crowded? *Very*..... *A little*..... *Not at all*..... .....
21. Are you happiest when you are working? *Yes*..... *No*..... .....
22. Has your appetite got less recently? *No*..... *Yes*..... .....
23. Do you wake unusually early in the morning? *Yes*..... *No*..... .....
24. Do you enjoy being the centre of attention? *No*..... *Yes*..... .....

25. Would you say you were a worrying person?
Very..... Fairly..... Not at all..... .....

26. Do you dislike going out alone? *Yes..... No.....* .....

27. Are you a perfectionist? *No..... Yes.....* .....

28. Do you feel unduly tired and exhausted?
Often..... Sometimes..... Never..... .....

29. Do you experience long periods of sadness?
Never..... Often..... Sometimes..... .....

30. Do you find that you take advantage of circumstances for your own ends?
Never..... Sometimes..... Often..... .....

31. Do you often feel 'strung-up' inside? *Yes..... No.....* .....

32. Do you worry unduly when relatives are late coming home?
No..... Yes..... .....

33. Do you have to check things you do to an unnecessary extent?
Yes..... No..... .....

34. Can you get off to sleep alright at the moment? *No..... Yes.....* .....

35. Do you have to make a special effort to face up to a crisis or difficulty?
Very much so..... Sometimes..... Not more than anyone else..... .....

36. Do you often spend a lot of money on clothes? *Yes..... No.....* .....

37. Have you ever had the feeling you were 'going to pieces'? *Yes..... No.....* .....

38. Are you scared of heights? *Very..... Fairly..... Not at all.....* .....

39. Does it irritate you if your normal routine is disturbed?
Greatly..... A little..... Not at all..... .....

40. Do you often suffer from excessive sweating or fluttering of the heart?
No..... Yes..... .....

41. Do you find yourself needing to cry?
Frequently..... Sometimes..... Never..... .....

42. Do you enjoy dramatic situations? *Yes..... No.....* .....

43. Do you have bad dreams which upset you when you wake up?
Never..... Sometimes..... Frequently..... .....

44. Do you feel panicky in crowds? *Always..... Sometimes..... Never.....* .....

45. Do you find yourself worrying unreasonably about things that do not really matter? *Never..... Frequently..... Sometimes.....* .....

46. Has your sexual interest altered? *Less..... The same or greater.....* .....

47. Have you lost your ability to feel sympathy for other people?
No..... Yes..... .....

48. Do you sometimes find yourself posing or pretending? *Yes..... No.....* .....

PLEASE CHECK THAT YOU HAVE ANSWERED ALL THE QUESTIONS

HOSTILITY AND DIRECTION OF HOSTILITY QUESTIONNAIRE

1 ☐

Remember to answer each statement.

1. Most people make friends because friends are likely to be useful to them .	True	False
2. I do not blame a person for taking advantage of someone who lays himself open to it	True	False
3. I usually expect to succeed in things I do	True	False
4. I have no enemies who really wish to harm me	True	False
5. I wish I could get over worrying about things I have said that may have injured other people's feelings	True	False
6. I think nearly anyone would tell a lie to keep out of trouble . . .	True	False
7. I don't blame anyone for trying to grab everything he can get in this world	True	False
8. My hardest battles are with myself	True	False
9. I know who, apart from myself, is responsible for most of my troubles .	True	False
10. Some people are so bossy that I feel like doing the opposite of what they request, even though I know they are right	True	False
11. Some of my family have habits that bother and annoy me very much . .	True	False
12. I believe my sins are unpardonable	True	False
13. I have very few quarrels with members of my family	True	False
14. I have often lost out on things because I couldn't make up my mind soon enough	True	False
15. I can easily make other people afraid of me, and sometimes do for the fun of it	True	False
16. I believe I am a condemned person	True	False
17. In school I was sometimes sent to the principal for misbehaving . .	True	False
18. I have at times stood in the way of people who were trying to do something, not because it amounted to much but because of the principle of the thing	True	False
19. Most people are honest chiefly through fear of being caught . . .	True	False
20. Sometimes I enjoy hurting persons I love	True	False
21. I have not lived the right kind of life	True	False
22. Sometimes I feel as if I must injure either myself or someone else . .	True	False
23. I seem to be about as capable and clever as most others around me . .	True	False
24. I sometimes tease animals	True	False

2 ☐

25. I get angry sometimes . . . . . True False

26. I am entirely self-confident . . . . . True False

27. Often I can't understand why I have been so cross and grouchy . . . True False

28. I shrink from facing a crisis or difficulty . . . . . True False

29. I think most people would lie to get ahead . . . . . True False

30. I have sometimes felt that difficulties were piling up so high that I could not overcome them . . . . . True False

31. If people had not had it in for me I would have been much more successful True False

32. I have often found people jealous of my good ideas, just because they had not thought of them first . . . . . True False

33. Much of the time I feel as if I have done something wrong or evil . . True False

34. I have several times given up doing a thing because I thought too little of my ability . . . . . True False

35. Someone has it in for me . . . . . True False

36. When someone does me a wrong I feel I should pay him back if I can, just for the principle of the thing . . . . . True False

37. I am sure I get a raw deal from life. . . . . True False

38. I believe I am being followed . . . . . True False

39. At times I have a strong urge to do something harmful or shocking . . True False

40. I am easily downed in an argument. . . . . True False

41. It is safer to trust nobody . . . . . True False

42. I easily become impatient with people . . . . . True False

43. At times I think I am no good at all . . . . . True False

44. I commonly wonder what hidden reason another person may have for doing something nice for me . . . . . True False

45. I get angry easily and then get over it soon . . . . . True False

46. At times I feel like smashing things. . . . . True False

47. I believe I am being plotted against. . . . . True False

48. I certainly feel useless at times . . . . . True False

49. At times I feel like picking a fist fight with someone . . . . . True False

50. Someone has been trying to rob me . . . . . True False

51. I am certainly lacking in self-confidence . . . . . True False

Please check to see that you have given answers for every statement.

2

GENERAL HEALTH QUESTIONNAIRE

Please read this carefully:

We should like to know if you have had any medical complaints, and how your health has been in general, *over the past few weeks*. Please answer ALL the questions on the following pages simply by underlining the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those that you had in the past.

It is important that you try to answer ALL the questions.

Thank you very much for your co-operation.

HAVE YOU RECENTLY:–

1.	–	been able to concentrate on whatever you're doing?	Better than usual	Same as usual	Less than usual	Much less than usual
2.	–	lost much sleep over worry?	Not at all	No more than usual	Rather more than usual	Much more than usual
3.	–	felt that you are playing a useful part in things?	More so than usual	Same as usual	Less useful than usual	Much less useful
4.	–	felt capable of making decisions about things?	More so than usual	Same as usual	Less useful than usual	Much less useful
5.	–	felt constantly under strain?	Not at all	No more than usual	Rather more than usual	Much more than usual
6.	–	felt that you couldn't overcome your difficulties?	Not at all	No more than usual	Rather more than usual	Much more than usual
7.	–	been able to enjoy your normal day-to-day activities?	More so than usual	Same as usual	Less so than usual	Much less than usual
8.	–	been able to face up to your problems?	More so than usual	Same as usual	Less able than usual	Much less able
9.	–	been feeling unhappy and depressed?	Not at all	No more than usual	Rather more than usual	Much more than usual
10.	–	been losing confidence in yourself?	Not at all	No more than usual	Rather more than usual	Much more than usual
11.	–	been thinking of yourself as a worthless person?	Not at all	No more than usual	Rather more than usual	Much more than usual
12.	–	been feeling reasonably happy, all things considered?	More so than usual	About same as usual	Less so than usual	Much less than usual
13.	–	been managing to keep yourself busy and occupied?	More so than usual	Same as usual	Rather less than usual	Much less than usual
14.	–	been getting out of the house as much as usual?	More so than usual	Same as usual	Less than usual	Much less than usual
15.	–	been feeling on the whole you were doing things well?	Better than usual	About the same	Less well than usual	Much less well

Please turn over

16.	–	been satisfied with the way you've carried out your task?	Better than usual	About as usual	Less well than usual	Much less well
17.	–	been taking things hard?	Not at all	No more than usual	Rather more than usual	Much more than usual
18.	–	found everything getting on top of you?	Not at all	No more than usual	Rather more than usual	Much more than usual
19.	–	been feeling nervous and strung-up all the time?	Not at all	No more than usual	Rather more than usual	Much more than usual
20.	–	found at times you couldn't do anything because your nerves were too bad?	Not at all	No more than usual	Rather more than usual	Much more than usual
21.	–	been having restless, disturbed nights?	Not at all	No more than usual	Rather more than usual	Much more than usual
22.	–	been managing as well as most people would in your shoes?	More so than usual	Same as usual	Rather less than usual	Much less than usual
23.	–	been able to feel warmth and affection for those near to you?	Better than usual	About same as usual	Less well than usual	Much less well
24.	–	been finding it easy to get on with other people?	Better than usual	About same as usual	Less well than usual	Much less well
25.	–	spent much time chatting with people?	Not at all	No more than usual	Rather more than usual	Much more than usual
26.	–	been finding life a struggle all the time?	Not at all	No more than usual	Rather more than usual	Much more than usual
27.	–	been getting scared or panicky for no good reason?	Not at all	No more than usual	Rather more than usual	Much more than usual
28.	–	felt that life is entirely hopeless?	Not at all	No more than usual	Rather more than usual	Much more than usual
29.	–	been feeling hopeful about your own future?	More so than usual	About same as usual	Less so than usual	Much less hopeful
30.	–	felt that life isn't worth living?	Not at all	No more than usual	Rather more than usual	Much more than usual

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Patient..... Case No..... Date.....

Please mark your answers with an X on each of the scales below.

W O R K

BECAUSE OF MY CONSTIPATION MY WORK IS IMPAIRED:

0	1	2	3	4	5	6	7	8
not at all		slightly		definitely		markedly		very severely I cannot work

---

HOME MANAGEMENT (cleaning, tidying, shopping, cooking, looking after children, paying bills.)

BECAUSE OF MY CONSTIPATION MY HOME MANAGEMENT IS IMPAIRED:

0	1	2	3	4	5	6	7	8
not at all		slightly		definitely		markedly		very severely I cannot cope

---

SOCIAL LEISURE ACTIVITIES (with other people, e.g. parties, pubs, clubs, outings, visits, dating, home entertainment.)

BECAUSE OF MY CONSTIPATION MY SOCIAL LEISURE IS IMPAIRED:

0	1	2	3	4	5	6	7	8
not at all		slightly		definitely		markedly		very severely I never do these

---

PRIVATE LEISURE ACTIVITIES (done alone, e.g. reading, gardening, collecting, sewing, walking the dog)

BECAUSE OF MY CONSTIPATION MY PRIVATE LEISURE IS IMPAIRED:

0	1	2	3	4	5	6	7	8
not at all		slightly		definitely		markedly		very severely I never do these

APPENDIX 7

PROSTAGLANDIN E2 STUDY

Introduction

Constipation had previously been reported to be associated with an increase in colonic segmenting activity. Colonic activity has also been shown to be reduced by the intravenous administration of prostaglandin E2. Originally this study was designed to investigate patients with slow transit constipation, but when it was discovered that they had reduced colonic activity only patients with the irritable bowel syndrome were studied.

Patients and methods

Nine patients were studied (8F,1M). All gave a long history of abdominal pain and constipation, but had a normal gut transit time estimated using polythene pellets. Following an overnight fast, 3 pressure recording balloons were placed in the rectum and sigmoid colon as described in Chapter 8. In 6 patients a slow infusion of normal saline (1 ml/minute) was started so that the fluid entered the bowel at 26 cm from the anus. Recordings of colonic pressure were made for 30 minutes and then a second infusion of saline containing PGE2 begun for a further 30 minutes. The concentration of PGE2 was adjusted so that the drug was introduced at rate of 1µg/Kg/Minute.

In 3 subjects, following the successful infusions PGE2 was introduced as a single dose of 1 mg in a witepsol

suppository after a suitable control period. A motility index as described previously (Chapter 8) was then calculated for the 30 minutes before and after drug administration.

Results

The motility index for 30 minutes fell after drug administration from 13,173 ± 3,136 (sem) to 1,669 ± 304 ($p<0.01$). In 3 patients all colonic activity was abolished. In 4 patients (two of whom had been given a suppository) the reduction in segmenting activity was associated with relief from abdominal pain. One patient from each group reported spontaneous defaecation at the end of the study. The fall in motility indices is illustrated in Figure c and an example of the complete abolition of pressure wave activity in Figure d.

Further studies were not carried out because of the possible teratogenic effects from long term administration of PGE2. However in view of the good results reported from administration of gamma-linoleic acid in Chapter 14, the possibility of a deficiency of prostaglandins in these patients might be worth investigating.

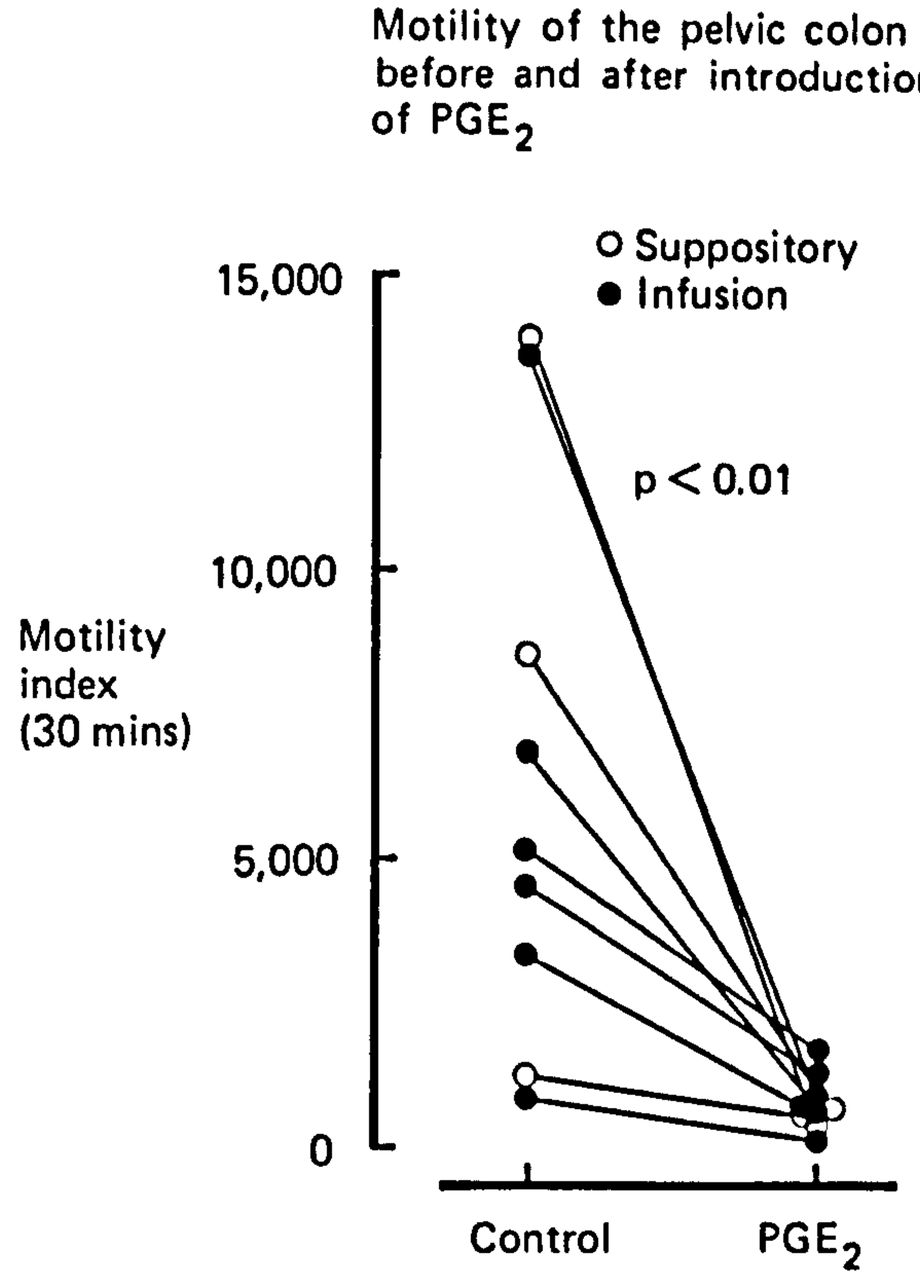


FIGURE c. RESULTS OF PROSTAGLANDIN E2 ADMINISTRATION.
The sum of colonic pressure wave activity before and after PGE2 administration either as suppository or infusion for 9 patients with constipation and the irritable bowel syndrome.

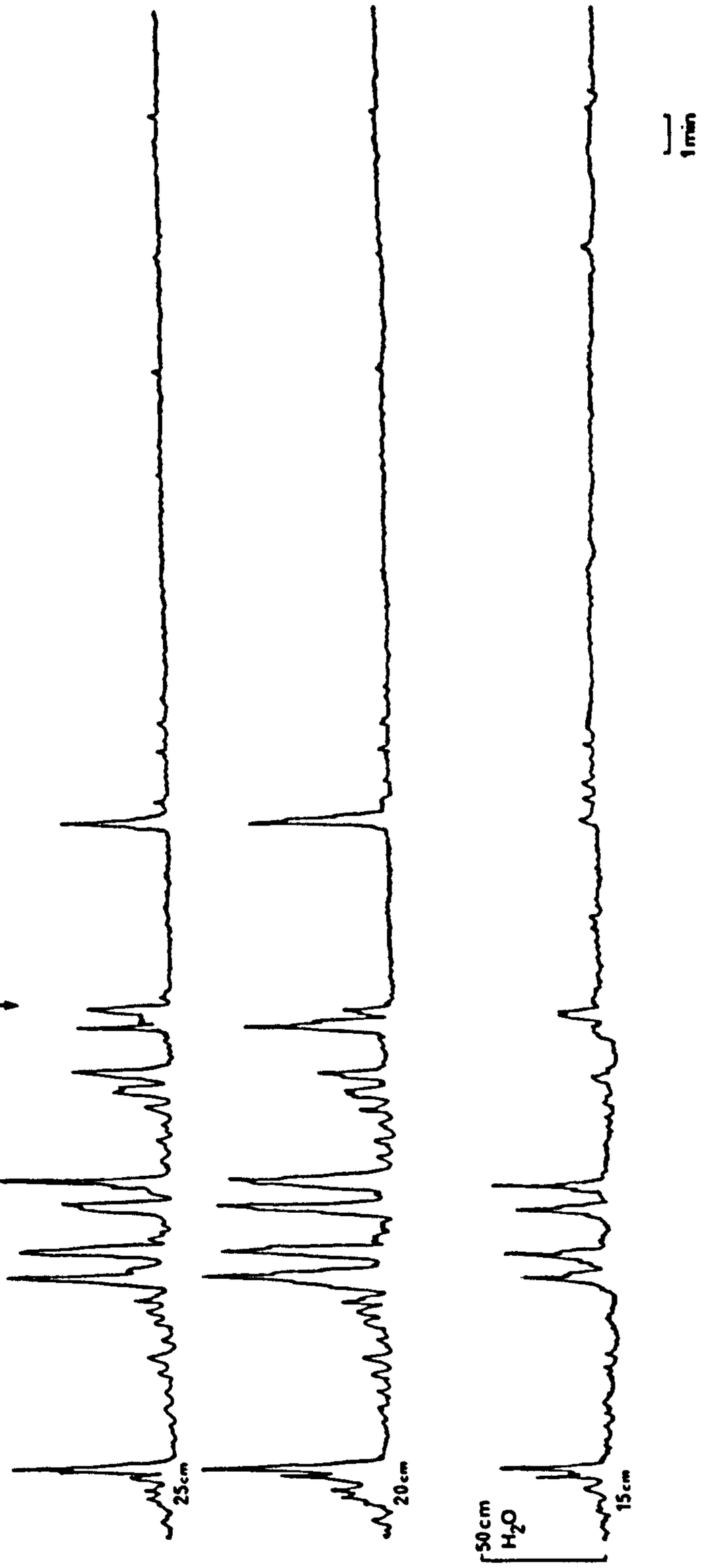


FIGURE d.
Effect of administration of PGE2 by colonic infusion in a 28 year old woman who complained of constipation. All segmenting activity is abolished.