STUDIES ON DIVERTICULAR DISEASE OF THE COLON AND
MOTILITY DISORDERS OF THE ANO-RECTUM

ADAM N SMITH

D.Sc
University of Edinburgh
1994
ABSTRACT

This thesis examines aspects of distal bowel function, principally by the registration of intra-luminal pressure. High fibre diets lowered the pressure in diverticular disease and reproduced the effect of operations. Fibre became a tool to elucidate the diverticular disease defect. Coarse bran was more effective than fine bran, possibly by enhancing faecal bulk, or by the mechanical effect of particle size. This action was also true of coarser wheat, and was found in a rural more than an urban community. Pressure and transit were often inversely related. The reason for the thickened smooth muscle and raised pressure in diverticular disease was sought in release of GI hormones and the smooth muscle stimulating properties of bile acids and prostaglandins. Weakness of the colon wall was reflected in increased compliance. The tensile strength of the colon was reduced with age, but remained high in Africans who have a high fibre intake, but no diverticular disease. The collagen fibril size was changed in the colon wall particularly in the sigmoid colon where the intra-luminal pressure is highest and most of all in diverticular disease. The condition may owe its origin to chronic under-filling of the colon and this may be the means through which fibre reverses the aetiological factors.

Pressure studies were also applied to ano-rectal functional disorders along with newer methodology, such as the measurement of the pudendo-anal reflex. Neural factors were found as aetiological mechanisms in faecal incontinence, severe constipation and radiation damage. The effects of operations for radiation damage were assessed. A stimulator acting by repetitive bombardment of the pudendo-anal reflex was devised to treat faecal incontinence and the improved pressure and proctographic changes produced were recorded. Using anal endosonography it was possible to study the interrelation of the external and internal anal sphincters in faecal incontinence. Brindley stimulators implanted in paraplegics for the control of micturition were used as a model to investigate the neural control of the distal bowel and the pelvic floor. The success of biofeedback treatment of obstructive defecation was assessed by intra-rectal pressure, isotope proctography and EMG changes. Some hysterectomy patients have severe constipation and the motility findings suggest a denervation lesion of the autonomic nervous system in the pelvis. An eight year survey of the work of an ano-rectal unit which had investigated and treated patients with distal bowel problems was examined by audit.
CONTENTS

Statement

Summary of published work - PART 1
Publications
Appendix I

Summary of published work - PART 2
Publications
Appendix II
Appendix III

Acknowledgment
STATEMENT

This is a record of published work on studies undertaken into the pathophysiology of the distal colon and ano-rectum, mainly into their most important motility and surgical disorders. The work was performed in collaboration with several colleagues, many of whom held training awards, grants and fellowships, applied for, managed and brought to conclusion by myself. Many of the research fellows involved were also candidates for Doctoral theses or Masterships and are listed below. These research fellows worked under my direction and their theses are partly the source of many of the papers quoted. The work included here has not been submitted by me in whole or in part for any other degree.

I had the benefit of prolonged collaboration with Dr Martin Eastwood, Consultant Gastroenterologist at the Western General Hospital and Reader in Medicine, University of Edinburgh in the studies on diverticular disease. His main interest lay in the intraluminal action of dietary fibre, while mine came from an interest in the motility of the lower bowel. In often 'combined studies' we undertook work on how fibre alters colonic physiology. My role was to define changes attributable to smooth muscle function such as pressure changes and their effect on the bowel wall. It was hoped that by using fibre as a tool for the investigation of diverticular disease more could be learned about the aetiology and prevention of this condition.

All the papers, other than review articles and selected chapters in books, are from refereed journals. Photocopies replace reprints no longer available and are used with the permission of collaborators. In many instances, I am the 'first' author but where this is not so I had the leadership role in the work presented since it was with a view to enhancing a junior colleague's standing that I took a subsidiary role. I can claim, however, that I was the instigator of the work quoted, obtained the grant support for it and saw it executed and brought to publication: thus was maintained the continuity of the work and the sequence of papers quoted.
The undernoted worked in the Motility and Ano-rectal laboratory for 1 - 3 years. Their grant support and theses awarded are recorded.

1. R P Attisha, Clark Fellowship, University of Edinburgh 1968-70
2. Shirley Clarke, SHRT Grant 291; 1970
3. W O Kirwan, SHRT Grant 418, 'The motor function of the colon', University of Cork. MCh 1975
4. G S Srivastava, Indian Army Award, 1976-77
5. J Diane Falconer, SHR Grant 491, GI Unit Research Fellowship 1976-78
7. H J Thomson, G I Unit Research Fellowship 1986-87
9. N R Binnie, SHRT Grant 720 and Paraplegic Research Foundation Award, 'The effect of spinal cord injury on the motor function of the human colon and the assessment of the influence of implanting radio-frequency stimulating electrodes'. University of Edinburgh, MD 1989

Others who were attached for lesser periods were -

T Balfour, V Giannakos, S Shariff, J Shepherd, G G P Browning, T Taylor, P Hatcher
SUMMARY OF PUBLISHED WORK

The papers, though presented chronologically, fall naturally into two distinct sections. These are summarised as (1) studies on the colon, mainly in regard to diverticular disease; (2) studies of intraluminal pressure and related investigative measures, as applied to ano-rectal disease, principally to faecal incontinence and idiopathic constipation.

PART 1 - Studies on diverticular disease of the colon

Initial studies on raised intraluminal pressure in diverticular disease of the colon showed that it was reduced by myotomy (1) which also relieved pain (2). This underlined the importance of the smooth muscle of the bowel wall in creating symptoms. The pressure reduction was however short-lived (3), though it could be extended by bran (4). A high-fibre intake by adding bran to the diet produced similar reduction of pressure, reduced the transit time with pain relief and thus reproduced the operative effect, virtually abolishing the need for operations in uncomplicated diverticular disease (5). Coarse bran with its greater particle size had greater water-binding capacity, giving rise to a greater faecal mass and more pronounced effects (6). Fibre became a tool to study how it acted and thus what the inherent defect of diverticular disease was. Studies with markers of the solid and liquid phases of the intestinal contents had shown that solids and liquids move at different rates along the intestinal tract (7). An isotope capsule was designed to identify the colonic component of transit (8). It had its specific gravity altered to make it both lighter and heavier in turn than the faecal content. Both alterations speeded up transit. It was suggested that when made heavier the greater mechanical contact with the colon stimulates peristalsis and that this might be how coarse bran exerts its faecal bulking effect. The agent, sternculia containing an antispasmodic, was however more effective than a bulking agent alone, implying another mode of action, possibly the antagonism of a 'spasmogen' (10).

Primary bile acids, and to a lesser degree secondary ones, might occupy a candidate role for this effect if concentrated in the 'dehydrated' firm stools of diverticular disease subjects, because of their ability to stimulate colonic motility in the experimental animal (rabbit) (22) and human (9). The motility effect in the rabbit may involve prostaglandin release (18).
There is a clinical association between diverticular disease of the colon and biliary disease, perhaps extending to abnormal release of GI hormones such as cholecystokinin, gastrin etc. Gastrin effects on the motility of the GI tract had been described (see Appendix I (i)) as had those of 5-hydroxytryptamine and kinins on its pathology (see Appendix I (ii - v)). Gastrin levels rose (11) at the time of a gastrocolic reflex stimulation by food, but there were no differences in diverticular disease subjects (unpublished). Experiments on cholecystokinin and 5-hydroxytryptamine and kinin release or formation were also negative.

The faecal characteristics of the irritable bowel syndrome and diverticular disease suggested a common aetiology (12), though motility studies tend to give them a separate identity. Two groups of diverticular disease were defined, one with high pressure and only slightly prolonged transit. Another had these features reversed (13). Differences in colonic motility of constipation of the young (15) and the elderly (21) were next examined as well as clarifying the efficacy of bran in comparison to other colonic stimulant agents (16). The central position of bran in the management of diverticular disease was restated (14), drawing attention to the physical characteristics, not only to the particle size but also to factors inherent in the fibre origin of the wheat used (24, 25). The relationship of fibre to effects on transit were also reviewed (19) and of the faecal characteristics to dietary changes (20). It was postulated that dietary variation might be a means whereby the asymptomatic case might become the symptomatic one.

Studies on diverticular disease had shown that pressure is not invariably raised (13, 17) and emphasised other factors (26) inherent in the extrusion of the diverticulum, one of which is weakness of the colon wall. The diverticular colon had marked yielding properties, seen as compliance changes present both in vitro and in vivo (23). A method was developed to measure the tensile strength of the colonic wall tissue and showed changes with age and sex of animals (29) and in humans (30). Differences were particularly marked between African and European subjects but there was no difference between diverticular disease subjects and 'normal' Westernised adults (30). Further work on the strength of the colon wall showed changes in the supportive collagen fibril distribution (32), both regionally in the pelvic colon where the intraluminal pressure is thought to be highest and more so in diverticular disease subjects (33).
Field studies in a rural community with a naturally high-fibre intake demonstrated that they had a lower intracolonic pressure and a shorter transit time than an urban one in Turkey (28). In Scotland (27), after a decade of 'exposure' to high fibre diets, there was no reduction in the numbers with diverticular disease seen as hospital patients and again little change at 15 years (34); but there may be factors acting against any quick change such as the widespread use of non-steroidal anti-inflammatory agents which tend to worsen diverticular disease effects (36), thus perhaps boosting hospital admissions. Although lessened fibre intake is said to be a factor in the causation of both cancer of the colon and diverticular disease, a radiological survey showed little evidence of overlap (35) suggesting more important differences in the aetiology than lack of fibre intake. The inter-relationship of intraluminal pressure change and the properties of the colonic wall were again reviewed (31). Watters and Smith (37) finally proposed that chronic under-filling of the colon, corrected by fibre bulk, might reconcile both views and this suggests a role for fibre in both prophylaxis and management (38).
Studies on diverticular disease of the colon


MUSCULAR hypertrophy was first associated with diverticular disease of the colon by Habershon in 1857. The significance of this hypertrophy (Fig. 1) was poorly appreciated till Morson (1963) and Slack (1966) pointed out that a study of surgical specimens of symptomatic diverticular disease showed it to be an almost invariable feature. The colonic diverticula could result from intraluminal pulsion forces developed by the hypertrophied and, presumably, hyperactive musculature. This conjecture was, in turn, substantiated by the manometric studies of Painter and Truelove (1964b), who measured the intraluminal pressures of the colon in the areas containing the diverticula and showed that some commonly used drugs which stimulated the colonic muscle produced not only high intraluminal pressures but also an exaggerated response in the diseased areas. Reduction of the muscular hyperactivity should lead to a lowering of the pulsion forces. The operation of sigmoid colomyotomy (Reilly, 1966) is based on the principle of interruption of the rings of hypertrophied smooth muscle in a manner comparable to Heller's procedure at the cardia or Ramstedt's procedure at the pylorus and, therefore, appears rational. The operative procedure involves incision of the circular muscle through an antimesenteric taenia, extending from the lower descending colon through the sigmoid as far as the peritoneal reflection, and is deepened as far as the submucosa. There is no evidence, to date, that this operation alters the disordered processes which the raised pressures reflect, nor that it induces beneficial changes. The primary objective of this study was, therefore, to determine whether the operation achieved a reduction in intraluminal pressure by comparison of the pre- and postoperative manometric results.

METHODS

Manometric studies were undertaken on three groups: those with diverticular disease, those who had undergone sigmoid myotomy, and normal controls. Selection of the groups was as follows:—

a. Twenty-nine untreated patients with diverticular disease were studied.

b. Fourteen patients were studied from 1 to 6 months after sigmoid myotomy. Nine of these had been studied prior to the operation.

c. Nine volunteers who had no abnormality in bowel habit or any clinical, radiological, or sigmoidoscopic evidence of alimentary disease served as controls.

Miniature balloon-covered, air-filled polythene tubes were connected by Statham Transducers to electromanometers within a photo-recording device. The tubes were inserted via a sigmoidoscope to 25, 20, and 15 cm. from the anal margin. Balloon-covered manometers were used in preference to open-tipped tubes because of fewer technical difficulties and because changes were to be studied in similar segments of bowel, not at specific sites of diverticular formation.

The technique used was standardized as to timing, sequence of events, and personnel present. Bowel preparation was by a mild aperient taken 24 hours previously. Recordings were undertaken only when the distal colon was clear of faeces.

RESULTS

1. Basal Activity.—There was no statistical difference in the basal pressure activity (Table 1) recorded as a motility index between the groups depicted in Fig. 2A. Painter and Truelove's (1964a) observation of no difference in the basal pressure in the colon of normal subjects and those with diverticular disease is, therefore, confirmed by us. Basal pressure was never recorded more than 10 cm. H2O higher than atmospheric, and it altered infrequently
even when contractions were frequent. The number of waves in the basal period was increased in diverticular disease compared with normal controls (Fig. 3A); this was particularly true for waves above 50 cm. H2O pressure (Fig. 4A).

The mean motility index ranged from 42 to 8822 in the diseased group with a mean of 2856 (Table 1). The patients who had a poor motor response (motility indices 42 and 68) were grossly affected by disease and a fibrosed colon was later resected in each case. The natural history of the disease may be changed from muscular hypertrophy and hyperactivity to fibrous degeneration and hypoactivity and the pressures may vary accordingly (Smith, 1969).

Table 1.—Significance of Sigmoid Colon Motility Index Changes

<table>
<thead>
<tr>
<th></th>
<th>Normals</th>
<th>Diverticular Disease</th>
<th>After Sigmoid Myotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal activity</td>
<td>151</td>
<td>143</td>
<td>110</td>
</tr>
<tr>
<td>Gastrocolic reflex</td>
<td>263</td>
<td>Significantly higher than normals (P &lt; 0.001)</td>
<td>240</td>
</tr>
<tr>
<td>After prostigmine</td>
<td>791</td>
<td>Significantly higher than normals (P &lt; 0.001)</td>
<td>2856</td>
</tr>
</tbody>
</table>

2. Responses to Food and Drug Stimuli.

a. Gastrocolic Reflex.—There was an invariable increase in the motor activity of the bowel with the ingestion of a meal (Fig. 2B). Patients with diverticular disease responded more than controls, the response of the sigmoid colon being three times greater than in the control group (Table 1). The amplitude was affected more than the frequency for this mode of stimulation. Abnormally high pressures have been found by others to develop in the colon in diverticular disease, under similar normal influences (Arfwidsson and Kock, 1964).

b. Prostigmine.—This parasympathomimetic agent has been shown to be effective in stimulating the colon (Painter and Truelove, 1964b). Both the amplitude (Fig. 4C) and frequency were increased by prostigmine, so that the motility index rose (Fig. 2C) both for normals and those with diverticular disease.

3. Effects of Sigmoid Myotomy.—In myotomy subjects the gastrocolic response to food reached values (Table 1) half those of the untreated diverticular group (Fig. 2B). A statistically significant difference was recorded between myotomy subjects provoked by prostigmine and diverticular ones (Table 1). Basal activity was not different after myotomy from normal controls. The change from basal activity in the myotomy subjects to that induced by prostigmine was considerable, though nearer normal after myotomy than the dramatic rise in untreated diverticular disease (Fig. 5). The myotomy effects were observed in 9 subjects with diverticular disease before and after operation. The mean fall in the motility index was of the order of 2000. Fig. 6 shows that 8 cases contributed to this fall, but that 1 case had a rise in the motility index when examined at 3 months. It appeared that there had been healing.
with narrowing of the lumen at sigmoid level. The myotomy incision was adequately performed at the rectal level because there was a fall of 920 in the motility index at this site. Comparison of the recto-sigmoid results with the sigmoid ones in Figs. 2 B, C shows that there is usually a smaller reduction in motor activity after myotomy at the lower rectal level than at the higher sigmoid one.

4. Analysis of Wave Amplitude.—Examination of the wave amplitudes reflected the motility index trend. Waves above 20 cm. H_2O increased after food and prostigmine (Fig. 3 B, C) and there was an increase in waves above 50 cm. occasionally after food, but mainly after prostigmine (Fig. 4) when, in certain individuals with diverticular disease, waves of 150 cm. H_2O were recorded. After myotomy there was a marked decrease in the number of waves exceeding 50 cm. H_2O in the test period. Nevertheless, intraluminal pressures could still frequently exceed this level, especially after prostigmine (Fig. 4 C).

61 also at this time by the anaesthetist. In this study atropine (0.4-0.6 mg.) was given to subjects already under the influence of prostigmine. In the untreated diverticular disease group the motility index fell in those subjects given atropine from a mean of 2852 to 1400. In subjects already myotomized the fall was from 1260 to 200. In both groups the basal pressure remained unchanged. Propantheline bromide even in small doses (3.5 mg.) virtually abolished all prostigmine effects in the diverticular disease group, before and after operation. There was, however, no alteration in the basal pressure.

DISCUSSION
The raised intraluminal pressures in the distal colon in diverticular disease might arise either from

5. Influence of Certain Therapeutic Agents.—The pressure increase by prostigmine might cause harm to the incised bowel when this agent is given at the end of operations to reverse the action of curare-like drugs (Bell and Lewis, 1968). Atropine is given
hypertrophied smooth muscle or from its excessive activity. Like Painter and Truelove (1964a), we have found exaggerated responses on natural or artificial stimulation of colonic activity, but this is unaccompanied by changes in the basal pressure in the affected segment. The most likely change in the colonic musculature to explain one effect and not the other would be hypertrophy of smooth muscle producing excessive activity on stimulation, but no such activity at rest. The concept of ‘hypertrophy’ might seem at variance theoretically with the radiological concept of ‘spasm’, but the radiological appearances are evoked only after instillation of barium under pressure, and the consequent activity induced in the thickened muscle could induce the narrow appearance interpreted as ‘spasm’. If ‘spasm’ were present the motor responses of prostigmine succeeded by atropine or propantheline would have been followed by a change of luminal pressure.

The colonic responses to food and prostigmine were consistently raised in the diverticular groups provided there was no advanced post-inflammatory change in the bowel wall. When the colon wall was fibrosed, minimal responses were obtained, and variation in the response of the bowel as a result of varying severity of pathological change may explain why some observers (Painter and Truelove, 1964a; Arfwidsson and others, 1964) have noted exaggeration of motor responses in diverticular disease and others have not (Parks, 1968). Technical differences in the mode of recording may also be important.

Division of the circular muscle of the distal colon by myotomy was followed by marked reduction of the intraluminal pressure. This was demonstrated in surgically treated diverticular disease compared with an untreated group, but also in a small group before and after operation acting as their own controls. Paradoxically, in 1 case in the latter group the pressure had heightened when examined at 3 months and radiological examination showed narrowing. The post-myotomy changes in intraluminal pressure conversely could conceivably follow operative widening of the lumen of the colon, as well as being the result of division of its circular smooth-muscle coat. The effect of the myotomy, in either case, should be a beneficial one, since extrusion forces acting on the diverticula should be lessened. Many of these patients, it should be stressed, are capable of producing waves of considerable magnitude, though the numbers of these are reduced.

Colonic activity was stimulated more markedly by prostigmine than by a gastrocolic reflex. The action of prostigmine was readily reversed by propantheline bromide, atropine being only half as effective. Morphine was avoided as a test agent, because it is known to exacerbate symptoms, has potential dangers in diverticular disease (Painter and Truelove, 1964a), and is not so readily reversed. We have no information as to whether propantheline reduces the gastrocolic response, part of which is neurally mediated by cholinerge means but part of which may be dependent on humoral factors. The fact that some prostigmine stimulation occurs after myotomy and that atropine reverses it indicates that there must be some residual smooth-muscle activity, however weakly present. It may be dependent on luminal pressure. There were large falls in pressure after myotomy, which might seem at variance with the radioactivity at rest. The concept of ‘hypertrophy’ may be dependent on humoral factors. The fact that some prostigmine stimulation occurs after myotomy and that atropine reverses it indicates that there must be some residual smooth-muscle activity, however weakly present in the colon at or in zones close to the myotomy site. Nevertheless, there are large falls in the motility index after myotomy, which must indicate that there has been a profound effect on colonic muscle function following this operation.

**SUMMARY**

1. Intraluminal pressure has been studied in the distal colon in diverticular disease. The basal pressure was not raised in the diseased bowel. The colon responded excessively to gastrocolic reflex stimulation and to prostigmine. Propantheline bromide was effective in resolving all pressure-wave activity.

2. The operation of sigmoid colotomy was effective in reducing the exaggerated activity of the hypertrophied muscle in diverticular disease. The significance of this effect is discussed.

**Acknowledgements.**—R. P. Attisha held the Clark Fellowship of the University of Edinburgh and was seconded from the Department of Clinical Surgery to the Western General Hospital during this study by Sir John Bruce.

Acknowledgement of the technical aid of Mrs. Stella Whatmore and Staff Nurse Margaret Flint of the Motility Laboratory, Teaching and Research Centre, Western General Hospital, is gratefully made.

**REFERENCES**


CLINICAL AND MANOMETRIC RESULTS ONE YEAR AFTER SIGMOID MYOTOMY FOR DIVERTICULAR DISEASE

BY ADAM N. SMITH, R. P. ATTISHA, AND TOM BALFOUR

DEPARTMENT OF CLINICAL SURGERY AND THE GASTRO-INTESTINAL UNIT, WESTERN GENERAL HOSPITAL, EDINBURGH

The operation of sigmoid myotomy for diverticular disease was first performed by Reilly in 1962 to relieve local obstruction in diverticular disease by the division of the smooth-muscle coat of the affected part of the colon. The operation reduces natural and artificially induced pressure within the bowel lumen (Artisha and Smith, 1969). The permanence of these effects is unknown and may be doubted, as the operation site could heal with a scar which may restore the pull of muscle-fibres again. The later clinical outcome as well as the immediate effects of the operation was first performed by Reilly in 1962 (Attisha and Smith, 1969). The patients in this series were selected ones and were unfit, in almost every case, from a serious concomitant medical disease. For

died postoperatively, 2 of these from serious medical complications, with the 25 remaining patients making a smooth recovery. Twenty-three of these gave satisfactory results and were symptom-free. We report in this paper an experience of this operation in the management of 14 cases of diverticular disease selected because of a past history of left iliac fossa pain with obstructive effects locally in the distal bowel. The intraluminal pressure in the colon was raised as assessed by a prostigmine test (Attisha and Smith, 1969). The patients in this series were selected ones and were unfit, in almost every case, from a serious concomitant medical disease. For

Table I. — CLINICAL AND OPERATIVE DETAILS OF 14 PATIENTS SUBMITTED TO COLOMYOTOMY

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age and Sex</th>
<th>Pathological State</th>
<th>Associated Disease</th>
<th>Operation</th>
<th>Complications</th>
<th>Immediate Outcome (at 1 month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68 F.</td>
<td>Thick muscle</td>
<td>Former thyrotoxicosis; Encysted emphysema</td>
<td>Myotomy; colon exteriorized (not opened)</td>
<td>Distension</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>2</td>
<td>65 M.</td>
<td>Former perforated diverticulitis</td>
<td>Hiatus hernia with stricture</td>
<td>Myotomy; colostomy already present</td>
<td>—</td>
<td>Colostomy closed later; Stricture dilated (see Table II)</td>
</tr>
<tr>
<td>3</td>
<td>65 M.</td>
<td>Fibrosis and thick muscle over short segment</td>
<td>Myocardial infarction 2 years before</td>
<td>Myotomy; colostomy</td>
<td>Diarrhoea in first 2 weeks</td>
<td>Satisfactory; Colostomy later closed</td>
</tr>
<tr>
<td>4</td>
<td>69 F.</td>
<td>Chronic diverticulitis; thick muscle and fibrosis</td>
<td>Rheumatoid arthritis on medication</td>
<td>Myotomy</td>
<td>Diarrhoea in first 3 weeks</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>5</td>
<td>77 F.</td>
<td>Diverticular disease of pelvic colon</td>
<td>Para-aortic fibrosis hernia. Recent congestive cardiac failure</td>
<td>Myotomy</td>
<td>Distension</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>6</td>
<td>71 F.</td>
<td>Diverticular disease of pelvic colon; thick muscle only</td>
<td>Rheumatoid arthritis with poly-cythaemia vera</td>
<td>Myotomy with transverse colostomy</td>
<td>—</td>
<td>Died later of polycythaemia (see Table II)</td>
</tr>
<tr>
<td>7</td>
<td>47 M.</td>
<td>Short segment of diverticular disease with gross muscular thickening</td>
<td>Active duodenal ulcer</td>
<td>Myotomy</td>
<td>—</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>8</td>
<td>50 M.</td>
<td>Diverticulitis; thick muscle and chronic inflammation</td>
<td>Anxiety state</td>
<td>Myotomy</td>
<td>Dehiscence of colon, septis, septicaemia, liver damage, colostomy</td>
<td>Developed jaundice (see Table II)</td>
</tr>
<tr>
<td>9</td>
<td>65 F.</td>
<td>Diverticular disease of pelvic colon</td>
<td>Chronic bronchitis</td>
<td>Myotomy</td>
<td>Chest infection controlled by antibiotics</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>10</td>
<td>68 F.</td>
<td>Diverticular disease of left colon</td>
<td>Severe asthmatic on steroids</td>
<td>Myotomy</td>
<td>Colicky pain. Given steroids at fifth day; Perforated colon</td>
<td>Adrenocortical crisis, bacteraemic shock; Death</td>
</tr>
<tr>
<td>11</td>
<td>58 F.</td>
<td>Diverticulitis of pelvic colon</td>
<td>Previous urinary infection</td>
<td>Myotomy with caecostomy</td>
<td>—</td>
<td>Caecostomy closed satisfactorily</td>
</tr>
<tr>
<td>12</td>
<td>55 F.</td>
<td>Diverticulitis of pelvic colon</td>
<td>Malabsorption</td>
<td>Myotomy with caecostomy</td>
<td>—</td>
<td>Caecostomy closed satisfactorily</td>
</tr>
<tr>
<td>13</td>
<td>56 F.</td>
<td>Diverticulitis of pelvic colon</td>
<td>Treated for cancer of cervix</td>
<td>Myotomy with caecostomy</td>
<td>—</td>
<td>Caecostomy closed satisfactorily</td>
</tr>
<tr>
<td>14</td>
<td>62 F.</td>
<td>Diverticulitis of pelvic colon</td>
<td>Recurrent bronchitis; Malabsorption. 'Cachectic look'</td>
<td>Myotomy with caecostomy</td>
<td>Distension</td>
<td>Developed pelvic abscess; discharge per vaginam; small residual fistula (see Table II)</td>
</tr>
</tbody>
</table>
these patients, myotomy had the appeal of simplicity in contrast to a more exacting pelvic colon resection. The immediate postoperative effects, the follow-up of all the patients, and the motility in a selected group are detailed to 1 year later.

**OPERATIVE TECHNIQUE**

The patients in the series are listed in the order of operation date in Table I. Their age, sex, and concomitant medical conditions are stated. All patients subsequently narrowing. The sites of diverticula or of perforation could be recognized by compressing the bowel slightly; since diverticula fill with gas, bubbles even from minute perforations became apparent. Frank penetration of the muscle as far as the mucosa was avoided as far as possible. It was difficult, however, to avoid intramural diverticula when dividing the thick circular muscle and, when released from such muscle support, they tended to prolapse outwards and were more easily punctured.

**Table II.—Follow-up of Patients to 1 Year or More**

<table>
<thead>
<tr>
<th>Case</th>
<th>3 Months</th>
<th>6 Months</th>
<th>1 Year</th>
<th>18 Months</th>
<th>2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Slight diarrhoea (barium enema satisfactory)</td>
<td>Slight diarrhoea. Incisional hernia repaired</td>
<td>Slight diarrhoea, discomfort, and distension</td>
<td>Vomiting, diarrhoea, distension (manual evacuation of faeces). Sigmoidoscopy normal</td>
<td>Normal motions; slight reflux from hernia</td>
</tr>
<tr>
<td>2</td>
<td>Well; Wound sinus excised (present before myotomy). Colostomy closed</td>
<td>Well. Bowels good. Dysphagia—oesophageal structure dilated</td>
<td>Well. Bowels good. Still some dysphagia</td>
<td>Well; bowels acting satisfactorily</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Well until haematemeses from acute gastric ulcer; partial gastrectomy of Billroth-I type</td>
<td>Well. Bowels regular</td>
<td>Well, but colonic polyp removed; acute diarrhoea and vomiting for few days settled</td>
<td>Well. Bowels good</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>Well. Bowels satisfactory. Sinus in abdominal wall drained</td>
<td>Died. Hypoplastic phase of polycythaemia</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>Well; no complaints</td>
<td>Symptoms-free</td>
<td>Symptom-free</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>Well; no complaints other than slight diarrhoea</td>
<td>Well. One episode of diarrhoea and vomiting</td>
<td>Well; no complaints. Bowels satisfactory</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>Well. Occasional left iliac fossa pain. Bowels regular</td>
<td>Well. Bowels good. Some frequency of micturition</td>
<td>Well; bowels normal</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>Diarrhoea. ? Rectovaginal fistula, requiring colostomy</td>
<td>Colostomy closed after excision of fistula track</td>
<td>Reasonably well. Weight still down. Bowels satisfactory</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

had had symptoms for at least 5 years. The operation was performed according to Reilly’s description—the longitudinal division of the circular muscle coat through an antimesenteric taenia was continued upwards to normal bowel and downwards to the pelvic floor. The pelvic colon was mobilized to facilitate this. Pledgets of cotton-wool soaked in 1:1000 adrenaline minimized bleeding as the myotomy proceeded. Omental slips were stitched lightly below the edge of the cut taenia at the myotomy slit to control a bleeding point or to prevent perforation of the mucosa occurred in 3 cases and the site was closed with a purse-string of fine catgut. All cases treated by myotomy were recognized to have local ‘bars’ of thickened smooth muscle. The pelvis was drained by at least one suction Redivac drain, and the abdomen closed with or without a defunctioning procedure as indicated in Table I. All operations were undertaken after rigorous bowel preparation, but this had been ineffective in some instances because of the difficulty of enemas reaching the proximal colon owing to local obstruction at the diverticular...
The Fall in Pressure after Myotomy.—This has been detailed in a previous paper (Attisha and Smith, 1969).

The Immediate Postoperative Course.—Three patients developed serious intra-abdominal infection, and of these died of progressive peritonitis (Table I), paralytic ileus, and bacteraemic shock. Another patient developed signs of rupture of the colon and a transverse colostomy was instituted. Repeated discharge from sinuses followed, and at one stage jaundice developed from toxic damage to the liver (Table II). The liver function returned to normal 6 months later when the colostomy was closed. A third patient developed a pelvic abscess which discharged per vaginam; radiological examination revealed an underlying rectovaginal fistula and a temporary colostomy was established. Later, the fistulous track was excised with a local portion of the rectal wall.

Abdominal distension developed in more than half the patients treated by myotomy. This may have accounted for the presence of incisional and colostomy hernias in the subsequent course of 2 patients. Severe distension or diarrhoea was present in 5 patients and lasted from 1 to 3 months (Tables I, II).

The earliest cases in Table I (Cases 1–3) were done with a proximal colostomy or exteriorization of the bowel. In Cases 4 and 5 this was not performed, and the course appeared straightforward. In Case 10 a small perforation was made and sutured, but this patient was an asthmatic on full dosage of steroids; both circumstances contributed to failure of the repair and the lethal outcome.

As the motility studies, reported by us, progressed, it became more and more obvious that, although the motor activity of the colon is reduced by the operative procedure, high-pressure waves can still develop. For this reason, deflation was performed in the remainder of the series by caecostomy since its use can be terminated without formal closure.

Review of Personal Cases to 1 Year or More.—The progress of 12 patients was followed during this period (1 patient in the original 14 died postoperatively and another of polycythaemia at 6 months.)

**RESULTS**

**The Immediate Postoperative Course.**—Three patients developed serious intra-abdominal infection, and of these died of progressive peritonitis (Table I), paralytic ileus, and bacteraemic shock. Another patient developed signs of rupture of the colon and a transverse colostomy was instituted. Repeated discharge from sinuses followed, and at one stage jaundice developed from toxic damage to the liver (Table II). The liver function returned to normal 6 months later when the colostomy was closed. A third patient developed a pelvic abscess which discharged per vaginam; radiological examination revealed an underlying rectovaginal fistula and a temporary colostomy was established. Later, the fistulous track was excised with a local portion of the rectal wall.

**Abdominal distension** developed in more than half the patients treated by myotomy. This may have accounted for the presence of incisional and colostomy hernias in the subsequent course of 2 patients. Severe distension or diarrhoea was present in 5 patients and lasted from 1 to 3 months (Tables I, II).

The earliest cases in Table I (Cases 1–3) were done with a proximal colostomy or exteriorization of the bowel. In Cases 4 and 5 this was not performed, and the course appeared straightforward. In Case 10 a small perforation was made and sutured, but this patient was an asthmatic on full dosage of steroids; both circumstances contributed to failure of the repair and the lethal outcome.

As the motility studies, reported by us, progressed, it became more and more obvious that, although the motor activity of the colon is reduced by the operative procedure, high-pressure waves can still develop. For this reason, deflation was performed in the remainder of the series by caecostomy since its use can be terminated without formal closure.

**Review of Personal Cases to 1 Year or More.**—The progress of 12 patients was followed during this period (1 patient in the original 14 died postoperatively and another of polycythaemia at 6 months.)

**RESULTS**

**The Immediate Postoperative Course.**—Three patients developed serious intra-abdominal infection, and of these died of progressive peritonitis (Table I), paralytic ileus, and bacteraemic shock. Another patient developed signs of rupture of the colon and a transverse colostomy was instituted. Repeated discharge from sinuses followed, and at one stage jaundice developed from toxic damage to the liver (Table II). The liver function returned to normal 6 months later when the colostomy was closed. A third patient developed a pelvic abscess which discharged per vaginam; radiological examination revealed an underlying rectovaginal fistula and a temporary colostomy was established. Later, the fistulous track was excised with a local portion of the rectal wall.

Abdominal distension developed in more than half the patients treated by myotomy. This may have accounted for the presence of incisional and colostomy hernias in the subsequent course of 2 patients. Severe distension or diarrhoea was present in 5 patients and lasted from 1 to 3 months (Tables I, II).

The earliest cases in Table I (Cases 1–3) were done with a proximal colostomy or exteriorization of the bowel. In Cases 4 and 5 this was not performed, and the course appeared straightforward. In Case 10 a small perforation was made and sutured, but this patient was an asthmatic on full dosage of steroids; both circumstances contributed to failure of the repair and the lethal outcome.

As the motility studies, reported by us, progressed, it became more and more obvious that, although the motor activity of the colon is reduced by the operative procedure, high-pressure waves can still develop. For this reason, deflation was performed in the remainder of the series by caecostomy since its use can be terminated without formal closure.

**Review of Personal Cases to 1 Year or More.**—The progress of 12 patients was followed during this period (1 patient in the original 14 died postoperatively and another of polycythaemia at 6 months.)

**RESULTS**

**The Immediate Postoperative Course.**—Three patients developed serious intra-abdominal infection, and of these died of progressive peritonitis (Table I), paralytic ileus, and bacteraemic shock. Another patient developed signs of rupture of the colon and a transverse colostomy was instituted. Repeated discharge from sinuses followed, and at one stage jaundice developed from toxic damage to the liver (Table II). The liver function returned to normal 6 months later when the colostomy was closed. A third patient developed a pelvic abscess which discharged per vaginam; radiological examination revealed an underlying rectovaginal fistula and a temporary colostomy was established. Later, the fistulous track was excised with a local portion of the rectal wall.

Abdominal distension developed in more than half the patients treated by myotomy. This may have accounted for the presence of incisional and colostomy hernias in the subsequent course of 2 patients. Severe distension or diarrhoea was present in 5 patients and lasted from 1 to 3 months (Tables I, II).

The earliest cases in Table I (Cases 1–3) were done with a proximal colostomy or exteriorization of the bowel. In Cases 4 and 5 this was not performed, and the course appeared straightforward. In Case 10 a small perforation was made and sutured, but this patient was an asthmatic on full dosage of steroids; both circumstances contributed to failure of the repair and the lethal outcome.

As the motility studies, reported by us, progressed, it became more and more obvious that, although the motor activity of the colon is reduced by the operative procedure, high-pressure waves can still develop. For this reason, deflation was performed in the remainder of the series by caecostomy since its use can be terminated without formal closure.

**Review of Personal Cases to 1 Year or More.**—The progress of 12 patients was followed during this period (1 patient in the original 14 died postoperatively and another of polycythaemia at 6 months.)

**RESULTS**

**The Immediate Postoperative Course.**—Three patients developed serious intra-abdominal infection, and of these died of progressive peritonitis (Table I), paralytic ileus, and bacteraemic shock. Another patient developed signs of rupture of the colon and a transverse colostomy was instituted. Repeated discharge from sinuses followed, and at one stage jaundice developed from toxic damage to the liver (Table II). The liver function returned to normal 6 months later when the colostomy was closed. A third patient developed a pelvic abscess which discharged per vaginam; radiological examination revealed an underlying rectovaginal fistula and a temporary colostomy was established. Later, the fistulous track was excised with a local portion of the rectal wall.

Abdominal distension developed in more than half the patients treated by myotomy. This may have accounted for the presence of incisional and colostomy hernias in the subsequent course of 2 patients. Severe distension or diarrhoea was present in 5 patients and lasted from 1 to 3 months (Tables I, II).

The earliest cases in Table I (Cases 1–3) were done with a proximal colostomy or exteriorization of the bowel. In Cases 4 and 5 this was not performed, and the course appeared straightforward. In Case 10 a small perforation was made and sutured, but this patient was an asthmatic on full dosage of steroids; both circumstances contributed to failure of the repair and the lethal outcome.

As the motility studies, reported by us, progressed, it became more and more obvious that, although the motor activity of the colon is reduced by the operative procedure, high-pressure waves can still develop. For this reason, deflation was performed in the remainder of the series by caecostomy since its use can be terminated without formal closure.
selected from the most successful results. It will be seen from Table III that the manometric results (motility index after prostigmine stimulation) remain low and that the difference is statistically significant.

**Histological Appearance of Myotomy Site.**

The macroscopic appearance of the myotomy site was that the surrounding viscera had become adherent at the point of incision at autopsy and in the patient who had had repair of an incisional hernia performed. In the patient who died of polycythaemia, tissue from the healed myotomy site was examined histologically. The myotomy area was seen (by the use of van Gieson's stain) to be sharply demarcated from muscle by a broad fibrous scar (Fig. 2).

**DISCUSSION**

The operation of sigmoid colomyotomy is technically simple, though one must ensure intactness of the mucosa. Reilly (1966) claimed that, if the mucosa were punctured, this could easily be corrected by closure with a purse-string suture of catgut. Such potentially weak sites, however, must always be disconcerting. There was a known perforation in 2 of the patients who developed postoperative sepsis. In 1 of these cases death occurred in the postoperative period and necropsy examination revealed the reopened perforation at the proximal end of the incision where hypertrophic muscle was still present. This patient was also on full dosage of steroids, and this may have delayed healing or potentiated infection.

The operative procedure ought to produce an effective disturbance of the functional activity of the circular muscle. Initially, the myotomy may result in separation of fibres and consequent enlargement of the transverse lumen of the bowel and this could be one possible explanation of the reduced intraluminal pressure. Necropsy findings in a patient who died of concomitant disease at 6 months, however, did not reveal a widened bowel lumen and, on histological section, the myotomy scar had contracted sufficiently to restore the severed muscular ends almost to their original position. This might be prevented by implanting omentum or, alternatively, peritoneum (Daniels and Singh, 1969). But when one considers that, histologically, the circular muscle is really disposed in a spiral fashion, then the cut must involve severance of the individual fibres in more than one position; the majority of the fibres will have damage done to their nerve-supply and local reflex arcs must be disturbed, reducing motor activity, since no recurrent diverticula or bulge appeared at the operative site.

Contractility of muscle proximal to the myotomy site may recur after a few postoperative hours, but there may be a continuing hold-up at the myotomy site. If the colon is not entirely emptied of faeces, perforation through the weakened bowel may result, and this led us to fashion a prophylactic colostomy or a defunctional caecostomy till flatus was passed.

It would appear that the maintenance of a quiescent bowel during the early period of healing is important in ensuring that localized complications do not arise. Certain drugs, such as opiates, used in the postoperative period, may raise intraluminal pressure and so promote local perforation and pericolitis. If analgesics are required in the postoperative period non-stimulant agents such as pethidine should be used. The additional use of efficient anti-cholinergic drugs such as atropine or propantheline (Probanthine) would seem sensible, especially if prostigmine is to be used by anaesthetists. Additional important precautionary measures are adequate bowel preparation and antibiotic sterilization.

Myotomy is still effective 1 year later in reducing the high-pressure activity of the sigmoid colon. The motility pattern was near to normal levels. Twelve patients observed personally in follow-up had initial improvement in bowel function, and none of the 12 surviving patients had complications at 6 months related to the original disease or to the effects of the myotomy, the exception being the patient who had local perforation and abscess requiring a defunctioning colostomy for 6 months; once bowel continuity was restored, his defaecation habits had returned to normal.

In this trial a group of patients, often elderly or affected by concomitant diseases as well as diverticular disease, were chosen for colomyotomy. The procedure appeared to be worth while in such patients in spite of initial morbidity, partly related to their age-groups. Division of the circular muscle fibres relieved pain, and implies that a dysfunction of the muscle is of more consequence than inflammation in producing pain in this disease. Diarrhoea and distension followed the myotomy; the distension may have been the consequence of the localized interruption of muscle contractility imposing a state of temporary obstruction. The diarrhoea, which continued in some instances for a few months, could be interpreted as due to reduction of a 'peripheral resistance' to faecal passage, imposed perhaps by the circular musculature on gut contents.
If a greater margin of safety could be developed, it would seem logical to utilize myotomy more as a prophylactic procedure in the early stages of the disease when muscular hypertrophy and high pressures are the predominant features. Safety might ultimately be greatest if myotomy were combined with caecostomy, even in such cases. There would appear to be a place for the utilization of pre-operative motility studies in determining the presence and extent of muscular hyperactivity as a guide to the applicability of the procedure.

**SUMMARY**

1. The increased intraluminal pressure activity of the hypertrophied sigmoid musculature in colonic diverticular disease in response to natural and artificial stimuli had been used to select patients for colotomy. The high-pressure activity was reduced up to 1 year after operation and the clinical results of the procedure are assessed.

2. If the reduction in colonic pressure is effectively maintained, there is a return to satisfactory bowel habit without persistent complications of the original disease.

3. There was considerable initial morbidity, but the patients were elderly or were selected for this procedure because of the presence of concomitant diseases.

4. The operation has not been used in patients with active inflammatory disease. Its main use is for selected patients with muscle hypertrophy in diverticular disease. It would be rational to apply it prophylactically in early diverticular disease, but this cannot be recommended because of the continued presence of high-pressure waves in the distal colon.

**Addendum.**—Six additional cases of colotomy for diverticular disease have been performed in the Edinburgh teaching hospitals, and the result in 5 instances is reported as satisfactory, though 1 patient, suffering from essential hypertension, died post-operatively after a period of severe ileus and subsequent colonic dehiscence. The patient had been on medication with ganglion-blocking agents for blood-pressure control and these compounds have been known to be a cause of ileus and intestinal distension promoting a type of pseudo-obstruction. This untoward outcome and the factors related to it stress the need for strict appraisal of drugs which act on intestinal motor function, and the need for a deflationary procedure such as temporary caecostomy. This was performed in our series with a No. 30 Foley catheter, the removal of which 10 days later led, in most cases, to spontaneous closure.

**Acknowledgements.**—We wish to thank Sir John Bruce for his interest and encouragement. Mr. R. P. Attisha held the Clark Fellowship in the Department of Clinical Surgery during the performance of this work. Gratitude must be expressed to the physicians and surgeons of the Gastro-intestinal Unit, Western General Hospital, for their co-operation and to Mrs. Stella Whatmore and Staff Nurse Margaret Flint of the Motility Laboratory, Teaching and Research Centre, Western General Hospital, for much help.

**REFERENCES**


Late results of colomyotomy

Adam N. Smith¹, V. Giannakos¹ and Shirley Clarke¹

The basis of Reilly's (1966) operation of sigmoid colomyotomy for diverticular disease is division of the thickened circular muscle of the distal colon. This appears to be rational, for Arfwidsson (1964) showed enhanced motor activity in the distal colon in patients with diverticular disease after stimulation by food and drugs. Painter and Truelove (1964) recorded similar pressure increments in sigmoid colon compartments studied by manometry and simultaneous cine radiography at juxta-diverticular sites. Pressures were highest after parasympathomimetic stimulation. In a hypothesis on the aetiology of diverticular disease Painter (1969) suggested that the enhanced segmenting activity could result in a progressive local obstruction. Morson (1963) and Watt and Marcus (1964) focused attention on the particularly thick circular muscle in diverticular disease. This may be the pathological counterpart of the physiological disturbances.

Most surgeons accept the concept of an abnormality, largely an overgrowth of the circular muscle, which may lead to local obstruction of the colonic lumen, with consequent yielding of its wall and finally the extrusion of diverticula. Nevertheless, inflammatory damage in the late stages of the disease is impressive.

The present studies were undertaken to see if different types of diverticular disease with distinctive motility patterns could be recognised, and to assess the suitability of different stages of the disease for operative treatment either by colonic resection or by sigmoid colomyotomy.

Methods

Manometric studies were undertaken in three groups of patients with diverticular disease and contrasted with a series of normals (Fig. 1).

(1) Early diverticular disease

Patients with local obstructive features without inflammatory complications were included in this group. They were studied before and after sigmoid myotomy and subsequently at 3 months, at the end of one year, at 2 years and a few after 3 years.

¹ Department of Clinical Surgery, University of Edinburgh, and the Gastro-Intestinal Unit, Western General Hospital, Edinburgh.
(2) *Diverticular disease with local pain and obstruction*

The subjects were similar to those in Group (1) and complained of local pain and obstructive symptoms. Colonic resection was performed in this group.

(3) *Diverticular disease with inflammatory complications*

Patients in this group were studied before and after surgical treatment for the aftermath of inflammatory complications. Polythene tubes connected to transducer principle manometers were inserted via a sigmoidoscope, to 20 cm. and 15 cm. from the anal verge, the uppermost tube often being passed blindly to 25 cm. since spasm commonly precluded sigmoidoscopy beyond the rectosigmoid area. In the earliest studies miniature balloons were used because of fewer technical difficulties but latterly open-tipped tubes have been used throughout.

A mild aperient was given 24 hours before examination as bowel preparation, and recordings were made only if the distal colon was clear of faeces. Basal activity was recorded after a natural stimulus such as food, after an artificial stimulus (prostigmine 0.75-1 mg.) and also after propantheline. Recordings were taken serially and activity responses were recorded for 30-minute periods after a meal, 15 minutes after intramuscular and 5 minutes after intravenous injections. A motility index was calculated according to the formula:

\[
\text{motility index} = (\text{mean wave amplitude}) \times (\text{percentage of time that waves occurred during the recording period}).
\]

The number of waves exceeding 20 cm. and 50 cm. H\textsubscript{2}O was also studied.

**Results**

(a) *Myotomy effects*

Mean motility indices (with standard deviations) during periods of basal activity, after a gastrocolic reflex and after prostigmine stimulation of the sigmoid and rectosigmoid junction areas are shown in Fig. 1. 12 normal subjects, 35 patients with untreated diverticular disease and 16 post-myotomy patients were compared. There was no difference in basal motility between normals and diverticular disease subjects and this was unaffected by myotomy (0.3 < P < 0.2). Colonic activity was significantly increased after all forms of stimulation (P = <0.001), the degree being greatest after prostigmine. These responses were significantly reduced by myotomy (P = <0.001). There was no difference in the response to food and prostigmine between patients after myotomy and normals (0.4 < P < 0.3).

Comparable falls in the number of waves above 50 cm. H\textsubscript{2}O and 20 cm. H\textsubscript{2}O occurred in the 30-minute periods of observation (Attisha and Smith, 1969). The number of waves provoked by food and a prostigmine stimulus was greatly reduced, being more so for waves over 50 cm. H\textsubscript{2}O than over 20 cm. H\textsubscript{2}O. The colon was still capable of producing 50 cm. pressure waves after prostigmine, an agent given at the end of an operation by anaesthetists to reverse neuromuscular blocking agents.

(b) *Clinical outcome*

The indications for myotomy are shown in Table 1. The patients were mainly elderly and diverticular disease was often present with a concomitant disease. It was thought that myotomy might be less drastic than colonic resection. One death occurred in this series: a patient being treated with steroids for severe asthma developed peritonitis and bacteremic shock after myotomy and died. (A further 7 patients have been treated by myotomy in the Edinburgh area, with one death.) Severe intra-abdominal infection after leakage of colonic content
Late results of colomyotomy

Adam N. Smith¹, V. Giannakos¹ and Shirley Clarke¹

The basis of Reilly's (1966) operation of sigmoid colomyotomy for diverticular disease is division of the thickened circular muscle of the distal colon. This appears to be rational, for Arfwidsson (1964) showed enhanced motor activity in the distal colon in patients with diverticular disease after stimulation by food and drugs. Painter and Truelove (1964) recorded similar pressure increments in sigmoid colon compartments studied by manometry and simultaneous cine radiography at juxta-diverticular sites. Pressures were highest after parasympathomimetic stimulation. In a hypothesis on the aetiology of diverticular disease Painter (1969) suggested that the enhanced segmenting activity could result in a progressive local obstruction. Morson (1963) and Watt and Marcus (1964) focused attention on the particularly thick circular muscle in diverticular disease. This may be the pathological counterpart of the physiological disturbances.

Most surgeons accept the concept of an abnormality, largely an overgrowth of the circular muscle, which may lead to local obstruction of the colonic lumen, with consequent yielding of its wall and finally the extrusion of diverticula. Nevertheless, inflammatory damage in the late stages of the disease is impressive.

The present studies were undertaken to see if different types of diverticular disease with distinctive motility patterns could be recognised, and to assess the suitability of different stages of the disease for operative treatment either by colonic resection or by sigmoid colomyotomy.

Methods

Manometric studies were undertaken in three groups of patients with diverticular disease and contrasted with a series of normals (Fig. 1).

(1) Early diverticular disease

Patients with local obstructive features without inflammatory complications were included in this group. They were studied before and after sigmoid myotomy and subsequently at 3 months, at the end of one year, at 2 years and a few after 3 years.

¹ Department of Clinical Surgery, University of Edinburgh, and the Gastro-Intestinal Unit, Western General Hospital, Edinburgh.
(2) Diverticular disease with local pain and obstruction

The subjects were similar to those in Group (1) and complained of local pain and obstructive symptoms. Colonic resection was performed in this group.

(3) Diverticular disease with inflammatory complications

Patients in this group were studied before and after surgical treatment for the aftermath of inflammatory complications.

Polythene tubes connected to transducer principle manometers were inserted via a sigmoidoscope, to 20 cm. and 15 cm. from the anal verge, the uppermost tube often being passed blindly to 25 cm. since spasm commonly precluded sigmoidoscopy beyond the rectosigmoid area. In the earliest studies miniature balloons were used because of fewer technical difficulties but latterly open-tipped tubes have been used throughout.

A mild aperient was given 24 hours before examination as bowel preparation, and recordings were made only if the distal colon was clear of faeces. Basal activity was recorded after a natural stimulus such as food, after an artificial stimulus (prostigmine 0.75–1 mg.) and also after propantheline. Recordings were taken serially and activity responses were recorded for 30-minute periods after a meal, 15 minutes after intramuscular and 5 minutes after intravenous injections. A motility index was calculated according to the formula:

\[
\text{motility index} = (\text{mean wave amplitude}) \times (\text{percentage of time that waves occurred during the recording period}).
\]

The number of waves exceeding 20 cm. and 50 cm. H₂O was also studied.

Results

(a) Myotomy effects

Mean motility indices (with standard deviations) during periods of basal activity, after a gastrocolic reflex and after prostigmine stimulation of the sigmoid and rectosigmoid junction areas are shown in Fig. 1. 12 normal subjects, 35 patients with untreated diverticular disease and 16 post-myotomy patients were compared. There was no difference in basal motility between normals and diverticular disease subjects and this was unaffected by myotomy (0.3 < P < 0.2). Colonic activity was significantly increased after all forms of stimulation (P = < 0.001), the degree being greatest after prostigmine. These responses were significantly reduced by myotomy (P = < 0.001). There was no difference in the response to food and prostigmine between patients after myotomy and normals (0.4 < P < 0.3). Comparable falls in the number of waves above 50 cm. H₂O and 20 cm. H₂O occurred in the 30-minute periods of observation (Attisha and Smith, 1969). The number of waves provoked by food and a prostigmine stimulus was greatly reduced, being more so for waves over 50 cm. H₂O than over 20 cm. H₂O. The colon was still capable of producing 50 cm. pressure waves after prostigmine, an agent given at the end of an operation by anaesthetists to reverse neuromuscular blocking agents.

(b) Clinical outcome

The indications for myotomy are shown in Table 1. The patients were mainly elderly and diverticular disease was often present with a concomitant disease. It was thought that myotomy might be less drastic than colonic resection. One death occurred in this series: a patient being treated with steroids for severe asthma developed peritonitis and bacteremic shock after myotomy and died. (A further 7 patients have been treated by myotomy in the Edinburgh area, with one death.) Severe intra-abdominal infection after leakage of colonic content
occurred in 2 patients. A colostomy was therefore performed as a safeguard early in this series. Latterly, a caecostomy was preferred, and a No. 30 Foley catheter levels in the small and large bowel were noted on the 5th postoperative day and increased subsequently on further radiographs carried out on alternate days to

![BASAL ACTIVITY vs GASTROCOLOM REFLEX vs PROSTIGMINE](image)

**Fig. 1** Basal activity, food and prostigmine stimulation in normal subjects, diverticular disease and post-myotomy cases, expressed as a mean motility index, with standard deviation (SD) indicated. Sigmoid colon and rectum examined in 12 normal, 35 diverticular disease and 16 post-myotomy subjects.

inserted into the proximal colon through the stump of the appendix; it subsequently closed spontaneously.

Table 2 shows the results of follow-up in the surviving patients, several months to 3 years after operation. After a period of morbidity, which included intra-abdominal sepsis, distension and diarrhoea, the patients steadily improved and to date almost all have remained free of symptoms.

Postoperative distension and diarrhoea have not been commonly noted in accounts of myotomy. Serial abdominal radiographs (Fig. 2a, b) show this developing in a recent patient. Gas and fluid distinguish between mechanical obstruction, ileus or other response to myotomy. Gastrografin was instilled along the caecostomy tube and traversed the large bowel as far as the myotomy site but was held up there where the distension also stopped. It was possible that spasm at or above the myotomy site might lead to a pressure build-up and consequent dehiscence. These findings favour inserting a caecostomy tube in the right side of the colon; it should be passed well towards the hepatic flexure to permit spontaneous drainage of this part of the alimentary tract. When the functional "hold-up" subsides, reduction of the
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age and sex</th>
<th>Pathological state</th>
<th>Associated disease</th>
<th>Operation</th>
<th>Immediate outcome (at 1 month)</th>
<th>Late results of colomyotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68 (F)</td>
<td>Thick muscle</td>
<td>Former thyrotoxicosis, encysted empyema</td>
<td>Myotomy; colon dilated</td>
<td>Satisfactory</td>
<td>Developed jaundice, sepsis, septiciemia, liver damage, colostomy</td>
</tr>
<tr>
<td>2</td>
<td>66 (M)</td>
<td>Former perforated diverticulitis</td>
<td>Hiatus hernia with stricture</td>
<td>Myotomy; colostomy already present</td>
<td>Colostomy closed later</td>
<td>Died of polyuric renal failure</td>
</tr>
<tr>
<td>3</td>
<td>60 (M)</td>
<td>Fibrosis and thick muscle over short segment</td>
<td>Myocardial infarction 2 years before</td>
<td>Myotomy</td>
<td>Colostomy closed later</td>
<td>Died of polyuric renal failure</td>
</tr>
<tr>
<td>4</td>
<td>69 (F)</td>
<td>Chronic diverticular disease; thick muscle and fibrosis</td>
<td>Rheumatoid arthritis on medication</td>
<td>Myotomy</td>
<td>Satisfactory</td>
<td>Died of polyuric renal failure</td>
</tr>
<tr>
<td>5</td>
<td>77 (F)</td>
<td>Diverticular disease of pelvic colon</td>
<td>Para-esophageal hernia</td>
<td>Myotomy</td>
<td>Distension</td>
<td>Died of polyuric renal failure</td>
</tr>
<tr>
<td>6</td>
<td>71 (F)</td>
<td>Diverticular disease of colon; thick muscle and chronic inflammation</td>
<td>Rheumatoid arthritis with polycythemia</td>
<td>Myotomy</td>
<td>Distension</td>
<td>Died of polyuric renal failure</td>
</tr>
<tr>
<td>7</td>
<td>47 (M)</td>
<td>Short segment of diverticulitis; thick muscle and chronic inflammation</td>
<td>Active duodenal ulcer</td>
<td>Myotomy</td>
<td>—</td>
<td>Died of polyuric renal failure</td>
</tr>
<tr>
<td>8</td>
<td>50 (M)</td>
<td>Thick muscle and chronic inflammation</td>
<td>Anxiety state</td>
<td>Myotomy</td>
<td>—</td>
<td>Died of polyuric renal failure</td>
</tr>
</tbody>
</table>
occurred in 2 patients. A colostomy was therefore performed as a safeguard early in this series. Latterly, a caecostomy was preferred, and a No. 30 Foley catheter levels in the small and large bowel were noted on the 5th postoperative day and increased subsequently on further radiographs carried out on alternate days to levels.

![Graph](image)

**Fig. 1**

Basal activity, food and prostigmine stimulation in normal subjects, diverticular disease and post-myotomy cases, expressed as a mean motility index, with standard deviation (SD) indicated. Sigmoid colon and rectum examined in 12 normal, 35 diverticular disease and 16 post-myotomy subjects.

inserted into the proximal colon through the stump of the appendix; it subsequently closed spontaneously.

Table 2 shows the results of follow-up in the surviving patients, several months to 3 years after operation. After a period of morbidity, which included intra-abdominal sepsis, distension and diarrhoea, the patients steadily improved and to date almost all have remained free of symptoms.

Postoperative distension and diarrhoea have not been commonly noted in accounts of myotomy. Serial abdominal radiographs (Fig. 2a, b) show this developing in a recent patient. Gas and fluid distinguish between mechanical obstruction, ileus or other response to myotomy. Gastrografin was instilled along the caecostomy tube and traversed the large bowel as far as the myotomy site but was held up there where the distension also stopped. It was possible that spasm at or above the myotomy site might lead to a pressure build-up and consequent dehiscence. These findings favour inserting a caecostomy tube in the right side of the colon; it should be passed well towards the hepatic flexure to permit spontaneous drainage of this part of the alimentary tract. When the functional "hold-up" subsides, reduction of the
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age and sex</th>
<th>Pathological state</th>
<th>Associated disease</th>
<th>Operation</th>
<th>Complications</th>
<th>Immediate outcome (at 1 month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68 (F)</td>
<td>Thick muscle</td>
<td>Former thyrotoxicosis, Encysted empyema</td>
<td>Myotomy; colon exteriorised (not opened)</td>
<td>Distension</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>2</td>
<td>66 (M)</td>
<td>Former perforated diverticulitis</td>
<td>Hiatus hernia with stricture</td>
<td>Myotomy; colostomy already present</td>
<td>—</td>
<td>Colostomy closed later Stricture dilated</td>
</tr>
<tr>
<td>3</td>
<td>60 (M)</td>
<td>Fibrosis and thick muscle over short segment</td>
<td>Myocardial infarction 2 years before</td>
<td>Myotomy; colostomy</td>
<td>Diarrhoea in first 2 weeks</td>
<td>Satisfactory. Colostomy later closed</td>
</tr>
<tr>
<td>4</td>
<td>69 (F)</td>
<td>Chronic diverticular disease; thick muscle and fibrosis</td>
<td>Rheumatoid arthritis on medication</td>
<td>Myotomy</td>
<td>Diarrhoea in first 3 weeks</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>5</td>
<td>77 (F)</td>
<td>Diverticular disease of pelvic colon</td>
<td>Para-esophageal hernia, Recent congestive cardiac failure</td>
<td>Myotomy</td>
<td>Distension</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>6</td>
<td>71 (F)</td>
<td>Diverticular disease of colon; thick muscle only</td>
<td>Rheumatoid arthritis with polycythaemia vera</td>
<td>Myotomy with transverse colostomy</td>
<td>—</td>
<td>Died later of polycythaemia</td>
</tr>
<tr>
<td>7</td>
<td>47 (M)</td>
<td>Short segment of diverticular disease with gross muscular thickening</td>
<td>Active duodenal ulcer</td>
<td>Myotomy</td>
<td>—</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>8</td>
<td>50 (M)</td>
<td>Diverticulitis; thick muscle and chronic inflammation</td>
<td>Anxiety state</td>
<td>Myotomy</td>
<td>Dehiscence of colon, sepsis, septicemia, liver damage, colostomy</td>
<td>Developed jaundice</td>
</tr>
<tr>
<td>Case no.</td>
<td>Age and sex</td>
<td>Pathological state</td>
<td>Associated disease</td>
<td>Operation</td>
<td>Complications</td>
<td>Immediate outcome (at 1 month)</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
<td>------------------------------------</td>
<td>-------------------------------------</td>
<td>---------------------------</td>
<td>----------------------------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>9</td>
<td>65 (F)</td>
<td>Diverticular disease of pelvic colon</td>
<td>Chronic bronchitis</td>
<td>Myotomy</td>
<td>Chest infection controlled by antibiotics; Colicky pain. Given steroids at fifth day. Perforated colon</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>10</td>
<td>68 (F)</td>
<td>Diverticular disease of left colon</td>
<td>Severe asthmatic, on steroids</td>
<td>Myotomy</td>
<td>—</td>
<td>Adrenocortical crisis; bacteremic shock; Death</td>
</tr>
<tr>
<td>11</td>
<td>58 (F)</td>
<td>Diverticulitis of pelvic colon</td>
<td>Previous urinary infection</td>
<td>Myostomy with cecostomy</td>
<td>—</td>
<td>Cecostomy closed satisfactorily</td>
</tr>
<tr>
<td>12</td>
<td>55 (F)</td>
<td>Diverticulitis of pelvic colon</td>
<td>Malabsorption</td>
<td>Myotomy with cecostomy</td>
<td>—</td>
<td>Cecostomy closed satisfactorily</td>
</tr>
<tr>
<td>13</td>
<td>56 (F)</td>
<td>Diverticular disease of pelvic colon</td>
<td>Treated for cancer of cervix</td>
<td>Myotomy with cecostomy</td>
<td>—</td>
<td>Cecostomy closed satisfactorily</td>
</tr>
<tr>
<td>15</td>
<td>66 (F)</td>
<td>Diverticular disease of pelvic colon</td>
<td>Hypertension</td>
<td>Myotomy with cecostomy</td>
<td>—</td>
<td>Distension</td>
</tr>
<tr>
<td>16</td>
<td>68 (M)</td>
<td>Diverticular disease of pelvic colon</td>
<td>Recurrent bronchitis</td>
<td>Myotomy with cecostomy</td>
<td>—</td>
<td>Distension and diarrhea</td>
</tr>
<tr>
<td>17</td>
<td>73 (F)</td>
<td>Diverticular disease of pelvic and transverse colon</td>
<td>Carcinoma of breast</td>
<td>Myotomy with cecostomy</td>
<td>—</td>
<td>Distension and diarrhea</td>
</tr>
<tr>
<td>18</td>
<td>67 (F)</td>
<td>Diverticular disease of pelvic colon</td>
<td>Genital prolapse, Hiatus hernia</td>
<td>Myotomy with cecostomy</td>
<td>—</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>19</td>
<td>65 (M)</td>
<td>Diverticular disease of pelvic colon</td>
<td>Prostatism</td>
<td>Myotomy with cecostomy</td>
<td>—</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>20</td>
<td>60 (M)</td>
<td>? Diverticular disease; thick muscle syndrome</td>
<td>L.I.H.</td>
<td>Myotomy (no cecostomy)</td>
<td>—</td>
<td>Satisfactory</td>
</tr>
</tbody>
</table>
### Table 2
**Follow-up Clinical Status: 3 Months to 3 Years**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
<th>18 months</th>
<th>2 years</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Slight diarrhea (barium enema satisfactory)</td>
<td>Slight diarrhea. Incisinal hernia repaired</td>
<td>Slight diarrhea, discomfort, and distension</td>
<td>Vomiting, diarrhea, distension (manual evacuation of faeces). Sigmoidoscopy normal</td>
<td>Normal motions; slight reflux from hiatus hernia</td>
<td>Hiatus hernia symptoms</td>
</tr>
<tr>
<td>4</td>
<td>Well until hematemesis from acute gastric ulcer; partial gastrectomy of Billroth-I type</td>
<td>Well. Bowels regular</td>
<td>Well, but colonic polyp removed; acute diarrhea and vomiting for few days settled</td>
<td>Well. Bowels good</td>
<td>Well</td>
<td>Well</td>
</tr>
<tr>
<td>6</td>
<td>Well. Bowels satisfactory. Sinus in abdominal wall drained</td>
<td>Died. Hypoplastic phase of polycythaemia</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>Well; no complaints</td>
<td>Symptom-free</td>
<td>—</td>
<td>Symptom-free</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Case no.</td>
<td>3 months</td>
<td>6 months</td>
<td>1 year</td>
<td>18 months</td>
<td>2 years</td>
<td>3 years</td>
</tr>
<tr>
<td>---------</td>
<td>----------</td>
<td>----------</td>
<td>--------</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>10</td>
<td>Died. Postoperative collapse. Perforation of colon, bacteraemic shock</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>Well; no complaints other than slight diarrhoea</td>
<td>Well. One episode of diarrhoea and vomiting</td>
<td>Well; no complaints. Bowels satisfactory</td>
<td>Satisfactory</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>Well. Occasional left iliac fossa pain. Bowels regular</td>
<td>Well. Bowels good. Some frequency of micturition</td>
<td>Well; bowels normal</td>
<td>Satisfactory</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>Diarrhoea. Rectovaginal fistula; requiring colostomy</td>
<td>Colostomy closed after excision of fistula track</td>
<td>Reasonably well. Weight still down. Bowels satisfactory</td>
<td>Satisfactory</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>15</td>
<td>Well. Slight diarrhoea occasionally</td>
<td>Abdominal pain: admitted for re-investigation; nothing significant</td>
<td>Well</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>16</td>
<td>No complaints</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>17</td>
<td>No complaints</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>18</td>
<td>Symptoms of hiatus hernia; medically treated</td>
<td>Investigation of oesophageal motility; abdomen satisfactory</td>
<td>Well</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>19</td>
<td>Satisfactory</td>
<td>Satisfactory</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>20</td>
<td>Some lower abdominal discomfort</td>
<td>Satisfactory</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
"peripheral resistance" following division of the circular muscle of the distal bowel may explain the diarrhoea which frequently occurred for 2-3 weeks after operation (Table 2).

The intraluminal pressure (Table 4) was much lower than that in patients with muscle hypertrophy. The intraluminal pressure increased after operation but only slightly, presumably because of the presence of more normal tissue in the pelvic colon area after resection of damaged bowel. Postoperative pressures in these patients remain well below those listed in Table 3. By manometric criteria those more favourable for resection showed fibrosis rather than muscle hypertrophy.

(c) Changes after resection
In 12 patients with local obstruction and a thick muscle coat, resection of the sigmoid colon was performed. The motility index, high initially, remained raised after operation (Table 3). Thus local resection of the pelvic colon (this was all that was carried out) reduced but did not restore to normal the inherent abnormality of this segment. Many of the patients fared well clinically, but the potential in motility terms for the development of further diverticular disease may remain.

(d) Influence of pathological state on manometric results
In the 12 patients with diverticular disease and marked inflammatory changes after operation, (b) gastrografin in colon arrested at upper limit of myotomy incision where there is narrowing presumably due to spasm.
pressure activity though not to the high preoperative level. In contrast the motility index after colonic resection may rise even to levels slightly above those recorded before operation indicating that the musculature in diverticular disease is as abnormal in the residual portion as in the excised area of diverticula.

**Discussion**

The possibility of selecting patients with diverticular disease for surgical procedures on the basis of the motor reactions of the distal colon is suggested. There is little doubt that resection has the advantage of removing the offending diverticula with the risk of pathological change. Nonetheless it has the disadvantage of little reduction in pressure and perhaps even an eventual rise in intraluminal pressure. Significant bleeding from the diverticular area always necessitates resection.

**TABLE 3**

**MEAN MOTILITY INDICES AFTER PROSTIGMINE STIMULATION IN 12 PATIENTS WITH LOCAL OBSTRUCTION AND THICKENED MUSCULATURE BEFORE AND AFTER RESECTION OF THE PELVIC COLON**

<table>
<thead>
<tr>
<th>Mean motility index (±SD)</th>
<th>Normals</th>
<th>Pre-resection</th>
<th>Post-resection (at 3/12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>791 ± 102</td>
<td>2468 ± 850</td>
<td>1891 ± 480</td>
</tr>
</tbody>
</table>

Still significantly increased above normal after resection

\[ P < 0.001 \]

**TABLE 4**

**MEAN MOTILITY INDICES BEFORE AND AFTER PELVIC COLON RESECTION IN 12 PATIENTS WITH INFLAMMATORY COMPLICATIONS OF DIVERTICULAR DISEASE**

<table>
<thead>
<tr>
<th>Mean motility index (±SD)</th>
<th>Normals</th>
<th>Post-inflammatory group Pre-resection</th>
<th>Post-resection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>791 ± 102</td>
<td>852 ± 58</td>
<td>912 ± 110</td>
</tr>
</tbody>
</table>

Not significantly different \[ P < 0.2 \]
Myotomy is suitable for selected patients—for example, the elderly or unfit, and those with a marked motor reaction with pain in whom reduction of pressure or of the so-called “spasm” of originally promoted the development of diverticula.

Why post-myotomy patients have so few symptoms in the face of some return of high intraluminal pressures is not yet understood. It may relate to events not yet measured in the upper pelvic colon at or just above the myotomy area where a sphincter or a sphincter-like mechanism has been postulated. Alternatively, the good colonic function of these patients may be more dependent on the relief of mechanical obstruction promoted by the thick plaques of smooth muscle in the bowel wall rather than by the reduction of intraluminal pressure at the myotomy site.

Summary

(1) Effects of colomyotomy on the intraluminal pressure in diverticular disease are described for the basal state, after prostigmine and food stimulation. The wave forms were more reduced for
pressure activity though not to the high preoperative level. In contrast the motility index after colonic resection may rise even to levels—slightly above those recorded before operation indicating that the musculature in diverticular disease is as abnormal in the residual portion as in the excised area of diverticula.

Discussion
The possibility of selecting patients with diverticular disease for surgical procedures on the basis of the motor reactions of the distal colon is suggested. There is little doubt that resection has the advantage of removing the offending diverticula with the risk of pathological change. Nonetheless it has the disadvantage of little reduction in pressure and perhaps even an eventual rise in intraluminal pressure. Significant bleeding from the diverticular area always necessitates resection.

**TABLE 3**

**MEAN MOTILITY INDICES AFTER PROSTIGMINE STIMULATION IN 12 PATIENTS WITH LOCAL OBSTRUCTION AND THICKENED MUSCULATURE BEFORE AND AFTER RESECTION OF THE PELVIC COLON**

<table>
<thead>
<tr>
<th>Mean motility index (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals</td>
</tr>
<tr>
<td>Pre-resection</td>
</tr>
<tr>
<td>Post-resection (at 3/12)</td>
</tr>
<tr>
<td>791 ± 102</td>
</tr>
<tr>
<td>2468 ± 850</td>
</tr>
<tr>
<td>1891 ± 480</td>
</tr>
</tbody>
</table>

Still significantly increased above normal after resection

P < 0.001

**TABLE 4**

**MEAN MOTILITY INDICES BEFORE AND AFTER PELVIC COLON RESECTION IN 12 PATIENTS WITH INFLAMMATORY COMPLICATIONS OF DIVERTICULAR DISEASE**

<table>
<thead>
<tr>
<th>Mean motility index (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals</td>
</tr>
<tr>
<td>Post-inflamatory group</td>
</tr>
<tr>
<td>Pre-resection</td>
</tr>
<tr>
<td>Post-resection</td>
</tr>
<tr>
<td>791 ± 102</td>
</tr>
<tr>
<td>852 ± 58</td>
</tr>
<tr>
<td>912 ± 110</td>
</tr>
</tbody>
</table>

Not significantly different P < 0.2
Myotomy is suitable for selected patients—for example, the elderly or unfit, and those with a marked motor reaction with pain in whom reduction of pressure or of the so-called “spasm” of originally promoted the development of diverticula.

Why post-myotomy patients have so few symptoms in the face of some return of high intraluminal pressures is not yet understood. It may relate to events not yet measured in the upper pelvic colon at or just above the myotomy area where a sphincter or a sphincter-like mechanism has been postulated. Alternatively, the good colonic function of these patients may be more dependent on the relief of mechanical obstruction promoted by the thick plaques of smooth muscle in the bowel wall rather than by the reduction of intraluminal pressure at the myotomy site.

**Summary**

(1) Effects of colomyotomy on the intraluminal pressure in diverticular disease are described for the basal state, after prostigmine and food stimulation. The wave forms were more reduced for
pressures greater than 50 cm. than 20 cm. H₂O.

(2) The clinical features of 20 patients treated by colomyotomy and their follow-up are described.

(3) The late effects of myotomy on the colonic motility response to prostigmine are recorded. Comparisons are made with the pressure changes after resection of the pelvic colon.

(4) The pressure response of the colon has also been found to vary with the nature of the main pathological change in diverticular disease, i.e. whether muscle atrophy, inflammatory cell infiltration or fibrosis is present.

Acknowledgments

The work was carried out during the tenure of a Scottish Hospital Endowments Research Trust Grant, 291.

REFERENCES

pressures greater than 50 cm. than 20 cm. H₂O.

(2) The clinical features of 20 patients treated by colomyotomy and their follow-up are described.

(3) The late effects of myotomy on the colonic motility response to prostigmine are recorded. Comparisons are made with the pressure changes after resection of the pelvic colon.

(4) The pressure response of the colon has also been found to vary with the nature of the main pathological change in diverticular disease, i.e. whether muscle atrophy, inflammatory cell infiltration or fibrosis is present.

Acknowledgments

The work was carried out during the tenure of a Scottish Hospital Endowments Research Trust Grant, 291.

REFERENCES

Motility Effects of Operations Performed for Diverticular Disease

Diverticular disease of the colon has been described as a disease of Western civilization and its causation attributed to a deficiency of dietary fibre (Painter 1970). Bran has been shown to produce clinical improvement in patients with diverticular disease (Painter et al. 1972). Most patients who have operations for diverticular disease have had a preliminary period of management on a high fibre diet or hydrophilic colloid both of which produce bulkier fecal residues and, among other effects, lower colonic intraluminal pressure (Hodgson 1972, Findlay et al. 1974). If excessive intraluminal pressure, as emphasized by Arfwidsson (1964) and Painter (1964), is the important factor in the genesis of diverticular disease, it follows that operations for diverticular disease may have to be judged on their ability to reduce this and for a significantly lengthy period of time. Possible beneficial changes could easily lapse if patients continued to be exposed after operation to the same conditions of fibre deficiency as preoperatively.

It therefore seemed important to define the effect of the common operations performed for diverticular disease in motility terms and to determine how long the effects last in patients left on their original diet compared with others given bran supplementation postoperatively.

Material and Methods

Control subjects and patients with uncomplicated diverticular disease of the colon were studied on their habitual diet before and after the addition of 20 g of unprocessed bran. The patients with uncomplicated diverticular disease who had operations were suffering from local pain and semi-obstructive features. They were allotted to two groups for treatment by myotomy or resection of the pelvic colon. Myotomy of the sigmoid colon was electively performed in a group comparable to the myotomy cases, i.e. with local obstructive features, high intraluminal pressure and a thick bowel muscle at operation (Smith et al. 1971).

The motility index, high initially, remained raised after operation compared with normals (Table 2). Thus local resection of the pelvic colon

Intraluminal pressure activity was recorded as described by Attisha & Smith (1969) with the addition of analogue to digital conversion of wave forms, the data being fed to a computer program. A motility index expressing the product of the mean wave amplitude and the percentage of activity time was calculated for standardized recording periods, basally, after food and after prostigmine.

Results

Effects of myotomy on uncomplicated diverticular disease: There was no difference in basal motility between normals and diverticular disease subjects before and after myotomy. Colonic activity was significantly increased after all forms of stimulation in diverticular disease but the effect was greatest after prostigmine (Attisha & Smith 1969). These responses were reduced to normal levels by myotomy ($P < 0.001$) (Table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Significance of sigmoid colon motility index changes</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Basal activity</strong></td>
</tr>
<tr>
<td>Normals</td>
</tr>
<tr>
<td>Disease</td>
</tr>
<tr>
<td>Gastrocolic reflex</td>
</tr>
<tr>
<td>After prostigmine</td>
</tr>
</tbody>
</table>

9 normals and 9 diverticular disease subjects before and after myotomy

No significant difference between the groups ($0.3 < P < 0.2$)

Comparison with changes after resection: Resection of the sigmoid colon was electively performed in a group comparable to the myotomy cases, i.e. with local obstructive features, high intraluminal pressure and a thick bowel muscle at operation (Smith et al. 1971).

The motility index, high initially, remained raised after operation compared with normals (Table 2). Thus local resection of the pelvic colon

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean motility indices after prostigmine stimulation (in 12 patients with local obstruction and thickened musculature) before and after resection of the pelvic colon</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Mean motility index (± s.d.)</strong></td>
</tr>
<tr>
<td>Normals</td>
</tr>
<tr>
<td>Pre-resection</td>
</tr>
<tr>
<td>3 months after resection</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Still significantly increased above normal after resection $P &lt; 0.001$</td>
</tr>
</tbody>
</table>
Late pattern of pressure responses: Myotomy and resection patients have now been followed for more than three years (Fig 1). A fall in the mean motility index (shown for prostigmine stimulation only) occurred during the first year following myotomy but over the three year period there was considerable return in the mean pressure activity, though not to the same high preoperative level. In contrast, the motility index after colonic resection rose to levels very slightly above those recorded before operation. These findings are comparable to those of Parks (1970).

Comparisons of the effects of bran in normal subjects and in diverticular disease: The transit time was only significantly reduced \( (P<0.02) \) in diverticular disease patients on bran (Table 3). The stool weight was increased by an average of 63 g \( (P<0.02) \) in normals but not significantly in diverticular disease patients (17 g).

In patients with diverticular disease, basal motility (Table 4) was unaltered by bran therapy but the response to food fell below basal; the response to prostigmine fell by 50\% \( (P<0.01) \) after bran.

Intraluminal pressures in late myotomy and resection cases given bran: Figs 2 and 3 show the mean motility indices in patients after resection and myotomy, after prostigmine stimulation, and contrasted with a comparable group given 20 g of unprocessed bran daily. It is seen that the mean motility indices after resection rose, but that this level is markedly lower in resection patients on bran. The mean motility indices after myotomy fell at first, but by five years this trend had been fully reversed. Myotomy patients on bran showed a fall in pressure which was maintained, and at a lower level than in comparable patients with uncomplicated diverticular disease treated by resection and bran.

Discussion
When 20 g bran was fed to normals, stool weight increased by an average of 63 g, whereas the same quantity of bran fed to diverticular disease patients only increased stool weight by an average of 17 g.

The average transit time was longer in untreated diverticular disease than in normals; the consumption of 20 g bran reduced it in diverticular disease and normals however, but significantly only in diverticular disease, which confirms the finding of Parks (1970).

The motility studies indicate no significant change in basal activity but the pressure levels after food were below basal and the response to prostigmine fell by 50\% \( (P<0.01) \). There would thus appear to be a marked diminution in response to motor stimuli in patients who had diverticular disease who are fed bran. Findlay et al. (1974) have produced evidence that this may in part be due to overfilling of the colonic lumen.

Most patients with diverticular disease have first been treated with a bulk additive such as one of the hydrophilic colloids or by increasing the amount of natural fibre in their diet, most commonly done by the addition of bran. The rationale of this type of management is to overcome the action of the thickened circular muscle of the distal colon. This is also the basis of Reilly’s (1966) operation of the sigmoid colomyotomy for diverticular disease in which this muscle throughout the layers of the pelvic colon is divided. This appears to be as rational as resection, since Arfwidsson showed that this area was possessed of abnormally active motor activity in diverticular disease after stimulation by food and drugs. Painter et al. (1965) recorded similar pressure changes in the sigmoid colon.

Table 3

| Transit time (hours) in 6 normals and 7 diverticular disease patients: effect of bran |
|----------------------------------|-------------------|----------------|
|                                  | No bran | Taking bran | Effect of bran |
| Normals                          | 66 ± 18  | 50 ± 11     | -16            |
| Diverticular disease             | 93 ± 13  | 57 ± 8      | (P < 0.02)     |

Table 4

| Motility indices in 9 patients with diverticular disease: effect of bran |
|----------------------------------|-------------------|----------------|
|                                  | No bran | Taking bran | Change     |
| Basal                            | 892 ± 196 | 648 ± 339  | -244 ± 370 |
| After food                       | 1513 ± 436 | 446 ± 130  | -1067 ± 383 |
| After prostigmine                | 2120 ± 405 | 1216 ± 398 | -904 ± 347  |

(P < 0.01)
keeping the patient on bran prophylactically. The failure of resection to change intraluminal pressure can also be reversed by bran.

It would appear important not only to treat patients with diverticular disease, when indicated, by operation; but also to restore fibre to their diet, overcoming the deficiency which may have promoted or could recreate the vicious circle of low fecal residue, high intraluminal pressure, further extrusion of diverticula and semi-obstructive symptoms so commonly found in the pelvic colon in this condition.

Summary

In diverticular disease 20 g unprocessed bran shortens the intestinal transit time and lowers the intraluminal bowel pressure. It increases the stool weight in normals, but to a lesser extent in patients with diverticular disease. Some of its action could be related to enhanced colonic filling. Bran has been applied after the operations of myotomy and resection. Sigmoid colomyotomy reduces intraluminal pressure but the pressures return postoperatively over 3–5 years. The intraluminal pressure remains high after resection of the pelvic colon for diverticular disease. The pressures remain at a much lower level if operation is followed by the administration of bran. The operation of myotomy, which initially effectively lowers the intraluminal pressure, emphasizes the important role played by the circular muscle of the pelvic colon in diverticular disease.

Acknowledgment: This work was done during the tenure of a Scottish Hospitals Endowment Research Trust Grant.

REFERENCES

Arfwidsson S (1964) Acta chirurgica Scandinavica Suppl 342
Attisha R P & Smith A N (1968) British Journal of Surgery 56, 891
Hodgson J (1972) British Medical Journal ii, 720
Morson B C (1963) British Journal of Radiology 36, 385
Painter N S (1970) Divererticular Disease: a Disease of this Century. D.M. Publications, USA
Painter N S, Truelove S C, Ardron G M & Tuckey M (1965) Gut 6, 57
Park T G (1970) Gut 11, 121
Park T G (1973) Rendiconti di Gastro-Enterologia 5, 25
Reilly M (1965) British Journal of Surgery 52, 859
Watt J & Marcus R (1964) Journal of Pathology and Bacteriology 88, 97

Fig 2 Mean motility index for 5 years after resection: lower values in patients taking bran

Fig 3 Mean motility index for 5 years after myotomy: lower values in patients taking bran

and found in studies using cine-radiography and manometry simultaneously, that the diverticula were extruded as little bladder-like compartments when the pressure was highest. Morson (1963) and Watt & Marcus (1964) focused attention on the particularly thick circular muscle in diverticular disease, and suggested that this was the pathological counterpart of the physiological disturbance.

The present studies on operation and resection were undertaken to see if the motility pattern of excessive segmentation of the pelvic colon in diverticular disease was reversed by operations which divide the thickened circular muscle; alternatively, to determine if the activity of the part of the colon brought down to replace it repeated the phenomenon. The continuing high pressure found after resection suggests that patients could repeat the cycle of events which originally promoted the development of the diverticula.

The return of intraluminal pressure after myotomy is gradual but is present to approximately 60% at three years and is almost complete at five years. The eventual rise in intraluminal pressure after myotomy can be counteracted by...
EFFECTS OF UNPROCESSED BRAN ON COLON FUNCTION IN NORMAL SUBJECTS AND IN DIVERTICULAR DISEASE

J. M. Findlay A. N. Smith
W. D. Mitchell A. J. B. Anderson
M. A. Eastwood

Wolfson Laboratories of the Gastrointestinal Unit, the Medical Research Council Clinical and Population Cytogenetics Unit, and the Department of Clinical Surgery of University of Edinburgh, Western General Hospital, Edinburgh

Summary
20 g. of unprocessed bran each day significantly shortened the intestinal-transit time in diverticular disease; increased stool weight in normal people and to a lesser extent in patients with diverticular disease; and appeared to modify faecal flow patterns by acting as a vehicle for molecular or gel water in normal people, and as a vehicle for interstitial water in diverticular disease. These effects could be caused by enhanced colonic filling, which would account for the dilution of bile-acid concentrations. Bran also reduced the intraluminal increase in pressure in response to stimuli in the distal colon in patients with diverticular disease.

Introduction
DIVERTICULAR disease of the colon has been described as a disease of Western civilisation caused by deficiency of dietary fibre. Bran produced clinical improvement in patients with diverticular disease. We have investigated the effects of adding unprocessed bran to a habitual diet. Transit-times, stool weight, faecal-flow patterns, and output and concentration of faecal bile-acids in normal subjects and in patients with diverticular disease were measured before and after bran. In addition, the effects of bran on the motility of the distal colon were studied in diverticular disease.
Materials and Methods

Control subjects and patients with uncomplicated diverticular disease of the colon were studied in their normal environment, taking their usual diet. Six normal subjects whose ages ranged from 28 to 36 years were investigated, as well as seven patients with diverticular disease, aged 30–84. The diverticular disease was localised in the pelvic colon in four patients and extended proximally into the left colon in three.

Polyethylene glycol 4000 (P.E.G.) and chromium sesquioxide (Cr₂O₃) were used to mark the liquid³ and solid⁴ phases of the gastrointestinal content, respectively. No individual had diarrhoea or was taking any preparation containing Cr₂O₃ or P.E.G. The experimental design is given in Table I.

Transit-time

The patients swallowed 40 barium-impregnated pellets (Portex). Transit-time, regarded as the time taken for 80% of the opaque pellets to be passed, was assessed using the method of Hinton et al.⁵ by X-raying the stools.

Estimation of P.E.G. and Cr₂O₃

P.E.G. and Cr₂O₃ were estimated in duplicate from aliquots taken from pooled 24-hour collections. Cr₂O₃ was estimated using the method of Bolin et al.⁶ P.E.G. 4000 was estimated using the method of Malawer and Powell,⁷ using 9 mg. of acacia per litre. The amount of each marker was expressed in terms of output per 24 hours and also, cumulatively daily, during the period of collection. The recoveries of markers with the coefficients of variation are reported elsewhere.⁸

Faecal Bile-acid

Aliquots of the pooled 7-day faecal collection were freeze-dried and the faecal bile-acid output measured

<table>
<thead>
<tr>
<th>Period</th>
<th>Day no.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>40 barium-impregnated pellets before breakfast. Diet recorded.</td>
</tr>
<tr>
<td></td>
<td>1–7</td>
<td>500 mg. of Cr₂O₃ (2 capsules) and 500 mg. P.E.G. 4000 (2 capsules) Both three times daily synchronously. Individual stool collection, recording time of laxation.</td>
</tr>
<tr>
<td>II</td>
<td>8</td>
<td>Colonic motility study. Habitual diet and 10 g. twice daily bran. No markers</td>
</tr>
<tr>
<td></td>
<td>9–35</td>
<td>As day 1 period I. Diet recorded and 10 g. of bran twice daily.</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>Continued to take diet as recorded day 1–7 period I and 10 g. bran twice daily. Cr₂O₃ and P.E.G. 4000 as in period I three times daily synchronously. Stool collection, recording time of laxation. Colonic motility study.</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal subjects</td>
<td>Patients with diverticular disease</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td></td>
<td>Pre-bran</td>
<td>Post-bran</td>
</tr>
<tr>
<td>Transit-time (hr.)</td>
<td>66.3 ± 18.1</td>
<td>50.0 ± 11.5</td>
</tr>
<tr>
<td>Stool weight (g./day)</td>
<td>120.0 ± 17.9</td>
<td>182.8 ± 22.0</td>
</tr>
<tr>
<td>Freeze-dried weight (g./day)</td>
<td>32.8 ± 3.8</td>
<td>45.6 ± 3.3</td>
</tr>
<tr>
<td>Freeze-dried weight % of total weight</td>
<td>28.2 ± 1.9</td>
<td>25.8 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>Normal subjects</td>
<td>Patients with diverticular disease</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td></td>
<td>Pre-bran</td>
<td>Post-bran</td>
</tr>
<tr>
<td>$Cr_2O_3$ concentration (mg./g.)</td>
<td>$6.5 \pm 0.9$</td>
<td>$6.0 \pm 0.6$</td>
</tr>
<tr>
<td>P.E.G. concentration (mg./g.)</td>
<td>$6.3 \pm 0.5$</td>
<td>$3.2 \pm 0.5$</td>
</tr>
<tr>
<td>Cumulative P.E.G./Cr$_2$O$_3$ regression slope</td>
<td>$0.97 \pm 0.041$</td>
<td>$0.56 \pm 0.050$ Below unity ($p &lt; 0.01$)</td>
</tr>
</tbody>
</table>
according to the methods of Evrard and Janssen as modified by Mitchell.

**Measurement of Colonic Motility**

Intraluminal-pressure activity was recorded for a basal period of 30 minutes. Patients were then given a standard meal and activity was recorded for a further 30 minutes, after which 1 mg of prostigmine was given intramuscularly. Motility was recorded for a further 45 minutes. A motility index (mean wave amplitude x percentage of activity-time) was calculated for each recording period—i.e., basal, after food, and after prostigmine. The recording system was that of Attisha and Smith with the addition of analogue to digital conversion of wave forms, the data being fed to a computer program comparable to that of Misiewicz et al.

**Data Analysis**

Tests of significance assumed that the data were normally distributed. This cannot be verified because of the small numbers involved, but is expected to be approximately true. Standard errors for pre and post bran comparisons are based on “within-subject” differences.

**Results**

Transit-time and stool weights are shown in table II. Transit-time was only reduced significantly (<0.02) in patients with diverticular disease on bran. Stool weight increased by an average of 63 g. (p<0.02) in normal subjects, but did not increase significantly in patients with diverticular disease. Freeze-dried weight increased similarly (p<0.06) in controls, but did not increase significantly in patients with diverticular disease. There was no significant change in the freeze-dried weights as a percentage of total weight on bran.

The concentration of both markers was higher in untreated diverticular disease than in untreated normal subjects (table III), although the difference was not significant. In normal subjects the concentration of Cr₂O₃ remained unchanged on bran, but P.E.G. concentration decreased (p<0.02) on bran. In patients with diverticular disease the concentration of both markers fell by about 30% on bran (p<0.06). The cumulative P.E.G./Cr₂O₃ regression was not significantly different from unity in normal subjects, but fell below unity (p<0.01) on bran. In diverticular disease the cumulative P.E.G./Cr₂O₃ regression was below unity (p<0.01) and on bran reverted to near unity.

Taking bran did not significantly alter total faecal bile-acid excretion (table IV). The concentration of
<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Patients with diverticular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-bran</td>
<td>Post-bran</td>
</tr>
<tr>
<td>Total bile-acid (mg./day)</td>
<td>295.7 ± 32.5</td>
<td>352.2 ± 45.5</td>
</tr>
<tr>
<td></td>
<td>6.5 ± 0.5</td>
<td>5.0 ± 0.8</td>
</tr>
<tr>
<td>Bile-acid concentration (mM)</td>
<td>295.7 ± 32.5</td>
<td>352.2 ± 45.5</td>
</tr>
<tr>
<td></td>
<td>6.5 ± 0.5</td>
<td>5.0 ± 0.8</td>
</tr>
</tbody>
</table>

Change:
- Normal: +56.5 ± 62.0
- Patients: -32.2 ± 61.9

Change:
- Normal: -1.5 ± 0.8
- Patients: -3.7 ± 1.8
bile-acids in diverticular disease was higher than in the controls. The difference was not significant. Bile-acid concentration fell when patients with diverticular disease were on bran, but this difference was not significant.

In patients with diverticular disease basal motility (table V) was unaltered by bran therapy. The motility response to food was reduced, falling to the same level as the basal state. The response to prostigmine fell by 50% (p < 0.015) after bran.

Discussion

20 g. of bran fed to normal subjects increased stool weight by an average of 63 g., whereas the same quantity of bran fed to patients with diverticular disease only increased the stool weight by an average of 17 g. We confirmed that the patients took the bran (10 g. twice daily) by checking their bran supply, but they could have adapted their habitual diet by reducing their food intake to compensate for the feeling of fullness associated with consumption of bran.

The average transit-time was longer in untreated diverticular disease than in normal subjects, but the difference was not statistically significant.

Consumption of 20 g. of bran reduced the transit-time in diverticular disease and in the normal subjects, but only significantly in diverticular disease (table II). This accords with the findings of Parks. However, Harvey et al. found that, although bran reduced transit-time in subjects in whom transit was initially slow, bran increased the transit-time in those with rapid initial transit.

In normal subjects the stool weight increased significantly on bran (p < 0.01) but transit-time, although 23% faster, was not significantly different; the reciprocal of these changes was seen on bran. The rela-
Plot of transit-time against daily stool weight for normal subjects and patients with diverticular disease before and after bran therapy.

The curve is: \( \log_{10} (\text{transit}) = 3.54 (\pm 0.34) - 0.87 (\pm 0.17) \times \log_{10} (\text{weight}). \)

A relationship between stool weight and transit-time (see accompanying figure) is not linear but may be logarithmic, as noted by Burkitt et al.\textsuperscript{15}

Changes in fecal weight could occur as a result of altered water content of the stool. Water in relation to the dietary residue may exist in three phases. There is a bulk or free-water phase which is independent of the dietary residue. This is only seen in the diarrhoeal stool.\textsuperscript{16} Entrapped water lies in the interstices of the dietary residue and is marked by P.E.G.\textsuperscript{17,18} The gel or non-solvent water is intimately associated with dietary residue and is inaccessible to P.E.G.\textsuperscript{17,18} The solid dietary residue and its associated water is marked by Cr\textsubscript{2}O\textsubscript{3}.\textsuperscript{4,19}

In normal subjects taking bran the concentration of chromium did not change, but the concentration of P.E.G. marker fell by almost 50% \((p<0.02)\). This suggests that the component causing the increase in stool weight was marked by chromium but not by P.E.G. We conclude that the increase in stool weight observed in bran-fed controls was associated with an increase of solid material and associated non-solvent (gel) water, but not an increase in interstitial water. These findings probably reflect the simple observation that the stool of normal people on bran is relatively unformed, bulky, and gelatinous. Before they...
were fed bran, normal subjects excreted markers of the solid and liquid phases of the gut content at equal rates (table iii) (cumulative \(\text{P.E.G.}/\text{Cr}_2\text{O}_3\) regression = 0.97 ± 0.041). Bran reduced the rate of excretion of the liquid marker \(\text{P.E.G.}\) relative to solid marker (cumulative \(\text{P.E.G.}/\text{Cr}_2\text{O}_3\) regression = 0.56 ± 0.050). The solid and associated non-solvent (gel) water now travelled through the gut faster than liquids, thus indicating streaming of the solid and liquid phases.

In diverticular disease the rate of throughput of the solid phase was faster than that of the liquid phase (cumulative \(\text{P.E.G.}/\text{Cr}_2\text{O}_3\) regression = 0.78 ± 0.038). This has been attributed to retropulsion of the liquid phase of the gut contents, caused by the high distal intraluminal pressure in diverticular disease.\(^{11-21}\) Since the same quantity of marker was taken before and after bran, the fall in concentration of both markers with no change in stool weight, suggests that dilution of both solid and liquid phase markers was taking place within the gastrointestinal tract. This implies enhanced filling of the gastrointestinal tract. Painter,\(^{22}\) in a hypothesis to explain the cause of diverticular disease, has suggested that underfilling of the colon could increase intraluminal pressure. If this hypothesis is correct, colonic filling should result in the observed fall in intraluminal pressure and in elimination of streaming (\(\text{P.E.G.}/\text{Cr}_2\text{O}_3\) regression = 0.93 ± 0.081, which is similar to the values observed in the control before bran).

There have been no reports on faecal bile-acid excretion in diverticular disease, nor on how the excretion of bile-acids may be altered by feeding bran. Pomare and Heaton\(^{23}\) demonstrated that bile-acid patterns may be modified in the upper gastrointestinal tract by feeding bran. Our data do not suggest any qualitative or quantitative difference between faecal bile-acid excretion in controls and in diverticular disease. When normal subjects were fed bran, bile-acid excretion increased, but not significantly: patients with diverticular disease tended to have reduced bile-acid excretion when fed on bran. The concentration of bile-acids in patients with diverticular disease seemed to be higher than in the normal subjects (table iv), although this difference was not statistically significant. Bran lowered the concentration of faecal bile-acids in both groups, and in those with diverticular disease bran lowered the concentration to levels observed in normal subjects. The fall in bile-acid concentration was reflected by
the fall in P.E.G. and Cr₂O₃ concentration.

The motility studies in patients with diverticular disease (table III) indicate no significant change in basal activity, but the response to food was associated with a fall in motility index of some 30% after one month on bran; although this change was not statistically significant, on bran the pressure level achieved after food was of the same order as during basal activity. The response to prostigmine, which produces intense cholinergic stimulation of the colon, fell by 44% (p<0.015). There would thus appear to be a diminution in response to stimuli in patients with diverticular disease who are fed bran. Evidence suggests that bile-acids in high concentration in the colon cause increased colonic activity. Lowering of the concentration of the bile-acids could be a factor in the observed reduction in colonic activity.

This work was done in part during the tenure of a Scottish Hospitals Endowment Research Trust Grant (no. 418). We thank Sandoz for donating markers and Prewett's Ltd. (Horsham) for the supply of bran.

Requests for reprints should be addressed to A. N. S., Department of Clinical Surgery, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh EH4 2XU.

Action of Different Bran Preparations on Colonic Function

W. O. KIRWAN, A. N. SMITH, A. A. McCONNELL, W. D. MITCHELL, M. A. EASTWOOD

Summary

Two different types of commercially available bran were studied. One of these was composed of flake-like particles (coarse bran) whereas the other had smaller, finer particles with a floury component (fine bran). The effectiveness of the two preparations in lowering intraluminal pressure and decreasing transit time in patients with constipation and diverticular disease was assessed. Only coarse bran promoted changes at the dose used. The physical properties of the brans were examined in an effort to explain their differing effects. It is concluded that water-holding capacity, upon which the beneficial effect of bran may depend, is a function of particle size. The greater water-holding capacity of coarse bran makes it preferable for the treatment of colonic disorders.

Introduction

The value of bran in the symptomatic treatment of diverticular disease (Painter et al., 1972) and constipation (Harvey et al., 1973) has been established. It has been shown that intraluminal colonic pressure is abnormally high in diverticular disease and constipation (Arfwidsson and Kock, 1964; Painter and Truelove, 1964). Gastrointestinal transit time is prolonged in diverticular disease (Findlay et al., 1972) and constipation (Harvey et al., 1973) and it has been established that bran lowers intraluminal pressure and shortens the transit time in such patients (Findlay et al., 1974). This study was prompted by the observation that two types of bran differed in their appearance, in their clinical efficacy, and in their ability to lower intraluminal pressure and reduce transit time. Physical characteristics of the two brans were examined in an effort to explain their differing effect.

Methods

Two groups of patients were studied before and after taking bran 10 g twice daily for four weeks. One group took a coarse preparation of bran (Prewitt's) of which none of the particles or flakes passed through a sieve of 1-mm diameter and the other group took a fine preparation (Allinson's) which entirely passed through a sieve of 1-mm diameter pore size. Fine bran also contained appreciable amounts of endosperm (flour).

Coarse-bran Group.—This group consisted of nine patients with radiologically proved diverticular disease. Colonic motility before taking bran was measured using open-ended tubes (Smith et al., 1971) and gastrointestinal transit time was measured using radio-opaque pellets (Hinton et al., 1969). These investigations were repeated after four weeks of treatment with coarse bran 10 g twice daily.

Fine-bran Group.—This group consisted of five patients. Three had radiologically proved diverticular disease. Two patients complained of difficult and infrequent bowel movements and occasional abdominal pain. After investigations which failed to show any organic abnormality a diagnosis of constipation was made. Colonic motility before bran was measured using the same method as in the former group. Gastrointestinal transit time was measured using a radioisotope capsule (Kirwan and Smith, 1974). These investigations were repeated after four weeks of treatment with fine bran 10 g twice daily, and in four patients who consented to a third study the tests were again repeated after switching to the coarse bran for a further four weeks.

PHYSICAL CHARACTERISTICS OF BRANS

To determine the physical characteristics of the brans both were shaken for 90 minutes in test sieves and the flour from each bran which passed through the mesh was weighed. The acid detergent fibre, which measures the cellulose and lignin content of the brans, was determined by the method of van Soest (1963). The water-holding capacity of a fibre is a function of the ability of the fibre to retain water and is signified by the amount of water held by 1 g of the dried material (McConnell et al., 1974). It was measured for each bran by adding a known quantity of bran to a weighed tube, excess water then being added and the mixture being left to equilibrate for 24 hours. The tube was then centrifuged at 14,000 g for one hour and the supernatant was then removed leaving the bran with its associated water. The result was expressed as grammes of water per gramme of bran.
The cation exchange capacity was determined by the method of pH titration (Hefferlich, 1962). The bran was saturated with H+ ions, washed, and its capacity to exchange these H+ ions for Na+ ions was then determined by titration with NaOH. The result was expressed as mEq of Na+ per gram of bran.

The pore size distribution of the two brans was measured by a mercury penetration porosimeter (Micromeritics, Model 900, Coulter Electronics Ltd.). This technique determines the quantity of mercury forced into the pores of the material under investigation and then the quantity expelled at various decreasing pressures. At low pressures (less than 50 lb/in² (3.5 Kg/cm²)) some of the mercury is considered as entering “void spaces” among the particles while at higher pressures it penetrates pores within the particles themselves.

Results

Coarse-bran Patients.—The basal motility index (mean ± S.E.) was lowered from 882.8 ± 196 to 648.7 ± 339 but the change was not statistically significant. The motility index after food was lowered significantly from 1,513.2 ± 456 to 466.1 ± 130 (P < 0.01), and that after neostigmine was significantly lowered from 2,120.0 ± 405 to 1,216.8 ± 398 (P < 0.01). The gastrointestinal transit time was significantly lowered from 93.4 ± 13.8 to 57.9 ± 8.0 hours (P < 0.01).

Fine-bran Patients.—All the motility indices (Mean ± S.E.) increased after bran. The basal, post-food, and post-neostigmine motility indices increased from 1,181.8 ± 489 to 1,269 ± 503, and 4,075 ± 873 to 4,611 ± 410 respectively. The gastrointestinal transit time fell from 98 ± 32 hours to 86 ± 34 hours. These changes were not statistically significant.

Coarse versus Fine Bran.—The change in motility index produced by coarse bran was compared with that produced by fine bran. There was a significant difference between the effect of the two brans in the phase after food (P < 0.05) and in the phase after neostigmine (P < 0.05).

Coarse Bran after Fine Bran.—In four patients first given fine bran who agreed to change to coarse bran and undergo a third series of tests the mean transit time (± S.E.) after four weeks of coarse bran was lowered from 96 ± 43 hours to 51 ± 26 hours, the basal motility index was lowered from 1,202 ± 506 to 303 ± 168, the motility index after food was lowered from 2,369.8 ± 811 to 1,459 ± 637, and the post-neostigmine motility index was lowered from 4,726 ± 522 to 2,746 ± 749 (P < 0.05). The overall motility result in 13 patients treated by coarse bran is shown in table I. The basal motility fell from 878 ± 192 to 335 ± 108 (P < 0.01), the motility after food from 1,812 ± 391 to 733 ± 237 (P < 0.01), and the post-neostigmine motility from 2,758 ± 514 to 1,545 ± 355 (P < 0.01).

Table I—Mean Motility Indices (± S.E.) in 13 Patients with Diverticular Disease before and after Four Weeks of Treatment with Coarse Bran

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>After Food</th>
<th>After Neostigmine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before coarse bran</td>
<td>878 ± 192</td>
<td>1,012 ± 391</td>
<td>2,758 ± 514</td>
</tr>
<tr>
<td>After coarse bran</td>
<td>335 ± 108</td>
<td>733 ± 237</td>
<td>1,545 ± 355</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Properties of Brans

The moisture contents of coarse and fine bran were 9.6% and 11.1% respectively; the protein contents were 14.0% and 13.3% respectively.

The amount of each bran passing through different mesh aperture sizes is shown in table II. Much more of the second bran than the first bran passed through the small aperture mesh, thus confirming that it had many more small particles.

Table II—Percentage of Brans filtering through different Mesh Sizes

<table>
<thead>
<tr>
<th>Mesh No.</th>
<th>Aperture Size (mm)</th>
<th>Coarse Bran</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Filtering through Mesh</td>
<td></td>
</tr>
<tr>
<td>&gt;14</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>&gt;12</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>&gt;10</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>&gt;6</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>&gt;2</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>&lt;2</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>&lt;0.2</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

The water-holding capacities of coarse and fine bran were 6.15 g and 2.36 g of water per g of bran respectively. The respective acid detergent fibre contents were 15.1% and 9.65%, the lignin contents 4.1% and 2.63%, and the cation exchange capacities 1.2 mEq and 0.7 mEq per gramme.

After milling both brans to a particle size of 1 mm the water-holding capacity of the first bran became 3.94 g/g and the water-holding capacity of the second bran became 2.16 g/g. After milling the cation exchange capacities became respectively 0.4 and 0.7 mEq NaOH per g of bran.

When both brans were examined for pore size distribution there was marked intrusion between 1 and 50 lb/in² (0.07 and 3.5 kg/cm²) atmospheric, which was probably related to uptake of mercury into the interparticle space. This was measurably greater for coarse bran than fine bran. The computed pore size, however, was the same for the two brans.

Discussion

The marked difference in the effect of the two brans on bowel function was unexpected. Fine bran failed completely at a dosage of 20 g/day to produce significant changes in the colonic motility index or the gastrointestinal transit time. Substitution of coarse for fine bran, however, greatly reduced transit time and the intraluminal pressure in four weeks. Because of its ineffectiveness fewer patients were treated with fine bran than coarse bran.

The beneficial effect of bran is probably due to its water-holding effect, giving rise to a soft bulky stool which is easily passed. The water-holding capacity of fibre depends on the type of plant from which the fibre is derived (McConnell et al., 1974). Water is associated with fibre in various phases—surface water, entrapped or interstitial water, and free water (Findlay et al., 1974). The water-holding capacity of brans must be influenced by the capacity of the interstices to hold water. With large particle size the intra- or interparticulate spaces should be larger and become more available for the carriage of interstitial water. An analogy with sponges of different sizes and with different-sized pores is appropriate. Our observations suggest that bran with coarse particles holds more water and thus provides more bulk in the stool than does bran with finer particles. The change in motility index resulting from bran may depend on the bulk provided since intraluminal pressure depends not only on force exerted by muscle but also upon diameter of the bowel lumen and the viscosity of its contents. Coarse bran was found to hold much more water than fine bran (6.15 g and 2.36 g respectively) and it seems likely that the low water-holding capacity of the fine bran accounts for its failure to improve colonic function. Milling coarse bran to a particle size of 1 mm (thus considerably lowering its particle size) almost halved its water-holding capacity from 6.15 g to 3.54 g of water per g of bran. Milling fine bran to a similar size had little effect on water-holding capacity (2.36 g to 2.15 g per g). These results indicate that particle size is of fundamental importance in determining the water-holding capacity and clinical efficacy of bran.

The coarse bran contained more acid detergent fibre than the fine bran. Coarse bran also contained more lignin than fine bran. The cation exchange capacity of coarse bran was greater than that of fine bran. All of these differences were less marked than...
those in the water-holding capacity. Since changing the particle size greatly alters the water-holding capacity but does not alter the fibre or lignin content it seems that particle size is more important than fibre or lignin content.

The coarse-bran preparation was closer to pure bran, which is the material left after the flour has been separated from the grain. The fine-bran appeared to contain an appreciable amount of what seemed to be flour (endosperm). The difference between the two preparations is a reflection of the degree of milling or the stage of extraction at which the brans were obtained.

In the treatment by bran of diverticular disease and constipation it seems that a useful criterion for success is the amount of alteration of the stool weight (Burkitt et al., 1972). Theoretically increasing the stool weight should be achieved by increasing the dietary intake of fibre from any plant source, from vegetables and fruits as well as bran, so long as there is a substantial water-holding capacity as has been shown, for example, in carrots, apples, oranges, Brussels sprouts, etc. (McConnell et al., 1974). While the water-holding capacity of bran is in comparison modest one the fact that it is 85% dry material magnifies its importance. It is easier for most people to take 20 g of bran as a source of fibre than the comparable amount of fibre from other sources (200-300 g raw material).

It is possible that if fine bran were given in a larger dose there would be sufficient large particles and water-holding capacity for it to improve bowel function also. This form of bran, however, contains considerable amounts of absorbable carbohydrate (two of our female patients complained of having put on 4 lb and 5 lb in weight over four weeks) and increasing the dose might result in unacceptable weight gain.

This work was done during the tenure of Scottish Endowments Hospitals Research Trust Grant No. 418 and with support from the British Nutrition Foundation.

We thank Miss E. G. P. Drummond for skilled technical help and Dr. J. B. Hutchinson, Flour Milling and Baking Research Association, Chorleywood, for advice and help.

Requests for reprints should be sent to A.N.S.

References

Intestinal streaming patterns in cholerrhoeic enteropathy and diverticular disease

J. M. FINDLAY, W. D. MITCHELL, M. A. EASTWOOD, A. J. B. ANDERSON, AND A. N. SMITH

From the Wolfson Laboratories of the Gastro-Intestinal Unit, the Medical Research Council Clinical and Population Cytogenetics Unit, and the Department of Clinical Surgery of the University of Edinburgh, at Western General Hospital, Edinburgh

SUMMARY Streaming of gastrointestinal contents depends on the demonstration of differential rates of recovery of equal doses of two synchronously fed markers. There was no significant difference in the rate of throughput of polyethylene glycol (a liquid phase marker) and chromium sesquioxide (a solid phase marker) in healthy volunteers (n = 7) and hospital inpatients (n = 5) with normal bowel habit, so that streaming does not usually occur. In cholerrhoeic enteropathy (n = 5), however, the rate of throughput of polyethylene glycol was increased. In colonic diverticular disease (n = 7) the rate of throughput of polyethylene glycol was significantly lower. In cholerrhoeic enteropathy the liquid phase marker was excreted 1-5 times faster than the solid phase, but in the diverticular disease group the liquid phase was excreted 0-75 times more slowly than the solid phase marker. This may reflect the effects of colonic hypersegmentation on the relative distribution of the liquid and solid phases.

Whitby and Lang (1960) suggested the possibility that streaming might occur in the gastrointestinal tract, and this suggestion was further examined by Wilkinson (1971). Proof of streaming of solid and liquid phases depends on the demonstration of differential rates of recovery of synchronously fed markers of the solid and liquid phases. A satisfactory solid phase marker is one that is insoluble and unabsorbed; a marker of the aqueous phase needs to be water soluble and unabsorbed.

Chromium sesquioxide \((\text{Cr}_2\text{O}_3)\) satisfies these criteria for a marker of the solid phase. It has been used since 1947 (Kreula) and its usefulness has been commented on by Whitby and Lang (1960) and Davignon, Simmons, and Ahrens (1968). Polyethylene glycol 4000 (PEG) is water-soluble and is a suitable marker of the water phase of the gastrointestinal contents (Wilkinson, 1971). It has been shown to be unabsorbed in both healthy and diseased bowel (Shields, Harris, and Davies, 1968). This marker has been in use since 1956 (Hyden) and was first used in man by Beeken (1967).

The aim of the present study was to investigate the rates of recovery of marker of the solid and the liquid phase in a variety of clinical situations.

Clinical Material and Methods

Streaming of intestinal contents was investigated in two clinical situations. In the first experiment streaming patterns in subjects with formed stools and those with diarrhoea were investigated. In the second experiment streaming patterns of normal subjects were compared with those from a group of patients with colonic diverticular disease. These two abnormal groups represented two apparent extremes of disturbance of gastrointestinal physiology.

The clinical details of all those studied are given in table I.

The first study involved 14 individuals, five patients with chronic diarrhoea (1-5), four normal subjects (11-14), and five patients (6-10) with a variety of disorders, all of whom had formed stools. The diarrhoeal patients had frequent (more than four) watery stools that were capable of separation into a pellet and supernatant on centrifugation (Findlay, Eastwood, and Mitchell, 1973). Their faecal bile...
Table I  Clinical details of four groups of subjects studied

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Study (Days)</th>
<th>Stool Weight (g)</th>
<th>Clinical Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoeal patients</td>
<td>1</td>
<td>70</td>
<td>F</td>
<td>7</td>
<td>581</td>
<td>Strangulated small bowel; total ileal resection; jejuno-ileal anastomosis</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>58</td>
<td>F</td>
<td>8</td>
<td>505</td>
<td>Infarcted bowel; resection 90 cm of small bowel (jejunum and ileum)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>62</td>
<td>M</td>
<td>4</td>
<td>485</td>
<td>Crohn's disease; resection 50 cm distal ileum; half of ascending colon resected</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>37</td>
<td>F</td>
<td>7</td>
<td>395</td>
<td>Crohn's disease; resection 100 cm distal ileum; plus excision of ascending and transverse colon; former pelvic colectomy</td>
</tr>
<tr>
<td>Non-diarrhoeal patients</td>
<td>5</td>
<td>46</td>
<td>M</td>
<td>7</td>
<td>363</td>
<td>Pyloroplasty and vagotomy</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>35</td>
<td>M</td>
<td>5</td>
<td>83</td>
<td>Morbidly obese patient—losing weight in hospital</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>32</td>
<td>M</td>
<td>6</td>
<td>142</td>
<td>Crohn's disease; ileo-ileal fistula</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>51</td>
<td>F</td>
<td>7</td>
<td>56</td>
<td>Thyrotoxicosis before therapy</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>41</td>
<td>M</td>
<td>4</td>
<td>430</td>
<td>Crohn's disease; resection of 50 cm distal ileum; on hydrophilic colloid (Hogel)</td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>10</td>
<td>71</td>
<td>F</td>
<td>11</td>
<td>107</td>
<td>Infarction of lower 2/3rd ileum, caecum midtransverse colon; jejuno-transverse colon anastomosis</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>37</td>
<td>M</td>
<td>7</td>
<td>193</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>35</td>
<td>M</td>
<td>7</td>
<td>154</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>34</td>
<td>F</td>
<td>7</td>
<td>79</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>36</td>
<td>M</td>
<td>7</td>
<td>93</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>29</td>
<td>M</td>
<td>7</td>
<td>185</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>28</td>
<td>M</td>
<td>7</td>
<td>92</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>28</td>
<td>F</td>
<td>7</td>
<td>125</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>75</td>
<td>F</td>
<td>7</td>
<td>63</td>
<td>Diverticula in sigmoid colon</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>60</td>
<td>F</td>
<td>7</td>
<td>150</td>
<td>Extensive diverticular disease in distal colon</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>80</td>
<td>M</td>
<td>7</td>
<td>89</td>
<td>Extensive diverticular disease in sigmoid colon</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>73</td>
<td>M</td>
<td>7</td>
<td>82</td>
<td>Marked diverticular disease of distal descending colon and sigmoid colon</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>82</td>
<td>M</td>
<td>7</td>
<td>57</td>
<td>Well marked muscular thickening with early diverticular disease high up in the pelvic colon</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>51</td>
<td>F</td>
<td>7</td>
<td>107</td>
<td>Sigmoid and descending colonic diverticular disease</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>31</td>
<td>F</td>
<td>7</td>
<td>50</td>
<td>Sigmoid diverticula</td>
</tr>
</tbody>
</table>

acid excretion exceeded 2 g per day, suggesting cholerrhoeic enteropathy (Hofmann, 1967). Normal faecal bile acid excretion in our laboratory is less than 700 mg per day. Patients 6-10 had stools that did not separate into pellet and supernatant on centrifugation.

The second study involved 13 individuals, six normal subjects (12-17), and seven patients with uncomplicated diverticular disease (18-24). All the individuals were studied at home; none of them were taking any aperient or had diarrhoea during the study.

All of those studied were on their habitual diet. No individual was taking any preparation containing either Cr$_2$O$_3$ or PEG.

During the period of study each individual took 500 mg of PEG (two capsules of PEG 4000 Sandoz) and 500 mg of chromium sesquioxide (two capsules of chromium Sandoz) thrice daily synchronously. Stools were collected individually in plastic bags, using the technique of Hinton, Lennard-Jones, and Young (1952). PEG and Cr$_2$O$_3$ were estimated in duplicate from aliquots taken from pooled 24-hour collections. Cr$_2$O$_3$ was estimated using the method of Bolin, King, and Klosterman (1952). PEG 4000 was estimated using the method of Malawer and Powell (1967) using 9 mg of acacia per litre. The amount of each marker was expressed in terms of output per 24 hours.

The data were studied by regression analysis. This technique finds the line of best fit of a variable $y$ on a variable $x$, ie, estimates the values of $a$ and $b$ in the relation

$$y = a + bx$$

The variable $y$ increases more or less rapidly than the variable $x$ according as the slope $b$ is greater than or less than unity.

**Recoveries of Markers (Added to Faeces)**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG</td>
<td>101 ± 5</td>
</tr>
<tr>
<td>Cr$_2$O$_3$</td>
<td>97 ± 5</td>
</tr>
</tbody>
</table>

**Coefficient of Variation Between Assays of a 10 mg Standard**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Coefficient (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG</td>
<td>4.6</td>
</tr>
<tr>
<td>Cr$_2$O$_3$</td>
<td>3.4</td>
</tr>
</tbody>
</table>

**Results**

Tables II and III show estimated values of $b$, regression slope, for the groups of subjects studied. It will be seen that, for the two groups of normal...
subjects and the non-diarrhoeal patients there is no evidence of a differential rate of throughput of polyethylene glycol and chromium. For both groups of healthy normals, a comparison of polyethylene glycol and chromium output with intake, ie, the slopes of cumulative polyethylene glycol and chromium regressed on cumulative dose, do not differ significantly from unity. This indicates a rapid attainment of equilibrium in which output matches input for both markers. For the non-diarrhoeal subjects, the outputs are considerably depressed and variable indicating that these subjects had not all reached equilibrium. Nevertheless, the polyethylene glycol and chromium throughputs are consistent and the pooled slope for the four normal and non-diarrhoeal subjects (6-14) is 1.016 ± 0.036.

For the diarrhoeal subjects, the slope of polyethylene glycol on chromium is significantly elevated to 1.55 (p < 0.001) indicating that the polyethylene glycol throughput is about one and a half times that of chromium during the period studied. This appears to be due to elevated throughput of polyethylene glycol and depressed throughput of chromium.

The seven colonic diverticular patients have a low throughput of polyethylene glycol in relation to chromium (which is passed at a rate consistent with he dose) indicating a lag in the liquid phase.

Discussion

In this study we have attempted to investigate differences in the throughput of two markers, PEG 4000 and Cr₂O₃. For this reason we did not attempt to study patients who had achieved equilibrium.

In the proximal part of the colon there is a high proportion of water which decreases as the contents move distally. Water in the proximal part of the colon is in three phases: (1) molecular or gel water, ie, water bound to the dietary residue and which is inherently part of the residue (Manners and Kidder, 1968); (2) interstitial water, ie, water that lies in the interstices of the dietary residue and cannot be expressed from formed stools, even if the stool is centrifuged at 14 000 g (Findlay et al, 1973); (3) free water, ie, water which lies freely in the bowel and which is not particularly associated with the dietary residue. It is this free water that makes a stool diarrhoeal. Free water can be expressed on centrifugation at 14 000 g, but no free water can be expressed from a formed stool on centrifugation (Findlay et al, 1973).

It can be seen from the data (tables II and III) that in both experiment I and experiment II the groups of normal subjects behaved identically. A typical example of a normal excretion pattern of PEG and Cr₂O₃ is shown in figure 1a. Two conclusions can be drawn from the results of these normal subjects. First, as the regression coefficients of PEG on Cr₂O₃ do not differ significantly from unity (table II) it can be deduced that an equal rate of throughput of solid and liquid markers exists, ie, no streaming. This conclusion differs from the observations of Wilkinson (1971) who found that by the end of one week 12 subjects excreted more PEG than Cr₂O₃ indicating streaming with the liquid phase moving faster than the solid phase. Wilkinson’s patients, however, were inpatients in a metabolic ward, and no information was given regarding their clinical state or their bowel habit. Our normal subjects were individuals taking their
FIG 1 Cumulative inputs and outputs of three subjects: (a) normal, (b) cholerrhoeic enteropathy, (c) diverticular disease.

Vertical axis, input (g) and output of markers Cr$_2$O$_3$ and PEG 4000

Horizontal axis duration of experiment in days.

Solid line synchronous input of both markers (cumulative).

Interrupted lines, outputs of the two markers (cumulative).
habitual and varied diets and pursuing their normal activities. Our conclusion regarding no evidence of streaming in normal people was based on 45 observations in seven subjects, as a result of measuring daily PEG and \( \text{Cr}_2\text{O}_3 \) output, whereas Wilkinson's observations were based on single measurements of these markers from aliquots taken from a week's collection. In addition, if one includes the data of the patients with formed stools and without diverticular disease our conclusions are unaltered and based on 70 observations.

The second conclusion to be drawn from the results for the normal subjects (tables II and III) is that PEG on dose (1.08 ± 0.14 and 1.09 ± 0.069) and \( \text{Cr}_2\text{O}_3 \) on dose (1.07 ± 0.14 and 1.08 ± 0.076) (table II) indicates that output of marker equalled input of marker, ie, equilibrium had been reached. The rapid attainment of equilibrium by our normal volunteers is of interest and differs from the findings of Davignon et al (1968), Whitby and Lang (1960), and Beeken (1967) where more than 20% of patients failed to attain a steady state. This difference possibly reflects the difference between inpatients, especially those on liquid formula diets used as controls, and truly healthy subjects studied under their normal environmental conditions. However, it should be noted that our non-diarrhoeal patients had not achieved equilibrium by the end of the study. Although this group did not stream PEG or \( \text{Cr}_2\text{O}_3 \) (slope 1.12 ± 0.070) they were far from being in equilibrium (PEG on dose being 0.25 ± 0.099 and \( \text{Cr}_2\text{O}_3 \) on dose being 0.23 ± 0.072). These observations would indicate that their medical condition was associated with a modified handling of these gastrointestinal markers of solid and liquid phases.

Patients with cholerhoeic enteropathy were chosen because they have continuous, frequent diarrhoeal stools and yet they remain well enough to be studied. Excessive amounts of bile acids are known to modify water and electrolyte absorption in the small and large bowel (Forth, Rummel, and Glasner, 1966; Mekhjian and Phillips, 1970; Mekhjian, Phillips, and Hofmann, 1971; Teem and Phillips, 1972) and also to cause secretion of water (Mekhjian, Phillips and Hofmann, 1968). These actions thus combine to cause an increased quantity of water in the gastrointestinal tract.

The water in the colon is therefore able to flow onwards to the rectum unimpeded by the haustra, and, normal segmental activity being much diminished, a 'conduit' situation exists (Connell, 1962). It is not surprising, therefore, that in patients with cholerhoeic enteropathy streaming occurs with liquid marker travelling faster than solid marker (1.55 ± 0.14) (see table II). An example of a typical diarrhoeal streaming pattern is shown in figure 1b.

This streaming pattern is achieved partly as a result of an increased throughput of PEG (1.31 ± 0.056) and partly as a result of a reduction in the rate of throughput of chromium (0.73 ± 0.046). These values differ significantly (p < 0.001) from the values obtained in normal subjects (table II). A possible explanation for the retarded rate of solid marker may be that patients with cholerhoeic enteropathy are advised to eat small quantities of fruit and vegetables (Barany, 1971; Dyer, 1972). This diminished intake of plant material may simply retard the effective transit rate of the solid phase. It must be stressed, however, that it is not reasonable to assume that the streaming pattern demonstrated in these patients with cholerhoeic enteropathy will be typical of all diarrhoeal subjects, nor of the entire cholerhoeic group.

Streaming also occurs in diverticular disease, the slope for PEG on \( \text{Cr}_2\text{O}_3 \) being 0.78 ± 0.038, differing at the 0.1% level, from normal subjects (table III). The streaming pattern is opposite in direction to that seen in the diarrhoeal patients referred to above, ie, the solid phase passes through more quickly than the liquid phase (figure 1c). The data in table III indicate that this streaming pattern occurs as a result of a relative diminution in the rate of throughput of PEG (0.57 ± 0.098) compared with the throughput of chromium (0.78 ± 0.11). This may be due to the increased colonic segmentation found in diverticular disease exerting an intraluminal pressure so that more than the usual quantity of interstitial water is expressed from the stool. As distal colonic activity is higher than proximal colonic activity, the interstitial water thus expressed and marked by PEG might be retropulsed (Misiewicz et al, 1966). This would cause the excreted faeces to be depletied in PEG. Evidence of retropulsion in the colon has been observed radiologically (Ritchie, Truelove, and Ardran, 1968). Although the figure for the regression coefficient of chromium on dose in the diverticular disease (0.078 ± 0.11) (table III) is not significantly different from the values found in either group of normal subjects (1.07 ± 0.14 and 1.08 ± 0.076) (tables II and III) it is lower, and it is possible that a study of a larger number of patients might establish a significant difference. Such findings would be compatible with the slower than normal transit times of patients with diverticular disease (Painter, 1972). It is important to realize that when transit times are measured using a marker of only one phase the time indicated does not necessarily represent the time of all phases of intestinal content. This is well illustrated by the different flow rates described.

The techniques described indicate the overall streaming effect that is taking place down the
gastrointestinal tract. Nevertheless, the conclusions drawn from the streaming patterns we have described confirm current views on the intestinal dysfunction in the two abnormal groups studied. Streaming patterns may therefore be regarded as indicators of highly complex intestinal dysfunction.

This work was performed in part during the tenure of a Scottish Hospitals Endowment Research trust grant (no. 418).

We are grateful to Dr. R. Evans of Sandoz Products Ltd for supplying the markers (PEG 4000 and Cr₂O₃).

It also forms part of an MD thesis to be submitted by J.M.F. to the University of Liverpool.

Requests for reprints should be addressed to M.A.E., Wolfson Laboratories, Gastro-Intestinal Unit, Western General Hospital, Edinburgh EH4 2XU.

References


Gastrointestinal Transit Estimated by an Isotope Capsule

W. O. KIRWAN & A. N. SMITH
Wolfson Gastrointestinal Laboratories, Western General Hospital, and
Dept. of Clinical Surgery, University of Edinburgh, Edinburgh, Scotland


An isotope capsule method of determining total gastrointestinal and colonic transit time is described. The method has been validated as a means of determining transit time by comparing it with radio-opaque markers. There was agreement in normals and in constipation but not in diarrhoea. The effect of varying the specific gravity on the rate of transit of the isotope capsule has been studied; transit was accelerated by increasing specific gravity from 1.1 to 1.35 and by reducing it to 0.93. Colonic transit has been measured directly and indirectly. There was delay at the splenic flexure and rectosigmoid in constipated subjects but at the rectosigmoid only in normals.

Key-words: Capsule; colon; constipation; diarrhoea; gastrointestinal tract; isotope; specific gravity

A. N. Smith, Dept. of Clinical Surgery, Western General Hospital, Edinburgh, Scotland

Many ingenious methods have been devised to study total gastrointestinal transit time. The simplest is that described by Hinton, Lennard-Jones & Young (2). By their method the transit time is the time necessary for the excretion of 80 per cent of a number of swallowed radio-opaque markers. The method estimates total gastrointestinal transit time but provides no precise information of the rate of progress through the various parts of the gastrointestinal tract. A simple method of measuring the transit time through the large bowel would be of value in the study of diseases such as diverticular disease and the irritable colon syndrome. No such method is currently available other than the use of a telemetering capsule to which an isotope has been added for localisation purposes (5). The aim of this study has been to assess a simple method of determining total gut transit time and large bowel transit time in particular.

This paper is to be submitted as part of an M.Ch. Thesis to University College Cork, Ireland.

MATERIALS AND METHODS

The marker used was a radioisotope capsule similar to that described by Rosswick, Stedeford & Brooke (4) and applied to the study of gastric emptying and small intestinal transit times. The capsule is easily machined from perspex, measures 1 cm by 4 mm, is weighted by the addition of a small amount of lead shot, and contains sealed within its centre not more than 10 micro-curies of $^{131}$I.

When the capsule has been swallowed, it is possible, using a portable collimated sodium iodide scintillation counter (Pitman), to determine its position accurately relative to the anterior abdominal wall. The capsule is taken with breakfast and is localised twice daily at 9 a.m. and 5 p.m. until it is expelled in the stool. The localisation points are plotted (Fig 1a) on a diagram. Usually the patient passes one stool between readings. If the capsule is no longer detectable in the abdomen, its time of excretion is taken as the time of the previous bowel action. Because of the more rapid transit
Fig. 1a. Illustrates the transit of the isotope capsule through the colon in 40 hours in a normal subject.

Fig. 1b. Illustrates the transit of the isotope capsule through the colon in 264 hours in a constipated subject. The capsule took approximately 96 hours to pass the rectosigmoid and was in the rectum at 248 hours.

through the bowel in patients with diarrhoea, more frequent readings are required.

It was decided to compare the transit time of radio-opaque markers (2) with the transit time of the isotope capsule both in normal subjects and in patients with diarrhoea and constipation. When comparison was being made with radio-opaque markers, stools were collected separately in plastic bags and labelled with the date and time of collection. Collection was continued until at least 80 per cent (in practice usually over 90 per cent) of the radio-opaque markers as well as the isotope capsule were recovered. The presence of the isotope capsule was easily determined by scanning the stools with the isotope monitor.

The specific gravity of the radio-opaque markers is 1.19, which is approximately the specific gravity of gut contents. Because Hoelzel (3) found that the transit time of solid objects varied with their specific gravity, it was decided to test the transit time of isotope capsules of different specific gravities varied by the addition or removal of lead shot. Thirty isotope capsules were divided into three groups of 10 with specific gravities of 1.35, 1.1, and 0.93, and were taken with breakfast along with 40 radio-opaque markers by 30 normal subjects.

RESULTS

Specific gravity. The results (Fig. 2) for a comparison of the transit time of a capsule of specific gravity 1.1 with the transit time of radio-opaque markers fall about a line the regression coefficient of which is 0.95. The results for the transit time of a capsule of specific gravity 1.35 compared with the transit time of radio-opaque markers show a regression coefficient of 0.59 (Fig. 2). For the transit time of an isotope capsule of specific gravity...
compared with the transit time of radio-opaque markers, the results show a linear distribution of regression coefficient 0.84 (Fig. 2). There is thus a good correlation between the transit time of radio-opaque markers and the transit time of a capsule of specific gravity 1.1 but an inferior one for the other two capsules. The regression lines imply that capsules of specific gravity 1.35 and 0.93 travel faster, relative to the radio-opaque markers, than a capsule of specific gravity 1.1.

When a capsule of physiological specific gravity (1.1) was used to measure total gastrointestinal transit time, 81.8 ± 5.3 per cent of the radio-opaque markers were passed in equivalent time. For the capsule of specific gravity 1.35, 72.3 ± 7.8 per cent of the radio-opaque markers, and for the capsule of specific gravity 0.93, 62.5 ± 8 per cent of the radio-opaque markers were excreted in equivalent time.

**Constipation and diarrhoea.** In five elderly patients with constipation (age 71 to 81 years) the transit time of the radio-opaque markers was compared with the transit time of the isotope capsule of specific gravity 1.1. The results are plotted on Fig. 3 and fall about a line the regression coefficient of which is 0.99. The high degree of correlation between the two methods thus confirms that the isotope capsule method is as reliable as the radio-opaque markers' method in determining total gastrointestinal transit time in constipated patients.

In five patients with diarrhoea (ileal resection, ulcerative colitis, Crohn's disease, post-vagotomy diarrhoea, and episodic diarrhoea) the transit time of the radio-opaque markers was compared with the transit time of the isotope capsule of specific gravity 1.1. The results are plotted on Fig. 4. The correlation between the two methods in diarrhoea was less (regression coefficient 0.58) than in constipated and in normal subjects.

**Differential colonic transit time.** Using an isotope capsule of specific gravity 1.1 in 10 normal subjects and 5 subjects with constipation, a capsule taken at 9 a.m. had always reached the right iliac fossa by 5 p.m. of the same day, i.e. within 8 hours. The colonic transit time in normal subjects and in constipation was therefore the total gastrointestinal transit time minus 8 hours. In 10 normal subjects the estimated colonic transit time ranged between 16 and 88 hours (mean 23 hours ± 8 hours). In 5 constipated subjects the estimated colonic transit time varied between 92 and 281 hours (mean 187 ± 85 hours). When the colonic transit time was measured directly, commencing from the time that the capsule was first located in the right iliac fossa to its time of expulsion, the results were comparable to those determined indirectly: 10 normal subjects had an average colonic transit time of 25 ± 8 hours and constipated subjects had an average colonic transit time of 192 ± 92 hours. In the
5 constipated subjects, one example of which is shown in Fig. 1b, the time taken to pass the hepatic flexure averaged 24 hours, 78 hours to pass the splenic flexure, and a further 82 hours to pass the rectosigmoid. This was in contrast to 5 normals, one example of which is shown in Fig. 1a, in whom the capsule took an average of 10 hours to pass the splenic flexure, and 20 hours to pass the rectosigmoid.

DISCUSSION

The advantages of using an isotope capsule to measure gastrointestinal transit time are considerable. The technique is simple, it can be applied as a ward test, the equipment required is inexpensive, and stool collections or repeated x-rays are not required. Our results show (Fig. 2) that an isotope capsule of specific gravity 1.1 is as reliable as radio-opaque markers when used to measure total gastrointestinal transit time not only in normal subjects but also in constipation.

The rate of transit of the capsule relative to the markers is increased when its specific gravity is increased or decreased within narrow limits. Hoelzel (3) found that the transit of solid particles slowed when their specific gravity was increased beyond the range of our experiments, from between 1 and 1.5 to 2.6. It is possible that the isotope capsule of specific gravity 1.1 and the radio-opaque markers, both being of similar specific gravity to the gut contents, are suspended in equilibrium with those contents and are propelled at a similar rate. When, however, a slightly heavier or a lighter capsule is used, it could separate from the gut contents and take up a position close to the bowel wall and thus be more effectively propelled and more rapidly excreted. These observations raise the possibility of a differential rate of transit of solid particles of differing specific gravity in the gastrointestinal tract. They offer a part explanation of the mode of action of agents such as bran, which is known to alter intestinal transit rate by adding to the weight of the stools (1).

The correlation between the radio-opaque markers and the isotope capsule was maintained in constipated subjects. There was agreement between directly recorded colonic transit and indirect estimates of transit in the large bowel arrived at by taking the total transit time and subtracting the small bowel transit time. Direct recording illustrates important qualitative 'regional' differences in the transit through the various sectors of the large bowel. We have confirmed the finding of Waller (5) that in constipation colonic transit is slow, with a delay in the region of the splenic flexure as well as a considerable delay in the rectosigmoid (Fig. 1b). If the rectosigmoid area acts as a barrier to the expulsion of faeces in the normal subject, this effect is apparently increased by an additional barrier to propulsion at the splenic flexure in constipation.

In diarrhoea the capsule was excreted more rapidly than the markers. The total transit time of 4½ hours observed in one of our patients is difficult to reconcile with the report (5) that small intestinal transit time is not abnormal in diarrhoea. Because of rapid transit through the entire alimentary tract in diarrhoea (less than 14 hours in 3 cases), it has not been possible to measure accurately the large bowel transit time by this method.

ACKNOWLEDGEMENTS

This study was done during the tenure of Scottish Hospital Endowment Research Trust Grant No. 418.

We thank our colleagues in the Gastrointestinal Unit, Western General Hospital, particularly Dr. M. A. Eastwood, and also Dr. C. P. Lowther of the Royal Victoria Hospital for permission to study his patients, and Miss E. G. P. Drummond and Mrs. A. Jenkinson for their valuable assistance.

REFERENCES

3. Hoelzel, F. Amer. J. Physiol. 1930, 92, 466-497.
Bile acids and colonic motility in the rabbit and the human

Part 1 The rabbit

W. O. KIRWAN, A. N. SMITH, W. D. MITCHELL, J. DIANE FALCONER, AND M. A. EASTWOOD

From the Department of Clinical Surgery and Wolfson Gastrointestinal Laboratories, Western General Hospital and University of Edinburgh

SUMMARY Colonic motor activity was initiated by infusions of bile salts into the caecum or rectum of the anaesthetized rabbit. Primary bile acids were examined proximally and distally in the colon and elicited marked motor responses. Since dihydroxy bile acids are known to be potent inhibitors of electrolyte and water absorption in the colon, the secondary bile acid deoxycholic acid, the dihydroxy compound most related to cholic acid which is the main bile acid in the rabbit, was examined distally and was also active, but to a lesser extent than cholic acid conjugates in this species. In man, a relationship was found between the faecal bile acid excretion and colonic motility: the introduction of bile acids directly into the human sigmoid colon and rectum also stimulated colonic motility. In man, the dihydroxy compound chenodeoxycholic acid was slightly more active than conjugates of cholic acid.

Reports on the motor action of bile salts on the gastrointestinal tract have been conflicting. Inhibition of the contractility of strips of intestinal smooth muscle has been reported (D’Errico, 1910; Boulet, 1921; Schwartz and Magerl, 1924). In vivo experiments indicate that bile salts may stimulate motility (Horrall, 1938; Haney et al., 1939) and the introduction of bile into the colon and rectum results in defaecation (Hollion and Nepper, 1907; Schüpbach, 1908). However, the purity must nowadays be questioned of bile salt preparations which were formerly precipitated or crystallized from bile with other biliary constituents present as contaminants. Since these were the ones used in the experiments before modern methods of preparation, it was decided to reinvestigate the effect of some bile acids, in the rabbit.

Cholic acid was examined for its action on the proximal colon, since it is the principal primary bile acid present at that site, and also because it is known to have a modest effect on water and electrolyte reabsorption; any motor effect would be more clearly shown to be independent of this action, and attributable to true motor stimulation of the bowel, more so if precipitate defaecation or diarrhoea were also produced. In the rabbit, the principal faecal or secondary bile acid is deoxycholic acid, derived from cholic acid and conjugated with glycine. The effects of cholic acid were therefore contrasted with deoxycholate, but the taurocholate conjugate was used more frequently than the glycocholate because of its greater solubility.

Methods

The animals used were Edinburgh University Bush strain rabbits, 4 to 6 months old, weighing between 2·5 and 3 kg. They were fed on rabbit pellets, were free of disease, and were fasted for a period of 12 hours preceding each experiment.

The bile acid conjugates used were obtained from the Maybridge Chemical Company, Tintagel, Cornwall, and their purity was at least 90% as measured by gas liquid chromatography.

Three types of animal experiments were performed.

ACUTE EXPERIMENT

The abdomen was opened under general anaesthesia (nitrous oxide, oxygen, halothane) and the appendix cannulated. A pressure recording tube was passed...
per rectum and motility recorded 15 cm from the sphincter. Basal motility was recorded for one hour. At the end of this period 50 ml glyco- or tauro-cholic acid, dissolved in distilled water, was infused into the caecum over five minutes. Motility was measured by the method described by Smith et al. (1971) and the results expressed as a motility index. A basal motility index was calculated from the 15 minutes of maximum motility in the 30 minutes before infusion and a post-infusion motility index was calculated from the 15 minutes of maximum motility after infusion. In five acute experiments indigo carmine dye was added to the infused bile acid solution. The animals were killed at the end of the recording period.

In some experiments the rabbits were repeatedly used, thus serving as their own control and minimizing within-subject differences. In this group a Portex intravenous cannula, implanted under general anaesthesia through the rabbit's abdominal wall, was inserted into the appendix which was sutured to the peritoneum of the abdominal wall. The proximal end was buried under the skin. After a two week interval, when the animal had recovered from the operation, infusion experiments were performed by the mere puncture of the skin with a needle. Motility was recorded under general anaesthesia as in the acute experiments. A basal motility index was calculated as described above.

Motility indices were calculated for the four 15 minute periods following the start of infusion. The animals were allowed to recover after each experiment and were used not more than 10 times. Liver function tests were repeated after each experiment. At the end of the series of experiments the histology of the liver, appendix, and colon was examined.

**INTRODUCTION OF BILE SALTS INTO THE SIGMOID**

The animal was anaesthetized as before and the pressure recording tube passed rectally into the large intestine to 15 cm. Basal motility was recorded and calculated as in the previous experiment. Five millilitres of the test solutions (glyco- or tauro-cholic acid and deoxycholic acid) were infused through the pressure recording tube into the sigmoid at 15 cm. The post-infusion motility was calculated from the 15 minutes of maximum activity during the 30 minutes after infusion.

**DETERMINATION OF CHARACTERISTICS OF RABBIT BOWEL CONTENT**

The gastrointestinal tract was removed from five fasted rabbits and the quantity, pH, osmolality, and bile acid concentration of its contents measured in order to establish baseline values for the rabbit.

**Results**

**RABBIT BOWEL CONTENT**
The results are set out in Table 1.

**INTRODUCTION OF BILE SALTS INTO CAECUM**

1. **Single experiments**

In five single experiments where indigo carmine dye was added to the infused bile acid the colour was confined to the proximal

<table>
<thead>
<tr>
<th>Weight (g)</th>
<th>pH</th>
<th>Osmolality (m. mol/kg)</th>
<th>Bile acid concentration (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Caecum</td>
<td>Ileum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>936 ± 37</td>
<td>2.2 ± 0.44</td>
</tr>
<tr>
<td>Caecal contents</td>
<td>Ileal contents</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1 (Part 1) Characteristics of ileal and caecal content of five rabbits (mean ± SD)

**Table 2 (Part 1) Response to different concentrations of bile acids and control solutions in single experiments**

<table>
<thead>
<tr>
<th>Concentration (mM)</th>
<th>Pre-infusion (±SE)</th>
<th>Post-infusion (±SE)</th>
<th>Change in MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium taurocholate</td>
<td>2 4</td>
<td>871 ± 276</td>
<td>1531 ± 219</td>
</tr>
<tr>
<td></td>
<td>4 4</td>
<td>433 ± 151</td>
<td>1211 ± 394</td>
</tr>
<tr>
<td></td>
<td>8 8</td>
<td>385 ± 165</td>
<td>932 ± 428</td>
</tr>
<tr>
<td></td>
<td>16 16</td>
<td>195 ± 193</td>
<td>373 ± 209</td>
</tr>
<tr>
<td></td>
<td>3 3</td>
<td>23 ± 13</td>
<td>397 ± 147</td>
</tr>
<tr>
<td>Sodium glycocholate</td>
<td>24 24</td>
<td>186 ± 73</td>
<td>484 ± 124</td>
</tr>
<tr>
<td>Distilled water</td>
<td>6</td>
<td>867 ± 230</td>
<td>819 ± 281</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>0.9 g/100 ml 7</td>
<td>100 ± 38</td>
<td>165 ± 159</td>
</tr>
</tbody>
</table>

*MI: motility index*
colon at the end of the experiment. This experiment was performed on 34 animals (23 bile acid and 11 control solutions) using solutions of bile acids (sodium taurocholate (2mM to 16mM) and sodium glycocholate (8mM to 24mM)). It is possible to group the taurine and glycine salts together as their effect was similar in equivalent concentration. The results are set out in Table 2. All the concentrations of bile acid conjugates infused stimulated colonic motility, whereas water and sodium chloride in the same volume had no such effect. Only in the 8mM concentration of sodium taurocholate did the motility response fail to reach statistical significance. When the 23 rabbits, of this experiment, were considered as a group, there was a statistically significant difference between the pre-infusion motility index (501 ± 100) and the post-infusion motility index (1005 ± 139) (p < 0.005). The osmolality of the bile salt in solution was 40 mmol. Since the osmolality of the caecal contents (containing bile) was 466 ± 74, equivalent concentrations of bile salts but of osmolality of less than 40 and of 466 (increased with NaCl), were compared and gave similar responses. The maximum motility response occurred between 30 and 45 minutes after infusion. The relationship between the basal motility and the percentage change in motility after bile acid infusion is plotted on Fig. 1.

2. Repeated experiments The response to control solutions and cholic acid solutions (two each of 1mM, 3mM, and 6mM sodium glycocholate) in the chronic experiments is illustrated in Fig. 2. Bile acid solutions caused an increase in motility maximal at 30 to 45 minutes, whereas control solutions had a slight inhibitory effect, again maximal at 30 to 45 minutes. There was a statistically significant difference (p < 0.01) between the effect of bile acid and control solutions in the 30 to 45 minute period.

As in the single experiment it was established, using dye, that the infused fluid remained confined to the proximal colon and at the end of the tests the histology of the liver, appendix, and caecum was found to be normal. The serum lactic dehydrogenase was unchanged following the repeated anaesthesia (179 I.U./l before; 134 I.U./l after); the SGOT also remained unchanged (6 I.U./l before; 6 I.U./l after).

3. Introduction of bile acids into sigmoid colon The colonic motility response after infusion of various concentrations of sodium glycocholate (1mM to 30mM) and sodium deoxycholate (3mM to 24mM) into the sigmoid colon relates to the concentration of bile acid injected (Fig. 3). The effect for each compound is different, sodium glycocholate being more active in eliciting motility effects. Defaecation resulted from concentrations greater than 15mM. The change in motility occurred within 10 to 15 minutes of the infusion and was therefore much more prompt than with bile salts given into the caecum. Control experiments with water caused no
Bile acids and colonic motility in the rabbit and the human

Fig. 2 (Part 1) Increments of motility after bile acid infusion (maximal at 30-45 minutes) and the inhibition of motility by control solutions (again maximal at 30-45 minutes).

Fig. 3 (Part 1) Correlation between the change in motility and the concentration of primary (as sodium glycodeoxycholate) and secondary (as sodium deoxycholate) 5 ml bile acids infused into the sigmoid at 15 cm.

Discussion

The bile acid which is the end product of cholesterol catabolism in the rabbit is cholic acid, conjugated with glycine (Haslewood, 1968); there is virtually no chenodeoxycholic acid in these animals. Our studies were therefore confined to cholic acid and the secondary bile acid deoxycholic acid which, in the rabbit, is the principal bile acid present in the faeces. It is known from other animal and human experiments that dihydroxy bile acids—namely, chenodeoxycholic acid and deoxycholic acid—are potent inhibitors of sodium and water reabsorption from the colon (Mekhjian and Phillips, 1970; Mekhjian et al., 1968, 1971); hence their association with watery diarrhoea. But the diarrhoeal effect of bile acids could independently be exerted on the motor function of the gut. It seemed necessary therefore to examine the parent cholic acid since it is
present in the proximal gut, with modest effects on sodium and water reabsorption; deoxycholic acid was also examined since it is the predominant compound in the distal colon and, as a dihydroxy compound, might be expected to have contrasting actions with cholic acid on salt and water reabsorption. In preliminary experiments, taurocholate behaved as glycocholate so that, despite the inappropriateness to the species, the biologically equivalent taurine salts were used because of greater water solubility leading to greater ease of experimental handling.

Our results show that there was a statistically significant increase in sigmoid colonic motility after the infusion of conjugates of primary bile acids into the caecum (*p < 0.005*). This motility response was not likely to be due to the infused bile acids advancing directly along the lumen to stimulate the sigmoid directly as dye infusion showed that the bolus remained in the right side of the colon throughout the experiment. Similarly volume alone or osmolality were not responsible: the osmolality of the bile salt solution was <40 mmol in contrast with distilled water (0) and saline (275); neither of the latter had stimulating effects.

The experiment involving the indwelling cannula was developed to allow repeated experiments and to eliminate inter-animal variation. It is interesting that the maximal response was obtained after the same interval (30 to 45 minutes) as in the single experiment. The control solutions (both saline and water) exerted an inhibitory effect which was most marked at the same time interval as that observed after maximum stimulation by bile acid solutions. The interval before the response is recorded suggests a response beginning in the caecum and propagated distally. The delay in the motility response could also be due to the secondary release by bile acids of intermediary factors which themselves stimulate the colon.

In the acute experiments, there appears to be an exponential relationship between the basal motility and the percentage change in motility in response to bile acid solutions. Animals with a high basal motility had a poor motility response to the injection of bile acids, while animals with a low basal motility had a high motility response. The possibility exists that the high basal motility found in some animals might be accounted for by the presence in the caecum, before the experiment, of a high concentration of bile acids.

The response of the sigmoid colon to direct contact with bile acids occurred at 10 minutes. In these experiments, there was a high degree of correlation between the response of the sigmoid colon and the concentration of the bile acids instilled, the effect being greater with primary bile acids than secondary ones. Since the secondary ones mainly reside in the distal colon, there would be little spontaneous tendency for motility to be stimulated by bile in the contents of the lumen at this level. But should primary bile acids for any reason predominate, then bile might begin to stimulate the gut via its constituent bile acids. In the rabbit, the dihydroxy compound most appropriate to cholic acid, deoxycholate, was less active than conjugates of this, the main bile acid of the rabbit; whereas in man the dihydroxy compound, chenodeoxycholic acid, has been principally associated with cholkhreotic enteropathy (Mitchell et al., 1973).

Although there is a dose-response relationship between bile acid concentration and change in the motility index with infusion of bile acids into the sigmoid colon, this relationship was not found after caecal instillation; this suggests a direct effect on the sigmoid colon when locally instilled, but perhaps only an indirect sigmoid motor response when the caecum is perfused. When abnormally high concentrations of bile acids were instilled (15mM to 30mM), the colon responded with abnormally high motor activity and defaecation resulted.

This study suggests that intraluminal bile acid conjugates can affect colonic motility. For this reason, endogenous and exogenous bile acids were examined for motor activity in humans (Part 2).

**Part 2 The human**

Bile flowing down the intestinal tract from the duodenum onwards has been shown to stimulate intestinal motility (Horrall, 1938). The availability of modern synthetic preparations of bile acids renders it possible to compare possible motor actions of primary and secondary bile acids. It is known that chenodeoxycholic acid is principally responsible for the watery diarrhoea of ileal resection (Mitchell et al., 1973). It is not known whether this effect relates to changes in water and salt excretion from the colon or to an alteration of its segmental motor activity.

As in the rabbit experiments (Part 1), the effect of bile acid on motility was studied by a somewhat indirect method.

A group of diarrhoeal patients with enhanced
faecal bile acid excretion were examined, all of whom had solely primary bile acids in the stool—that is, chenodeoxycholic and cholic acid (Mitchell and Eastwood, 1972).

A control group of diarrhoeal patients with normal faecal bile acid excretion was also studied; the bile acids in this situation were entirely secondary—that is, deoxycholic and lithocholic acid.

In a further group of patients the primary bile acids, chenodeoxycholic acid and cholic acid, were instilled into the sigmoid colon.

Methods

Group 1 consisted of seven patients with a daily bile acid excretion in excess of 1000 mg. Six of these patients had post-ileal resection and one had post-vagotomy diarrhoea. The second group consisted of five patients with a daily faecal bile acid excretion of less than 1000 mg. Two of these patients had post-ileal resection diarrhoea, one had Crohn's disease without resection, and two had post-vagotomy diarrhoea. Details of group 1 and group 2 patients are shown in Table 1. Group 3 consisted of patients who were referred for routine colonic motility studies as part of their investigation; for undiagnosed abdominal pain, because of the irritable colon syndrome, or diverticular disease. Seven were given taurocholic acid and seven sodium chenodeoxycholic acid in aqueous solution directly into the sigmoid colon. Daily faecal bile acid excretion was not measured in these seven patients.

Colon motility studies

Colonic motility studies were performed on all patients in groups 1 and 2 during basal, post food and post prostigmine periods (Smith et al., 1971). In the group 3 patients, however, the post food period was omitted and in its place 50 ml of a control solution or a bile acid conjugate solution was infused into the sigmoid at 25 cm over five minutes and the motility thereafter recorded for 30 minutes.

The results were expressed as a colonic motility index.

Faecal bile acid estimation

Stools were collected for a period of at least three days and daily faecal bile acid excretion was determined using the method of Evrard and Janssen (1968) as modified by Mitchell et al. (1973).

Results

Groups 1 and 2

The basal, post food and post prostigmine motility indices and the daily faecal bile acid and faecal fat results of patients in groups 1 and 2 are shown in

Table 1 (Part 2) Clinical details of group 1 and 2 patients in present series

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Clinical details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I. B.</td>
<td>Resection of 60 cm of terminal ileum for Crohn's disease</td>
</tr>
<tr>
<td>2</td>
<td>J. G.</td>
<td>Extensive resection removing multiple coils of terminal ileum and 20 cm of right colon</td>
</tr>
<tr>
<td>3</td>
<td>J. M.</td>
<td>Mesenteric infarct. Resection of 90 cm of terminal ileum</td>
</tr>
<tr>
<td>4</td>
<td>M. B.</td>
<td>Resection of 40 cm of terminal ileum and 12 cm of right colon for Crohn's disease</td>
</tr>
<tr>
<td>5</td>
<td>T. I.</td>
<td>Resection of 60 cm of terminal ileum for inflammatory bowel disease of uncertain pathology</td>
</tr>
<tr>
<td>6</td>
<td>J. McL.</td>
<td>Resection of 70 cm of terminal ileum and 25 cm of colon for Crohn's disease</td>
</tr>
<tr>
<td>7</td>
<td>T. S.</td>
<td>Vagotomy and pyloroplasty; post-vagotomy diarrhoea</td>
</tr>
<tr>
<td>8</td>
<td>A. McA.</td>
<td>Resection of 75 cm of terminal ileum for Crohn's disease</td>
</tr>
<tr>
<td>9</td>
<td>C. W.</td>
<td>Massive ileal strangulation and resection. Jejuno colic anastomosis</td>
</tr>
<tr>
<td>10</td>
<td>A. M.</td>
<td>Vagotomy and pyloroplasty; post-vagotomy diarrhoea</td>
</tr>
<tr>
<td>11</td>
<td>L. H.</td>
<td>Vagotomy and pyloroplasty; post-vagotomy diarrhoea</td>
</tr>
<tr>
<td>12</td>
<td>M. P.</td>
<td>Crohn's disease. No resection</td>
</tr>
</tbody>
</table>

Table 2 (Part 2) Patients with daily bile acid excretion greater than 1000 mg: colonic motility indices and daily bile acid and fat excretion (group 1)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Bile acids* (mg/day)</th>
<th>Faecal fat (g/day)</th>
<th>Motility indices</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. B.</td>
<td>2876</td>
<td>7.9</td>
<td>1174</td>
</tr>
<tr>
<td>J. G.</td>
<td>4251</td>
<td>9.9</td>
<td>573</td>
</tr>
<tr>
<td>J. M.</td>
<td>3340</td>
<td>10.0</td>
<td>305</td>
</tr>
<tr>
<td>M. B.</td>
<td>2091</td>
<td>28.0</td>
<td>312</td>
</tr>
<tr>
<td>J. McL.</td>
<td>1675</td>
<td>26.3</td>
<td>1415</td>
</tr>
<tr>
<td>T. I.</td>
<td>1138</td>
<td>7.0</td>
<td>724</td>
</tr>
<tr>
<td>T. S.</td>
<td>2310</td>
<td>5.5</td>
<td>643 ± 140</td>
</tr>
</tbody>
</table>

Mean ± SE 2528 ± 972 13.5 ± 3.4

Table 3 (Part 2) Patients with daily bile acid excretion greater than 1000 mg: colonic motility indices and daily bile acid and fat excretion (group 1)

*Only primary bile acids
Patients with daily bile acid excretion less than 1000 mg: colonic motility indices and daily bile acid and fat excretion (group 2)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Bile acids* (mg/day)</th>
<th>Faecal fat (g/day)</th>
<th>Motility indices</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. McA.</td>
<td>572</td>
<td>2.9</td>
<td>-</td>
</tr>
<tr>
<td>C. W.</td>
<td>664</td>
<td>13.3</td>
<td>-</td>
</tr>
<tr>
<td>A. M.</td>
<td>311</td>
<td>18.0</td>
<td>-</td>
</tr>
<tr>
<td>L. H.</td>
<td>723</td>
<td>7.1</td>
<td>-</td>
</tr>
<tr>
<td>M. P.</td>
<td>326</td>
<td>0.7</td>
<td>-</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>519 ± 86</td>
<td>8.4 ± 3.2</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3 (Part 2) Patients with daily bile acid excretion less than 1000 mg: colonic motility indices and daily bile acid and fat excretion (group 2)

*Soledy secondary bile acids

Tables 2 and 3 respectively. There was a significantly higher motility index after prostigmine in group 1 (3581 ± 525) compared with group 2 (1442 ± 262) (p < 0.005) and to a lesser degree after food (1463 ± 140, group 1: 655 ± 178, group 2, p < 0.05).

Although in the basal period the motility index was higher in group 1, this difference was not statistically significant.

Correlation between bile acid excretion and motility index The regression lines between the daily bile acid excretion and the basal, post food and post prostigmine motility indices are plotted in the Figure. The correlation was statistically significant in the post prostigmine period (p < 0.01) and in the post food period (p < 0.05), but not in the basal period. There was no significant correlation between the faecal fat excretion and colonic motility in any of the three periods.

GROUP 3
Instillation of bile acids into the sigmoid The results of infusing solutions of differing concentrations of the bile acids, chenodeoxycholic acid and taurocholic acid, into the sigmoid of 14 patients are shown in Table 4. These solutions caused a significant increase in colonic motility.
Bile acids and colonic motility in the rabbit and the human

<table>
<thead>
<tr>
<th>Solution</th>
<th>Osmol. (mM)</th>
<th>MI Before injection</th>
<th>MI After injection</th>
<th>Change in MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sod. tauro. chol.</td>
<td>2.5</td>
<td>1030 (n = 2)</td>
<td>1366 (n = 2)</td>
<td>+ 336</td>
</tr>
<tr>
<td>Cheno. deoxy.</td>
<td>2.5</td>
<td>820</td>
<td>1266</td>
<td>+ 446*</td>
</tr>
<tr>
<td>Sod. tauro. chol.</td>
<td>5</td>
<td>973 (n = 2)</td>
<td>1274 (n = 2)</td>
<td>+ 301</td>
</tr>
<tr>
<td>Cheno. deoxy.</td>
<td>5</td>
<td>219 (n = 2)</td>
<td>1190 (n = 2)</td>
<td>+ 971</td>
</tr>
<tr>
<td>Sod. tauro. chol.</td>
<td>10</td>
<td>619</td>
<td>1581</td>
<td>+ 962</td>
</tr>
<tr>
<td>Cheno. deoxy.</td>
<td>10</td>
<td>806</td>
<td>2014</td>
<td>+ 1205*</td>
</tr>
<tr>
<td>Sod. tauro. chol.</td>
<td>15</td>
<td>619</td>
<td>1467</td>
<td>+ 846</td>
</tr>
<tr>
<td>Cheno. deoxy.</td>
<td>15</td>
<td>1003</td>
<td>2275</td>
<td>+ 1272</td>
</tr>
<tr>
<td>Sod. tauro. chol.</td>
<td>20</td>
<td>947</td>
<td>1346</td>
<td>+ 399</td>
</tr>
<tr>
<td>Cheno. deoxy.</td>
<td>20</td>
<td>259 (n = 2)</td>
<td>845 (n = 2)</td>
<td>+ 586</td>
</tr>
<tr>
<td>Distilled water</td>
<td></td>
<td>677</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 4 (Part 2)  Motility response to injection of bile acids into sigmoid

*Estimated from part of record; defaecation produced after five to 10 minutes.

Discussion

Diarrhoea patients with a primary bile acid excretion (group 1 patients) had a significantly greater motility index (p < 0.005) than patients with diarrhoea and secondary bile acid excretion only (group 2 patients). The finding that diarrhoea patients with a high faecal bile acid excretion had a significantly higher colonic motility index in the post food and post prostigmine periods than patients with a much lower faecal bile acid excretion suggests that bile acids may be a factor in the production of this abnormal motility. There was a significant correlation (Figure) between motility caused by food and prostigmine and the daily faecal bile acid excretion. The motor action is further supported by the results obtained when solutions of taurocholic acid and chenodeoxycholic acid were infused into the sigmoid colon (Table 4). In view of these findings, it seems possible that abnormally high quantities of bile acids, mainly primary ones, in the colon cause diarrhoea not only by inhibiting the absorption of water and electrolytes but also by eliciting colonic motor activity.

These observations in the human subject are not exactly the same as in the rabbit experiments (Part 1). Whereas, in the rabbit, bile acids were infused into the caecum, in the human observations we have resorted to measurement of the faecal bile acid content as a means of determining the activity of the compounds present in the colon and passing through it. The association of diarrhoea with a raised motility and raised bile acid excretion, in many instances after an ileal resection, may be a special case and is not necessarily the same as diarrhoea studied by Connell (1962) where the motility index was low. Our second group with diarrhoea had both a low motility index and quantitatively and qualitatively a normal bile acid excretion and these cases are perhaps more akin to those studied by Connell (1962). The bile acids which could be most of all implicated as raising the motility—for example in group 1—were chenodeoxycholic acid and cholic acid. The motor effects found were marginally higher for the dihydroxy bile acid, chenodeoxycholic, than for cholic acid, when these compounds were introduced into the distal bowel, which contrasts with the situation in the rabbit where the most appropriate dihydroxy compound was less active than a cholic acid conjugate.

The motor effect might thus appear to be more related to the primary or secondary status of the bile acid than to the number of hydroxyl groups. The group 1 patients with primary bile acid excretion had a higher motility index than the group 2 patients with secondary bile acids. These two groups differed in other respects. Firstly, the group 1 patients had a higher total bile acid excretion than the group 2 patients, and, secondly, the group 1 patients had solely primary bile acids in their stool, whereas the group 2 patients had solely secondary bile acids. The conclusion that the difference in motility index is related to total bile acid excretion is supported by the finding of a significant correlation between these two variables (Fig. 1; Part 2). The secretory effect of bile acids is related to the number of hydroxyl groups rather than to the division into primary and secondary bile acids, dihydroxy bile acids producing...
the more marked secretory effect. The precise site and mechanism of the motility effect of bile acids however, remains to be elucidated.

This work was done during the tenure of Scottish Hospitals Endowment Research Trust Grant No. 418, to Mr. A. N. Smith. We are indebted to Miss E. G. P. Drummond for skilled technical assistance.

References


Sterculia bulk-forming agent with smooth-muscle relaxant versus bran in diverticular disease

G S SRIVASTAVA, A N SMITH, N S PAINTER

Summary

Sterculia with and without a smooth-muscle relaxant (alverine citrate) had similar beneficial effects on constipation and reduced the transit times in diverticular disease. Intracolonic pressure, however, varied with the preparation used. Though both preparations relieved the symptoms of diverticular disease, the one containing alverine citrate was more effective. Part of the mode of action of bran may be to relax the smooth muscle of the gut, since its actions were more comparable to those of sterculia plus alverine citrate than to those of sterculia alone.

Introduction

Colonic diverticula are caused by high pressures produced by the segmenting action of the colonic muscle. Segmentation not only propels the colon's contents but halts material moving through the lumen. Cineradiography combined with pressure recording shows that natural stimulation or stimulation by drugs produces in the diseased sigmoid an excessive number of waves of high intracolonic pressure. These high pressures favour the progression of established diverticulosis and are almost certainly responsible for the initial herniation of the colonic

Wolfson Gastro-Intestinal Laboratories, Western General Hospital, Edinburgh

G S SRIVASTAVA, BSc, MS, Lieutenant-Colonel, Indian Army, trainee gastrointestinal surgeon (now surgical specialist (gastroenterology), Army Hospital, Delhi Cantt, India)

University Department of Clinical Surgery, Western General Hospital, Edinburgh EH4 2XU

A N SMITH, MD, FRCSEd, reader in clinical surgery

Manor House Hospital, London NW11 7HX

N S PAINTER, FRCS, FACS, senior surgeon

COPYRIGHT © 1975. ALL RIGHTS OF REPRODUCTION OF THIS REPRINT ARE RESERVED IN ALL COUNTRIES OF THE WORLD

BMJ/564/76
mucosa. Extreme degrees of segmentation may cause intermittent occlusion of the lumen of the sigmoid and recurrent functional obstruction, which result in episodes of abdominal pain. In about two-thirds of patients this pain is not due to inflammatory diverticulitis, and most clinicians believe that the colic of painful diverticular disease is caused by strong contractions of the colonic muscle. Contractions of the colon have been correlated with episodes of severe abdominal pain in the “irritable bowel syndrome.” Hence the behaviour of the colonic muscle probably plays an important part in the genesis of diverticular disease and other colonic disorders.

The intraluminal pressure may be reduced in diverticular disease by adding cereal fibre to the diet in the form of millers’ bran, particularly when the fibre is coarsely ground. Not all patients, however, tolerate bran, and as the bulk-forming agent sterculia (Normacol) has been shown to relieve the symptoms of diverticular disease we decided to test two preparations of sterculia—one of sterculia alone and one containing a smooth-muscle relaxant—to see what effect they would have on intracolonic pressures and transit times and on the symptoms of proved diverticular disease.

Materials and methods

The two preparations of sterculia—here designated A (sterculia alone) and B (sterculia plus the smooth-muscle relaxant alverine citrate)—were tested in two groups of 10 patients suffering from symptomatic diverticular disease without organic stenosis. The preparations were made similar in taste and appearance and were given in comparable dosage—namely, 10 g daily. Each was given for one month. Their identities were unknown both to the patients and to the consultant who assessed the clinical effects. Colonic motility and transit times were measured and the patients interviewed before and at the end of each month of treatment. After each course the patients were given no medication for one month, partly to see how long the beneficial effects lasted, and partly to estimate the severity of symptoms when these returned. For comparison, all the patients were then given coarse bran for one month.

Pressure measurements—Motility was recorded with the use of a multilumen tube inserted into the distal colon. Pressure was measured before food (basal period), after food, and after intramuscular neostigmine 0.75-1.0 mg. The wave forms were given an x and y significance on an analogue-to-digital converter, from which a motility index was calculated. Changes in motility indices with the two preparations were compared by means of Student's t test.

Transit times—The patients swallowed 40 barium-impregnated pellets (Portex Limited), the transit time being calculated as the time taken for 32 (80%) of these to be passed.

Clinical assessment of effect on symptoms—Each patient filled in a progress sheet giving the main symptoms before treatment and showing the effects of sterculia at the end of one month. Symptoms were grouped under three main headings—constipation, pain, and other. Severity was graded by calculating a clinical score for each symptom group (table I), the maximum score possible being five for any group.
FIG 1—Colonic motor activity in basal period. Motility index is recorded before and after administration of preparations A and B.

FIG 2—Colonic motor activity after food. Motility index is recorded before and after administration of preparations A and B. Changes produced by the preparations were significantly different.

and thus 15 for all three. To assess pain or constipation patients were allowed to take medication once if needed and were graded according to their response to it.
TABLE II—Symptom scores before and after preparations A and B, and, one month later, scores before and after bran in the same patients

<table>
<thead>
<tr>
<th></th>
<th>Sterculia</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before*</td>
<td>After</td>
<td></td>
<td></td>
<td>Before*</td>
<td></td>
<td>After</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
<td></td>
<td>Formerly given A</td>
<td>Formerly given B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>50</td>
<td>3</td>
<td>9</td>
<td>56</td>
<td>10</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>46</td>
<td>24</td>
<td>9</td>
<td>36</td>
<td>12</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>25</td>
<td>29</td>
<td>13</td>
<td>20</td>
<td>8</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
<td>56</td>
<td>31</td>
<td>112</td>
<td>30</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted to score of 10 patients.

TABLE III—Numbers of patients in whom preparations A and B and bran (in the same patients) reduced constipation and pain to trivial levels (scores less than 2)

<table>
<thead>
<tr>
<th>Score</th>
<th></th>
<th>Constipation</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Pain</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sterculia</td>
<td></td>
<td>Bran</td>
<td></td>
<td></td>
<td>Sterculia</td>
<td></td>
<td>Bran</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
<td>Formerly given A</td>
<td>Formerly given B</td>
<td></td>
<td>A</td>
<td>B</td>
<td>Formerly given A</td>
<td>Formerly given B</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>9</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
CLINICAL EFFECTS

A clinical score that reflected any change in the severity of the symptoms was derived in the 20 patients, as described above. The clinical score before treatment was halved to adjust it to 10 "notional" patients to compare with the 10 patients each receiving preparations A and B (table II). Before treatment the total clinical score was 121. This fell to 56 after preparation A and to 31 after preparation B. The "pretreatment" scores for constipation and pain were 50 and 46 respectively. These were reduced to 3 and 24 with preparation A, and to 9 and 9 with preparation B. "Other" symptoms—namely, the passage of blood and mucus, diarrhoea, and the excessive passage of flatus, together with sensations of flatulence and distension—accounted for a pretreatment clinical score of 25; this rose to 29 after preparation A but fell to 13 after preparation B. After one month without treatment the total clinical score returned to 112, which was near to the original value. After coarse bran the scores were closer to those obtained with preparation B than to those obtained with preparation A.

The numbers of returns for each score were also listed, as shown in table III. The number of times each compound reduced the symptoms of constipation or pain to a trivial level (less than 2) was compared with the number of times it failed to do so. For constipation, preparations A and B and bran were equally effective in reducing the score; for pain, however, both preparation B and bran were significantly more effective than preparation A (fourfold test: P < 0.005) in producing, more often, low scores.

Discussion

Preparation A contained 62% sterculia and was a simple bulk former, whereas preparation B contained the same proportion of sterculia with 0.5% alverine citrate, a smooth-muscle relaxant used to relieve "spastic colon" and dysmenorrhoea.12

Preparation A raised the mean intraluminal pressure in the resting sigmoid colon after it had been activated by food and neostigmine. By contrast, preparation B reduced the motility index basally, after food, and also after neostigmine. The difference between the effects of the two preparations reached greater statistical significance after food than after neurohumoral stimulation. The changes after preparation B were comparable to those that result from one month's treatment with bran7 and also to the pressure reduction after the use of coarse bran.8 Coarse bran was thought by Kirwan et al8 to absorb water more readily; it may dilute or remove an irritant that the antispasmodic in preparation B antagonises.

Two types of diverticular disease have been described. Some colons beset with diverticula are extremely active (spastic colon diverticulosis), and others that are fibrous due to previous inflammatory episodes are less able to contract and generate pressure. Possibly intraluminal pressure studies might enable the two types of diverticular disease to be separated, so that treatment might be given a more logical basis.13 Theoretically, preparation B should be the more effective in lessening the activity of the colonic muscle and hence should reduce the intracolonic
pressures, and our results support this contention. The average transit time of 86 hours in 10 patients with diverticular disease was reduced to 59 hours by preparation A and to 68 hours by preparation B. These transit times, however, are still longer than the 45 hours recorded for British vegetarians and patients adding millers' bran to their diets. Not surprisingly, preparation B, which reduces the motility of the colon, was slightly less effective in increasing the speed at which the bowel contents were propelled through the intestine.

Both preparations relieved constipation. Our results suggest that sterculia alone (preparation A) should be used in patients with diverticulosis who complain of constipation, while it would be better to give it coupled with a smooth-muscle relaxant (preparation B) to patients with “spastic” diverticulosis or painful diverticular disease. Relaxation of the segmental contraction rings widens the colonic lumen and facilitates the onward passage of the faecal stream, as was shown by cineradiography for pethidine by Painter et al.

When the clinical effects of the two preparations on pain, abdominal distension, flatulence, and episodes of diarrhoea were considered, preparation B was found to be the more beneficial and to compare more favourably than preparation A with the actions of coarse bran. This is not surprising if the colic of painful diverticular disease is attributed to contraction of the colonic muscle. Flatulence, abdominal fullness, and intermittent diarrhoea may also owe their origin to a disordered intestinal motility caused by a low-residue diet. The addition of alverine citrate to the bulk-forming sterculia was also found to be clinically effective in relieving this group of symptoms. Hence, this preparation may be used in the treatment of diverticular disease in patients who cannot tolerate millers' bran.

We are grateful to Norgine Limited for supplies of preparations A (Normacol Special) and B (Normacol Antispasmodic). This work was done during the tenure of Scottish Hospital Endowments Research Trust grant No 418 to Mr A N Smith. Lieutenant-Colonel G S Srivastava participated in this work while on two years' secondment to the UK from the Indian Army Medical Corps.

Requests for reprints should be sent to Dr A N Smith.

References
**Post Prandial Changes in Colonic Motility Related to Serum Gastrin Levels**

W. O. KIRWAN & A. N. SMITH

Dept. of Clinical Surgery and Wolfson Gastro-Intestinal Laboratories,
Western General Hospital and University of Edinburgh,
Edinburgh, Scotland


Colonic motor activity and serum gastrin levels were correlated during a basal period and after a meal in 16 subjects. Motor activity preceded the gastrin response. The motility index and the serum gastrin levels rose in parallel, but the motility fell before later showing a second rise. The frequency response showed the earliest change and since it preceded the gastrin rise may be neurogenic. This response was later 'extinguished' and replaced by one of waves of increasing amplitude; the sustained nature of this response fitted more closely the gastrin response.

**Key-words:** Colonic motility; motility index; post prandial; serum gastrin; wave amplitude; wave frequency.

W. O. Kirwan, M.D., Dept. of Clinical Surgery, Western General Hospital, Edinburgh, Scotland.

The increased intestinal activity which follows the intake of food was observed clinically by Macewen (12), radiologically by Hertz & Newton (9), and manometrically by Connell, Avery-Jones & Rowlands (3). Increase in motor activity along the entire length of the gastrointestinal tract results in increased colonic activity, which is often accompanied by a desire to defaecate. The phenomenon as a whole is referred to as the gastrocolic reflex. Although a neural mechanism is implied (6), the persistence of the phenomenon following destruction of the spinal cord (4) and vagotomy renders it unlikely that neural activity is its sole explanation. A humoral mechanism has therefore been sought as the explanation of residual activity after cord destruction.

It has been shown that gastrin or its analogues injected in pharmacological doses increase small bowel and colonic motility (1, 5, 7, 14). The persistence of the gastrocolic reflex, although modified following total gastrectomy (5) suggests that factors other than gastrin must be involved. It is still possible that gastrin may act as a mediator of post prandial activity, since gastrin-like activity has been isolated from the small intestine (10, 11).

The object of the present study was to examine the correlation of the motility response to food with the post prandial rise in serum gastrin.

**METHODS**

Colonic motility studies and serial serum gastrin estimations were performed simultaneously in 16 subjects.

*Colonic motility.* Using the method described by Smith, Giannakos & Clarke (13), sigmoid colonic motility was recorded during a basal half hour and for 90 minutes following the ingestion of a protein meal. The data were fed to an analogue to digital computer and the frequency of the waves and their amplitude derived. A motility index expressed the total motor activity from the product of the mean wave amplitude multiplied by the per cent activity time in periods of recording. It was
Table I. Serum gastrin response to a protein meal in 16 subjects. (Mean change above basal = 58±16; P<0.005)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Basal (Mean±S.E.)</th>
<th>After protein meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum gastrin (pg/ml)</td>
<td>58±11</td>
<td>58±12</td>
</tr>
</tbody>
</table>

calculated for the 10 minutes in a stable period (hereinafter called basal) preceding food and for each 10-minute period up to 90 minutes following food. Acceptable basal records were ones in which the motility index over 1 hour, i.e., for 6 successive 10-minute periods, had motility indices falling within the range of the mean ± the standard deviation for the laboratory; only the penultimate value for the 10-minute period before the application of the stimulus was chosen for comparison with post-stimulus values.

**Serum gastrin estimations.** Serum gastrin estimations were performed by the radioimmunoassay method of Yalow & Berson (15), as modified by Byrnes (2). Estimations were performed 10 minutes before feeding, at the commencement of feeding, and then 5, 10, 15, 30, 45, 60, and 90 minutes after a meal. The results were expressed as pg gastrin per ml of serum. The method of Yalow & Berson, as modified by Byrnes, measures the main gastrin fractions (34C, 17C, 13C) less likely the 40 amino acid sequences.

**RESULTS**

**a) Serum gastrin levels**

A basal level was determined for each individual by averaging the samples before eating taken at -10 and 0 minutes. Samples taken up to 90 minutes after eating are listed for 16 individuals in Table I (mean ± S.E.). The gastrin response curve to the meal (Fig. 1) is biphasic with an early and late peak of activity.

**b) Colonic motor activity**

The motility index in the 10-minute period prior to eating and for each 10-minute period up to 90 minutes after the meal was derived from the same 16 subjects (Mean ± S.E.) (Table II). The motility response curve also shows initial and late peaks of activity (Fig. 2).
c) Correlation of (a) and (b)

To examine the timing and the amount of the gastrin response in relationship to colonic motor activity, the first gastrin response to food (occurring 5 minutes after the meal) was made 100 per cent; all other results up to 90 minutes were scaled up from this. A figure representing motor activity at each comparable point in time was arrived at by averaging the motility index for each 10-minute period, in Table II, with the preceding or the succeeding one. Thus, for motor activity at 0 time the average was taken of the motility index in the periods -10 to 0 and 0 to +10; this figure was made 100 per cent and all the motility results scaled up or down from this, to give a motility value for each time at which a gastrin sample had been withdrawn. Gastrin and concomitant motility responses were then plotted on the same graph (Fig. 3).

The serum gastrin gave a response 5 minutes after the motility one began and thereafter climbed steeply and linearly to 80 per cent above basal at 20 minutes. This elevation was maintained at this level above basal for 35 minutes and then fell to 65 per cent at 50 minutes; thereafter there was a secondary rise to 92 per cent, this increase being reached at 90 minutes. In contrast, motility was already 30 per cent above basal by the beginning of the gastrin response, i.e. 5 minutes after the start of eating. The motility index rose in the next 5 minutes, till it was 85 per cent above basal. It then gradually fell to its lowest point (15 per cent above basal at 60 minutes) but later climbed to 60 per cent above basal values at 90 minutes.

d) Comparison of serum gastrin with changes in wave frequency and amplitude

The wave frequency (number of waves per 10-minute period) rose (Fig. 4) by 75 per cent during the first peak period of motor activity, i.e. during the first 10-minute period in Fig. 3, when the colonic motility index rose by 80 per cent. Though the wave frequency change was of the same magnitude as the colonic motility
index, it was not sustained; the colonic motility response lasted for 55 minutes, whereas the wave frequency one was almost over in 20 minutes (Fig. 4). The wave frequency response like the colonic motility index one preceded the gastrin response. The frequency response, after it had fallen, oscillated (Fig. 4) about a low level (mean ± 8 per cent above basal).

The average wave amplitude was the slowest parameter to change and only did so after the serum gastrin levels had risen. It took 20 minutes before there was a 45 per cent increase in the wave amplitude, a level which was however maintained for 40 minutes. There was a further rise to a level 65 per cent above basal between 70–80 minutes after the meal.

**DISCUSSION**

After the ingestion of food it is accepted that there is an invariable rise in both the serum gastrin and colonic motility. The first peak of motor activity was seen to be arrived at considerably sooner, in our 16 subjects, than the peak in serum gastrin level, when both were standardized on the same graph. Although the two peaks were arrived at separately, the motility index and the serum gastrin levels appeared to increase in parallel. The initial motility peak, which occurs 10 minutes before the peak in serum gastrin level, fits the accepted neurogenic component of gastrocolic motor activity after eating, which is mediated by the autonomic nervous system.

Following the initial brisk rise in serum gastrin, the gastrin level remains elevated approximately 90 per cent above the basal for at least 90 minutes. Colonic motor activity, however, behaves differently; it falls briskly from an initial peak, though remaining elevated at about 50 per cent above the basal for 4 minutes; the motility then falls to 20 per cent above the basal at 55 minutes but then shows a late climb to 60 per cent above the basal at 85 minutes. It would appear therefore that although the initial, proposed as neurogenic motility peak quickly disappears, there is a persisting fairly high level of motor activity which parallels the sustained serum gastrin levels. This observation suggests that the colonic motility remaining after the initial peak might be the result of the high level of serum gastrin. Following an initial brisk rise the wave frequency response falls to a low level (with 20 per cent of the basal level). During the motor activity the raised motility index therefore appears to be accounted for mainly increased wave amplitude. It is possible that a raised level of circulating serum gastrin reduces the frequency rate of colonic traction, so that each contraction is a more vigorous one. The frequency response, which its timing coincides with the presumed neurogenic phase of the gastrocolic response to a meal, appears to be 'extinguished' at the point...
which the high plateau levels of gastrin are first reached. This is also the point at which the wave amplitude change first reaches its plateau levels. It is also of interest that the late serum gastrin rise and the second increment in the wave amplitude response are in part coincidental. The sustained nature of the wave amplitude response more closely fits the gastrin response than do the other parameters; for example, the wave frequency response falls when the gastrin levels are still rising.

If humoral agents play a part in sustaining the high level of activity of colonic motility which constitutes the colonic response to a meal, and if there is a non-neurogenic component of this response, then it is likely that gastrin is only one of a group of agents active during this phase. Other peptide hormones are released from the alimentary tract by the intake of food, and several of these are known to stimulate the colon (8). As assay techniques are developed for each of the distinctive motor hormones of the upper gastrointestinal tract, it should be possible to determine the relative importance of each towards the colonic motility response to food.

ACKNOWLEDGEMENTS

We would like to acknowledge the assistance of Dr. A. J. B. Anderson, of the Medical Research Council Clinical and Population Cytophagenetics Unit, who gave us assistance with statistical calculation, and of Dr. Byrnes, who originally set up the plasma gastrin method in our laboratories.

We are indebted to support from the Scottish Hospitals Endowment Research Trust Grant No. 418. Requests for reprints to A.N.S.

REFERENCES


Received 25 June 1975
Accepted 26 August 1975
Fecal characteristics contrasted in the irritable bowel syndrome and diverticular disease¹,²


ABSTRACT A comparison has been made of the fecal characteristics in controls and patients with the irritable bowel syndrome and diverticular disease. No detectable difference was found in the fecal wet weight, dry weight, or total bile acid excretion in the four groups. A significant increase in the percentage of the water content of the stool was seen in the idiopathic diarrhea group with irritable bowel syndrome. Significantly less magnesium, potassium, and calcium was found in the stools of patients with diverticular disease and a similar trend was noted in patients with the spastic colon. These changes did not relate to the age of the patients. This suggests a common etiology for these disorders. The presence of increased water and primary bile acids in the feces of patients with idiopathic diarrhea suggests that this is a separate entity.

The irritable bowel syndrome and diverticular disease are in many ways similar in symptomatology and medical management. These similarities suggest a common etiology, possibly a deficiency of vegetable dietary fiber (1, 2). The irritable bowel syndrome occurs more frequently in a younger age group and may proceed to development of diverticular disease (3). Chaudhary and True-love (4) have classified patients with irritable bowel syndrome into two groups—spastic colon and idiopathic diarrhea.

This paper shows that measurements of fecal weight, water content, electrolytes, and bile acids show important similarities and differences between control subjects and patients with diverticular disease, spastic colon, and idiopathic diarrhea. The similar stool characteristics of spastic colon and of diverticular disease suggest a common etiology. Patients with the idiopathic diarrhea form of irritable bowel syndrome have different stool characteristics and possibly a different etiology.

Subjects and patients

The controls consisted of 11 healthy males, ages 22 to 36 years who ate their habitual diet, and led their normal life as medical practitioners. Fourteen patients with uncomplicated diverticular disease, demonstrated on barium enema, were studied (10 males and four females; ages 53 to 84 years). Seven patients (three males and four females; ages 23 to 58 years) with the spastic colon form of irritable bowel were studied, characterized by a history of colonic pain relieved by defecation and a tendency to constipation or "pellet" stools. Seventeen patients (seven males, 10 females; ages 19 to 62 years) with idiopathic diarrhea were also studied. All of these had a history of urgency or frequency of unformed stools with no associated abdominal pain.

All patients had a thorough history and examination, sigmoidoscopy, rectal biopsy, and barium enema. The diagnoses required the following to be normal: full blood picture, sedimentation rate, serum calcium, magnesium, liver function test, thyroid function test, fecal fat estimation, stool examination, and culture. The patients with spastic colon and idiopathic diarrhea had a jejunal biopsy and jejunal disaccharidase assay and microscopy were performed. Other investigations such as

¹Wolfson Gastrointestinal Laboratories, Departments of Medicine, Clinical Chemistry and Clinical Surgery, Western General Hospital, and University of Edinburgh, Edinburgh, Scotland.
²This study was supported by the Incorporated National Association of British and Irish Millers Limited.
barium follow through and colonoscopy were performed where indicated.

**Methods**

All subjects provided an accurate 3- to 5-day stool collection during symptoms, in plastic bags that were stored at -20°C until analyzed. The stools were weighed (total wet weight), homogenized with an equal volume of water and an aliquot was lyophilized to give the dry weight. Fecal bile acids were measured by the method of Brand and Janssen (5) as modified by Mitchell et al. (6). An aliquot of dried feces was digested in boiling concentrated nitric acid for 2 hr then further oxidized with concentrated hydrogen peroxide. The electrolytes were then determined by flame photometry and atomic absorption spectrometry.

**Results**

There was no significant difference between the wet or dry weights of feces excreted per day in the four groups (Table 1). The percentage of water content was significantly greater ($P < 0.05$) in the stools from patients with

<table>
<thead>
<tr>
<th>FAecal Weight and Water Content</th>
<th>CONTROLS</th>
<th>IDIOPATHIC DIARRHEA</th>
<th>SPASTIC COLON</th>
<th>DIVERTICULAR DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>WET</td>
<td>Mean 107.0</td>
<td>Mean 128.7</td>
<td>Mean 101.4</td>
<td>Mean 94.2</td>
</tr>
<tr>
<td>S.D. = 39.9 (Range 60-182)</td>
<td>S.D. = 51.6 (Range 23-222)</td>
<td>S.D. = 35.1 (Range 34-219)</td>
<td>S.D. = 35.1</td>
<td></td>
</tr>
<tr>
<td>DRY</td>
<td>Mean 27.3</td>
<td>Mean 24.2</td>
<td>Mean 21.1</td>
<td>Mean 23.3</td>
</tr>
<tr>
<td>S.D. = 7.6 (Range 16-43)</td>
<td>S.D. = 5.1 (Range 5.6-65)</td>
<td>S.D. = 7.7 (Range 10-34)</td>
<td>S.D. = 7.7</td>
<td></td>
</tr>
<tr>
<td>PERCENTAGE WATER</td>
<td>Mean 23.6</td>
<td>Mean 73.8*</td>
<td>Mean 78.5</td>
<td>Mean 74.5</td>
</tr>
<tr>
<td>S.D. = 5.6 (Range 63-84)</td>
<td>S.D. = 6.2 (Range 56-95)</td>
<td>S.D. = 6.1 (Range 71-86)</td>
<td>S.D. = 6.1</td>
<td></td>
</tr>
</tbody>
</table>

* SIGNIFICANTLY DIFFERENT FROM CONTROLS $P < 0.05$

![Figure 1](image.png)

**FIG. 1.** Shows daily fecal cation output in controls and patients with diverticular disease, spastic colon, and idiopathic diarrhea (mean ± standard deviation).

**FAecal Cations**

- **SODIUM**
- **POTASSIUM**
- **CALCIUM**
- **MAGNESIUM**
idopathic diarrhea when compared with controls.

The daily output of sodium in feces was similar in the four groups (Fig. 1). In patients with diverticular disease there was a significant reduction in the daily fecal output of magnesium ($P < 0.0025$), potassium ($P < 0.01$), and calcium ($P < 0.05$). Patients with the spastic colon form of irritable bowel disease showed a reduced output of these cations, although the results were not statistically significant. Similar findings were obtained when the cations were expressed as a concentration of the wet weight of feces.

The total fecal bile acid output was not significantly different among the four groups (Fig. 2). However, the feces of nine of the 17 patients with idiopathic diarrheal form of irritable bowel syndrome contained primary bile acids. Patients in the other three groups with one or two exceptions excreted only secondary bile acids.

Discussion

The irritable bowel syndrome is the term popularly used to describe the combination of disordered bowel habit, with or without the association of abdominal pain or discomfort. The main criterion for diagnosis is the absence of organic pathology, e.g., neoplasia, or inflammatory disease, infection, infestation, drugs, jejunal disaccharidase deficiency, malabsorption syndrome, metabolic and endocrine disorders, or previous abdominal surgery. Primary or idiopathic irritable bowel syndrome is a condition of unknown etiology and yet it is a common condition in gastrointestinal practice. Chaudhary and Truelove (4) have divided patients with the irritable bowel syndrome into two groups—spastic colon and idiopathic diarrhea, depending on whether pain or diarrhea predominated. They showed that resting motility in the spastic colon group with symptoms was significantly greater than in control subjects, whereas those patients with idiopathic diarrhea had a similar motility index to controls. Deller and Wangel (7) have shown a significantly increased responsiveness to prostigmine in the spastic colon whereas the response in idiopathic diarrhea tends to be less than normal. The patients with spastic colon tend to become chronic problems whereas over half the patients with idiopathic diarrhea return to normal (4).

Diverticular disease is thought to be the result of a chronically raised intraluminal pressure in the colon, acting on localized areas of weakness in the muscle walls at the...
Joint of entry of the blood supply. An important factor in the increased pressure is muscle hypertrophy, but there is considerable evidence to suggest that the high intraluminal pressure is also due to reduction in lumen diameter and relative emptiness of the colon (1,8). It has been suggested that a lack of vegetable dietary fiber can cause or aggravate the condition (1,2). Patients with diverticular disease when given a high fiber diet have relief of symptoms with a lowered colonic pressure and increased rate of transit (9).

The irritable bowel syndrome and diverticular disease are in many ways similar in symptomatology and medical management with the exception that diverticular disease presents later in life.

Our studies on stool weight and its water content of the stool showed that patients with functional diarrhea pass stools with more water than controls. However, the overlap is considerable and what was described as a watery or a loose stool bore no relation to its water content. Patients with spastic colon and diverticular disease frequently described their feces as being hard and pelletty and yet their feces contained, if anything, more water than the stools from control subjects. Clearly the consistency of the feces is not merely a function of water content alone but probably depends upon the physicochemical properties of the matrix. This is created by fiber and water bound to it both on the surface and interstitially with an additional component that is the "free" water (10). There is also the lubricating effect of colonic mucus to be considered. It is possible that the therapeutic effect of vegetable dietary fiber and bulking agents lies in their ability to alter the stool matrix.

Our studies on fecal cation excretion show that patients with diverticular disease pass significantly less magnesium, potassium, and calcium. The results in the spastic colon patients show a similar trend without reaching statistical significance. The observation that age does not affect fecal cation excretion suggests that this change is related to the disease process. The serum concentration of these cations and the serum alkaline phosphatase were all within normal limits. It is known that vegetable dietary fiber has cation exchange capacities (11). It may be that the efflux of electrolytes in the feces is related to the cation exchange properties of vegetable dietary fiber. We have suggested elsewhere that the fecal cation content may be an indirect indicator of the fiber content of the diet (W. D. Mitchell et al. manuscript in preparation).

The total output of bile acids is dependent on the rate of excretion by the liver to the gut and the efficiency of reabsorption of bile acids by the terminal ileum. We have found no difference in the total fecal bile acid output in the four groups of patients, however, the presence of primary bile acids, i.e., chenodeoxycholic acid and cholic acid in nine of the 17 patients with idiopathic diarrhea is interesting. In other studies from this laboratory with patients with cholera-like enteropathy, we have shown that chenodeoxycholic acid is associated with the development of watery diarrhea (6).

A fecal bile acid concentration greater than 15 mmole has been shown to inhibit bacterial 7a-dehydroxylation (12). However, in our patients with idiopathic diarrhea total fecal bile acid concentrations were less than 15 mmole and it seems unlikely that the presence of chenodeoxycholate in the feces of these patients is due to inhibition of 7a-dehydroxylation. It is possible that rapid transit through the colon or an altered bacterial flora or metabolism are not conducive to 7a-dehydroxylation of bile acids.

These results suggest that the spastic colon may have common features with diverticular disease. Possibly this is due to a deficiency of vegetable fiber in the diet, or to some other common etiological factor that results in a reduced fecal cation excretion. The addition of vegetable fiber to the diet as a therapeutic measure should increase the cation excretion in the stool perhaps beneficially. In an unpublished study we have shown that there is an inverse relationship between the calcium and magnesium content of the stool and the motility index.

The presence of primary bile acids in the feces of some patients with idiopathic diarrhea lends support to the suggestion that this disorder is in fact a separate entity. The primary pathophysiology in idiopathic diarrhea may be a more rapid transit or an abnormality in the bacterial flora, not neces-
sarily in the type of bacteria but in the ability to perform complex metabolic processes.

We are grateful to Dr. W. Sircus and Dr. Anne Ferguson for access to some of the patients.

References
Kirwan, W. O. & Smith, A. N. Colonic propulsion in diverticular disease, idiopathic constipation, and the irritable colon syndrome. Scand. J. Gastroent. 1977, 12, 331-335

Colonic intraluminal pressure and intestinal transit were examined in diverticular disease, idiopathic constipation, and the irritable colon syndrome. Small bowel transit was normal. Total gastrointestinal transit was prolonged. Colonic transit showed an equal delay in all segments, expedited by bran. In constipation, transit was the more prolonged, but in the irritable colon syndrome, pressure was more affected. Diverticular disease patients showed features resembling each of these two groups. Pressure and transit showed an inverse relationship maintained after bran.

Key-words: Bran; colonic; constipation; diverticular disease; irritable colon; isotope capsule; pressure; segmental; total; transit time

A. N. Smith, M.D., Dept. of Clinical Surgery, Western General Hospital, Edinburgh, Scotland

It has been shown (5) paradoxically that colonic intraluminal pressure is high in patients with constipation and low in patients with diarrhoea. From recordings at adjacent sites in the colon (4) it would appear that the vast majority of human sigmoid pressure waves are of the segmenting rather than the propagated type. The haustral contractions of the colon which radiologically move barium both proximally and distally are considered to be the radiological counterparts of the segmenting contractions of the colon (3).

The intraluminal pressure is abnormally high in diverticular disease (1, 2, 9) and in constipation (5). We have recorded both the intraluminal pressure and transit time simultaneously, in an attempt to clarify the mechanisms involved in the propagation of the colonic contents. Patients were also studied before and after bran to ascertain whether there was any preferential action on pressure or intestinal transit. Similar studies were also performed on patients with the irritable colon syndrome.

METHODS

Patients

Fifteen patients with uncomplicated diverticular disease, four with idiopathic constipation, and seven with the irritable colon syndrome, had been referred for investigation of bowel complaints. All gave informed consent to the study. None was taking bran or drugs beforehand.

Colonic motility studies

The patients took three sennokot tablets 24 hours before a colonic motility study at 9 a.m., fasting. Motility was recorded by using open-ended tubes (10) during basal, post-food, and post-prostigmine phases. The pressure tracings were processed by a computer technique, and the results were expressed as a colonic motility index.

Transit time studies

A method of studying total gastrointestinal transit time and differential colonic transit
time has been reported elsewhere: an isotope capsule is swallowed, and its progress through the gastrointestinal tract is monitored by means of an isotope localisation monitor (7). Total gastrointestinal transit time and the differential colonic transit time are determined, as are areas of transit delay.

**Bran regime**

Following the initial studies the patients were started on 10 g of coarse bran (8) twice daily for four weeks, with repeat studies at the end of this period.

**RESULTS**

(a) *Total gastrointestinal transit*

In a previous study the mean transit time for normal subjects by the isotope capsule method was 23 ± 1 h and in severely constipated subjects 187 ± 85 h (7). In diverticular disease it was 68 ± 14 h; after bran this was reduced to 32 ± 6 h. (P<0.05 t-test between means). The transit time was prolonged in idiopathic constipation (93 ± 23 h) and in the irritable colon syndrome (59 ± 18 h). The effect of bran was more pronounced (P<0.05) in the idiopathic constipation group than in the irritable colon patients (n.s.).

(b) *Colonic segmental transit*

Figure 1 illustrates the number of hours spent by the capsule in various segments of the colon in 12 diverticular disease subjects (in three it was not possible to determine the position accurately). The time spent in each area is reduced by bran but (Table I) is about the same in each colonic segment. The reduction was of the highest degree of significance in the splenic flexure area (P<0.0005). A comparable time was taken in each zone for idiopathic constipation and for irritable colon syndrome (Fig. 2). It was also reduced by bran, though less significantly, and the effect was also distributed throughout the colon. Moreover the most significant change was an effect at the splenic flexure (Table II). Small bowel transit was normal throughout.

(c) *Intraluminal pressures*

The mean colonic motility index (± S.E.) during basal, post-food, and post-prostaglandin phases was calculated in 15 patients with diverticular disease before and after bran. Both motility indexes was reduced from 2.387 ± 764 ± 214 (P<0.0125). The post-rectal motility index fell from 2,566 ± 1,771 ± 264 (P<0.10 t-test between means 0.05 paired t-test). Following bran therapy prostigmine motility index fell 5,298 ± 451 to 3,968 ± 375 (P<0.05) —

**Table I. Diverticular disease (n=15). Mean number of hours (±S.E.) spent by capsule in various colonic segments**

<table>
<thead>
<tr>
<th></th>
<th>Right colon</th>
<th>Transverse colon (including hepatic flexure)</th>
<th>Splenic flexure</th>
<th>Rectosigmoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before bran</td>
<td>25 ± 5</td>
<td>24 ± 0</td>
<td>26 ± 2</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>After bran</td>
<td>16 ± 2</td>
<td>16 ± 2</td>
<td>16 ± 2</td>
<td>16 ± 2</td>
</tr>
<tr>
<td></td>
<td>(P&lt;0.0025)</td>
<td>(P&lt;0.0025)</td>
<td>(P&lt;0.0005)</td>
<td>(P&lt;0.05)</td>
</tr>
</tbody>
</table>

**Table II.**

Group 1: 2 Group 2: 3, Group 3: 0.05

*Fig. 1. Differential colonic transit in diverticular disease (n=12).*

**Fig. 2.**

The uniform change in rectal pressure, responsible for the change in pressure in the rectosigmoid area was their combined effect. The mean motility index fell in Group 1 from 5,298 ± 451 to 3,968 ± 375 (P<0.05) —
Table II. Constipation and irritable colon syndrome (n = 11). No. of hours (±S.E.) spent by capsule in various colonic segments

<table>
<thead>
<tr>
<th></th>
<th>Right colon</th>
<th>Transverse colon (including hepatic flexure)</th>
<th>Splenic flexure</th>
<th>Rectosigmoid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before bran</td>
<td>20±2</td>
<td>22±2</td>
<td>24±3</td>
</tr>
<tr>
<td></td>
<td>After bran</td>
<td>11±2</td>
<td>13±2</td>
<td>18±2</td>
</tr>
<tr>
<td></td>
<td>(P&lt;0.01)</td>
<td>(P&lt;0.01)</td>
<td>(P&lt;0.005)</td>
<td>(P&lt;0.01)</td>
</tr>
</tbody>
</table>

Fig. 2. Differential colonic transit in idiopathic constipation (n = 4) and the irritable colon syndrome (n = 7).

3.968 ± 511 (P<0.05). Similar changes (P<0.05) were found for the irritable colon syndrome. The changes found in idiopathic constipation were not significant.

(d) Relationship between total transit time and intraluminal pressure

The patients with idiopathic constipation uniformly had a prolonged transit more readily changed by bran than was colonic intraluminal pressure. The patients with the irritable colon syndrome uniformly had a high intraluminal pressure, more readily affected by bran than was their transit time.

The motility and transit time results in the 15 patients with diverticular disease, however, fell into two groups (Table III).

Group 1 consisted of five patients with an extremely long transit time and a colonic motility index which was only moderately raised. The mean transit time was 147 ± 75 h, and the basal post-food and post-prostagmine motility indices respectively were 1346 ± 502, 1776 ± 850, and 3312 ± 94.

Group 2. In this group of 10 patients the transit time was only slightly increased while the colonic motility index was extremely high. The mean transit time was 41 ± 5 h, but the basal post-food and post-prostagmine motility indices respectively were 2,063 ± 510, 3,870 ± 466, and 5,961 ± 405. The difference between the transit and the post-prostagmine motility indices in the two groups were statistically significant (P<0.005).

Correlations between total gastrointestinal transit times and the basal, post-food and post-prostagmine motility indices are set out in Figs. 3a, b, and c respectively for diverticular disease. It can be seen that the relationship between intraluminal pressure and transit times is, throughout, an inverse one, but the negative correlation reaches statistical significance (P<0.05) only in the post-prostagmine phase. Following the administration of bran the negative correlation between intraluminal and transit time is still apparent. In patients with constipation or the irritable colon syndrome, when the prostagmine response was related to the total gastrointestinal transit time, an inverse relationship between the two was again demonstrable.

Table III. Motility indices and transit times in the two subgroups of patients with diverticular disease

<table>
<thead>
<tr>
<th></th>
<th>Transit time</th>
<th>Basal</th>
<th>Post-food</th>
<th>Post-prostagmine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>147 ± 35</td>
<td>1346 ± 502</td>
<td>1776 ± 850</td>
<td>3312 ± 94</td>
</tr>
<tr>
<td>Group 2</td>
<td>41 ± 4</td>
<td>2063 ± 510</td>
<td>3870 ± 466</td>
<td>5961 ± 405</td>
</tr>
<tr>
<td>(P&lt;0.01)</td>
<td>(P&lt;0.20)</td>
<td>(P&lt;0.15)</td>
<td>(P&lt;0.0005)</td>
<td></td>
</tr>
</tbody>
</table>
though not a significant one (Fig. 3d). The effect of bran was to displace the line downwards and to the left. Similar effects were found for the post-food and basal motility.

DISCUSSION

It has been shown that in constipation there is delayed transit in the colon at the recto-sigmoid region and possibly also at the splenic flexure (7, 11). There is the possibility that transit in the proximal colon is slightly shortened in some patients with diverticular disease and that transit is delayed after bran, perhaps because of increased bulk filling it. The present study has revealed, however, that the isotope capsule spends, on average, an unusually long period not only in the left colon but in the right colon also, and that delay throughout the colon contributes to the slow transit of the capsule in diverticular disease. Bran proved equally effective in diminishing the transit time through the right side and left segment of the colon.

The present study again confirms the previously published results of Findlay, Smith, Mitchell, Anderson & Eastwood (6) and Kirwan, Smith, McConnell, Mitchell & Eastwood (8) that bran effectively shortens the gastrointestinal transit time and lowers the intraluminal pressure in patients with diverticular disease. Since a high intraluminal pressure has been associated with constipation and a low intraluminal pressure associated with diarrhea, it has been assumed that the effect of a high intraluminal pressure is to increase the transit time. If this were true, the relationship between intraluminal pressure and gastrointestinal transit time would be a direct one. The present study, however, has revealed that relationship is an inverse one.

Patients with colonic diverticular disease...
into two groups on the basis of transit and motility study. One group had an extremely long transit time with a moderately raised intraluminal pressure, and the second group a normal or slightly prolonged transit time with an extremely high intraluminal pressure.

This proportionality was maintained after bran. These findings are difficult to reconcile with the paradoxical theory of colonic motility reported by Connell (5), who found that a high intraluminal pressure was associated with delayed transit. It is possible, however, that up to certain physiological levels of intraluminal pressure an increase in pressure serves to restrain the propulsion of the intraluminal contents, but that when the pressure rises above this level a further increase results in propulsion of the contents.

ACKNOWLEDGEMENTS

This work was done during the tenure of Scottish Hospital Endowment Research Trust Grant No. 418, to Mr. Adam N. Smith.

We are indebted to Miss E. G. P. Drummond for skilled technical assistance.

REFERENCES

projects, seeking and obtaining advice from others well-placed to give it.

In summary, the occasion demonstrated clearly that there exists among service general practitioners a number of doctors both willing and able to prosecute studies in their practices. Furthermore, service general practitioners can contribute useful ideas and work in addition to the gathering of data for others—however important that may be to those professional scientists carrying out their studies.

If this potential is to be developed to play its full part in helping health services to become more efficient, effective and economical, without encouraging mediocrity, appropriate support, advisory services and training are essential and must be made available wherever the enquiring mind is found in general practice.

Lack of vegetable fibre in the diet has been related to a whole range of diseases, but, particularly, to those of the colon, such as cancer and diverticular disease (Burkitt, 1969). It has been estimated that in Western countries diverticular disease begins to be seen in a hospital population at age 40, by 60 years of age 40% of hospital out-patients have colonic diverticula radiologically and by 70 years 50% can expect to have symptomatic diverticular disease with or without complications. The disease, while an important cause of death and morbidity in European and North American communities, is apparently very rare in Africans. The rural African consumes a high fibre-containing diet and passes approximately 500 grams of stool per day in contrast with modern European and North Americans who eat a low fibre-containing diet and who pass small stools of approximately 100 grams per day (Burkitt, Walker and Painter, 1972). Furthermore, added dietary cereal fibre relieves over 80% of the symptoms of complicated diverticular disease when given as miller's bran (Painter, Almeida and Colebourne, 1972). Their patients subsequently noticed a return of symptoms if they reverted to a low residue diet, which disappeared once more when they returned to a high fibre diet.

Concurrently, with increasing interest in all colonic disorders, it has become obvious that there is an underlying motility disturbance shared by all the distal bowel and measurable as a high pressure in its lumen, but seen at a maximum in the pelvic colon (Arfwidsson, 1964; Painter and Truelove, 1984). At this same part of the intestinal tract there may be a sphincter-like mechanism in operation. Whether the thick muscle of the pelvic

---

**Fibre, Intra-colonic Pressure and Diverticular Disease**

Adam N Smith, Reader
Deartment of Clinical Surgery and Wolfson Laboratories, Gastro-Intestinal Unit, University of Edinburgh

---

Readers may wish to be reminded that a more general article 'Gastric and Colonic Cancer in Scotland' by Professor K C Caiman and Dr I W Kemp was published in 'The Chief Scientist Reports' section of Health Bulletin, Vol 34, No 6, November 1976, 347-354.
colon is a response to chronic underfilling, to some active agent in the bowel lumen or local obstruction from a 'sphincter' at the rectosigmoid is also unknown. Operations which divide the sigmoid muscle locally by myotomy (Reilly, 1966) have now been devised, though as yet there has been no great tendency of surgeons to depart from the accepted practice of resection. This review deals with attempts to define the aetiology in terms of the pressure rise. Various assessments have now been made of what the underlying motor abnormality is and whether it can be reversed. Since fibre changes aspects of colonic propulsion, it may become acceptable not only as a means of therapy but also as a tool for the study of diverticular disease.

Fibre has had a chequered career! Formerly fibre was regarded as physiologically inert. It represents plant cell walls, and is mainly celluloses, hemicelluloses and lignins. Older plant cell walls are particularly impregnated with lignins, which are not broken down to any appreciable extent in the gut, and are rich in active chemical groups which bind bile acids and other organic radicals. They also indulge in ionic exchanges and water binding with sufficient activity to approximate to many commercially available weak ion exchangers (Eastwood, 1975).

Several investigators have now measured effects of bran or cereal fibre, usually in diverticular disease. Bran shortens the transit time measured by an isotope capsule. It increases the stool weight, enhances the filling of the colon lumen and reduces the manometric pressure within the lumen of the sigmoid colon (Figure 1) at which site it is particularly high in diverticular disease (Findlay et al., 1974). Bran also alters the consistency of the stool and may lessen the need to strain during defaecation. Taylor and Duthie confirmed (1976) these findings, and added to them an improvement after bran in the abnormal electrical rhythm which can be recorded from colonic smooth muscle in diverticular disease.

The effect and mode of action of bran in colonic function had earlier been investigated in the 1940's. Bran had been found to improve the frequency of bowel action (Hoppert and Clark, 1942), increase the stool weight (Fantus and Frank, 1941) and decrease the intestinal transit time (Streicher and Quirk, 1943) in constipated subjects. But its use in bowel diseases fell into disrepute because of the misconception that bran was 'roughage' and hence a colonic irritant. More recently, Eastwood et al., 1973 have shown in a group of normal subjects taking approximately 16 grams of cereal bran per day a decrease in the intestinal transit time, with softer bulkier stools

![Figure 1. Colonic motility activity, expressed as a motility index, recorded in 9 diverticular disease patients before and after bran; the motility reduced greatest after food stimulation, but also spared after prostigmine.](attachment:figure1.png)

**PARTICLE SIZE OF TWO BRANS USED IN COLONIC DISEASE**

![Figure 2. Fine bran passed proportionately more through narrow aperture sieves; coarse bran a greater aperture size to let it pass. Coarse Bran had a greater water holding capacity than fine bran. (Courtesy J A Eastwood).](attachment:figure2.png)
attributable to an increase in their water content. The mechanism of the action of bran has been further elucidated in a study of the respective actions of coarse and fine bran in diverticular disease (Kirwan et al., 1974). The former, which had a high fibre content, was much more effective than the latter, which had a lower fibre content, in reducing the intraluminal colonic pressure and the transit time. That one bran was coarser than the other was shown by shaking the two brans for 90 mins. in test sieves of increasing aperture. The flour from each bran which passed through the mesh (Figure 2) was weighed. Less of the coarse bran passed through the sieves of small pore size.

The water binding capacity was also more marked for the coarse bran. This was estimated by placing a known quantity of bran in a weighed tube to which excess water was added and the mixture left to equilibrate. The tube was later centrifuged for one hour and the supernatant was removed, leaving bran with the associated water. Coarse and fine bran respectively held 6-0 grams and 2-4 grams of water per gram of bran. The acid detergent fibre contents were 15-1% and 9-7% with a higher lignin content for the coarse (4-1%) than the fine (2-6%) bran. After milling both brans to a particle size of <1 mm in the laboratory, the water holding capacities approximated although the fibre contents remained the same. Our observations suggest that bran with coarse particles binds more water and thus provides more bulk in the stool than does bran with finer particles. The marked difference in the effect of the two brans on bowel function was unexpected. Fine bran failed completely, unlike coarse bran, to reduce the colonic motility index (Figure 3) and the gastro-intestinal transit time.

The beneficial effect of coarse bran is probably related to its water holding effect which gives rise to a soft bulky stool which is easily passed. The change in the motility index resulting from bran may also depend upon the bulk provided, since intraluminal pressure depends not only on the force exerted by the colonic muscle but also upon the diameter of the bowel lumen and the viscosity of its contents. These results indicate that particle size could be of fundamental importance in determining not only the water holding capacity but also the clinical efficacy of bran. It is possible, however, that if fine bran were given in a large dose, there would be sufficient large particles with water holding capacity sufficient to improve bowel function; but the fine bran contains considerable amounts of absorbable carbohydrate and the dose used might result in unacceptable weight gain.

Bran has also been shown to reduce the time by an intestinal transit capsule in the various colonic segments in diverticular disease (Kirwan and Smith, in press). It was first established that the time spent by an isotope capsule in each colonic segment in diverticular disease was about the same. Bran produced a reduction in the 'stay' of the capsule in all areas. It had previously been shown by Kirwan and Smith, 1974 that an isotope capsule of specific gravity 1-1 was as reliable as radiopaque markers and it was therefore used to measure total gastro-intestinal transit in normal subjects and in constipation. The rate of transit of the capsule relative to the markers was increased when its specific gravity was increased or decreased from 1-1 within narrow limits. It is possible that the isotope capsule of specific gravity 1-1 and radiopaque markers, both being of similar specific gravity to the gut contents, are suspended in equilibrium with those contents and are propelled at a similar rate. When, however, a slightly heavier or, alternatively, a lighter capsule is used each could separate from the lumen contents and take up a position close to the bowel wall and thus be more effectively propelled and more rapidly excreted. These observations raise the possibility of a differential rate of transit of solid particles of differing specific gravity in the gastro-intestinal tract. They offer a part explanation of the mode of action of an agent such as bran, which is known to alter intestinal transit rate, by adding to the weight of the stools. Direct recording by an isotope capsule also illustrated important qualitative regional differences in the transit through the various sectors of the large bowel. We have confirmed the finding of Waller, 1975 that, in constipation, colonic transit is slow with a delay in the region of the splenic flexure as well as the anticipated considerable delay in the rectosigmoid area.
Although bran relaxes the colonic muscle and reduces the intra-colonic pressure, it differs from simple bulk formers (Srivastava, Smith and Painter, 1976). The bulk-former sterculia (Normacol) is a resinous plant polymer which can absorb 60 times its own volume of water and to which the peristaltic stimulant frangula has been added (Eastwood, 1975). A preparation exists to which has been added the anti-spasmodic agent alverine citrate. Surprisingly, sterculia alone raised the intra-luminal pressure and only the form combined with an anti-spasmodic elicited a pressure fall. Although sterculia was found to act clinically satisfactorily in respect of constipation in patients with diverticular disease, this action was enhanced when combined with an anti-spasmodic and gave more complete relief of pain and other features. This was studied by asking a series of patients to score the severity of their constipation, pain, and other diverticular disease symptoms such as diarrhoea, flatulence and distension, before and after each agent (Srivastava et al., 1976). Each was taken for one month and then each subject switched after an interval of a further month to bran. Sterculia plus anti-spasmodic was consistently ahead of sterculia alone, in that there was not only a reduction of pressure but also a greater symptomatic relief, with results comparable to bran. One possible explanation for the efficacy of bran is that bran with a superior water holding capacity, may dilute an irritant substance, such as could be antagonised by the anti-spasmodic agent alverine citrate in the combination with sterculia. Thus, not all bulk additives share properties which make them ideal in the correction of abnormalities of colonic physiology. On these criteria, it may be more rational to restore fibre to a diet lacking in it than to use artificial bulk formers. On these grounds, too, the use of bran tablets (Taylor and Duthie, 1976) would seem less rational than the re-introduction of fibre in sufficient amounts into a normal diet.

Food stuffs have a wide range of fibre content, from cucumber (4%) to wheat bran (90%). The total water holding capacity of any food source is a function of both its fibre content and the water holding capacity of the particular fibre. Whilst bran has a modest water holding capacity it holds the greatest amount because of its high fibre content. Mangoes, carrots and Brussels sprouts each have a good water holding capacity but less fibre. Estimation of total water holding capacity enables one to select fibrous constituents of a diet likely to increase the stool weight (McConnell et al., 1974). 50 grams of bran was found to be capable of holding 220 grams of water and is thus functionally equivalent to 100 grams of raw carrot, 150 grams of apple or 200 grams of peeled orange. However, it would be necessary to eat 600 grams of potatoes to obtain the same overall effect!

Bile acids are concentrated in the diverticular stool (Kirwan et al., 1975) and the colon muscle is overactive in motility terms in diverticular disease. The exaggerated muscle action leads to a thick muscle anatomically and an overactive one functionally (Smith, 1975). Any motor action of bile acids in diverticular disease would have to be different from the usual acute irritative action produced when bile is suddenly discharged into the colon, as in the production of bile diarrhoea. The more chronic situation of diverticular disease would be one of continued exposure to a motor-stimulating agent concentrated in the faeces in the lumen of the colon and might explain why the muscle in the distal colon thickens and ultimately becomes self obstructing. Animal experiments have already indicated that bile salts may stimulate motility (Horrell, 1938; Haney et al., 1939) and that introduction of bile into the colon and rectum resulted in defaecation (Hallion and Nesse, 1975). Various bile acids were studied to determine their capability for the stimulation of bowel motility (Kirwan et al., 1975). Patients with a high faecal bile acid excretion had a significantly higher motility index after food and ptychumine stimulation, suggesting that bile acid may be a factor in the production of abnormal colonic motility. The abnormally high quantity of bile acids, mainly primary ones, in the colon, the more chronic situation of a rising concentration in the faeces or pellet stool of diverticular disease, produce the colonic motor activity that condition is as yet unknown.

After resection of the colon in diverticular disease the intraluminal pressure is unchanged or even rise. After myotomy, the division of the colon by an overactive colonic muscle of the sigmoid colon promptly leads to a fall in the intraluminal pressure (Attisha relative a et al., 1969) but this is followed by a slow restoration to the range characteristic of diverticular disease (Smith et al., 1974). The background contract and pressure for the return of the disease or its symptoms which this recreated because many of these patients to a low fibre diet. This can be prevented by administration of dietary bran (Figures 4a 4d).

Part of the abnormal response of the Western World diverticular disease may be because of a gastrointestinal reflex in some subjects in real effect to meals. Possible abnormal hormonal stimulants the distal colon has been investigated, et the bowel in relationship to release of gastrin by confirmed types of meal. Gastrin was shown by (Horrell and Smith, 1966) to have motor effects in the bowel and colon. Motor effects coincidences wi
Many other diverse effects of bran have been summed up in the report on a conference on fibre deficiency in colonic disorders convened by the University of Chicago in 1974 (Reilly and Kirsner, 1975). It may be concluded, at this stage, that fibre is much more effective in altering colonic physiology than had formerly been suspected and can certainly no longer be regarded physiologically as an 'inert' substance. There is little doubt that among the changes it produces are a reduction of the colonic intraluminal pressure and the intestinal transit time, changes which may explain its beneficial role in diverticular disease. Yet it would be premature to ascribe to fibre or its activity an aetiological role in diverticular disease. Little is known about 'ageing' in the gastro-intestinal tract and the ordinary 'wear and tear' effects to which this tissue like others must be subjected.

Acknowledgement

This paper reviews work supported by SHERT Grant No. 418. It constitutes part of a lecture given under the auspices of the Honeyman Gillespie Trust. Dr Martin Eastwood generously gave his co-operation throughout and the technical help of Miss Elizabeth Drummond is gratefully acknowledged.

Summary

Diverticular disease is on the increase in the Western World in the 20th Century, and has been associated with a reduction of the fibre content of our diet. One theory of diverticular disease suggests that it originates after a rise of pressure in the bowel; the work reported here firstly stimulated this by intubating the distal large bowel and recording its intraluminal pressure. Methods were developed to correlate the pressure changes with the intestinal transit time of a swallowed isotope capsule. Transit was slow in diverticular disease.

Fibre added to a normal diet as miller's bran increased the stool weight, decreased the intestinal transit time, and reduced the intestinal pressure in diverticular disease. These effects were all greater with 'coarse' bran and much less with 'fine' bran—coarse bran, with more fibre, had a greater water-binding capacity, and this may have contributed to the bulk of the stools. The actions of various bile acids on the motility of the colon were also examined, since a high concentration of bile acids had been found in the faeces of some patients with diverticular disease. Bran may act by diluting an as yet unidentified factor, which stimulates the muscle of the colon and thus the pressure within its lumen.

References

Hallion L and Nepper H (1907). *Comptes Rendus de medicine*, 64, 182.

**Research Notes**

**COMPUTER RESEARCH GRANTS AWARDED DURING THE PERIOD JULY-SEPTEMBER 1976 (ADDENDUM)**

**Professor G Murdoch**, Dundee Limb Fitting Centre, Broughty Ferry, Dundee and Professor J P Paul, Department of Bio-engineering, University of Strathclyde, Glasgow

'Television/Computer System for the Analysis of Normal and Pathological Gait—Clinical Application Phase'—a grant of up to £58,020 over a period of 3 years.

**HEALTH SERVICE RESEARCH GRANT AWARDED DURING THE PERIOD JULY-SEPTEMBER 1976**

**Dr D I A Cunningham**, General Practitioner, Dufftown, Banffshire

'Morbidity Study of a Distilling Community with Particular Reference to Alcohol Related Problems'—a grant of up to £2,150 over a period of 1 year.

**Dr Philip Sutcliffe**, Department of Restorative Dentistry, University of Edinburgh

'A Preventive Dental Health Programme for Nursery School Children'—a grant of up to £4,300 over a period of 3 years.

*Revised by the Editor in the light of subsequent developments and in the interests of economy.*

*Address
c/o Department of Surgery, University of Edinburgh, Edinburgh, Scotland.*
Colonic Motility in Children with Constipation*

W. G. Scobie, M.D., W. O. Kirwan, M.D., A. N. Smith, M.D.

From the Departments of Paediatrics and Clinical Surgery, University of Edinburgh, Western General Hospital, Edinburgh, Scotland

Constipation is a common complaint in children. For the purpose of this paper, it may be defined as incomplete evacuation of the rectum, leading to megarectum and megacolon. The condition may be acquired or congenital.

In those patients who have acquired megacolon, the rectum and distal colon dilate as they are filled by the propulsive activity of the normal proximal colon. These distal segments subsequently become inert, forming a large reservoir incapable of emptying unless stimulated by drugs or mechanical means. Eventually soiling occurs, either as a result of spurious diarrhea or from leakage of stool from the rectum as the fecal mass from above approaches the anus. Soiling is the main reason the patients seek medical help. In acquired megacolon, when carefully sought, a causative factor can be found, such as a previous episode of diarrhea, or an anal fissure, leading to anal discomfort and a reluctance to defecate. Domestic and psychologic problems may be a predominant factor.

In congenital megacolon or Hirschsprung's disease there is a history of difficulty or delay in passing meconium in the neonatal period. In the case of an older child this may be difficult to elicit, but the mother may recall that the child became constipated with the introduction of solid foods or had attacks of a diarrhea-like illness associated with abdominal distention suggestive of enterocolitis.

Whether the constipation is congenital or acquired, these children are often found attending medical and psychiatric clinics because of soiling. Outpatient visits are interspersed with admissions for "emptying out" procedures and toilet training. One hundred thirty-eight children with constipation were investigated in the period 1971–1975, inclusive, by anorectal manometry to diagnose Hirschsprung's disease. The present paper reports the colonic motility findings in 50 of these patients who were selected at random.

Method

Every patient had a digital rectal examination prior to testing, to ensure that the rectum was empty. When necessary, sedation with trimipramine was employed. Anorectal manometry was performed using an air-filled balloon system.

Those patients who manifested a failed "inhibition response" of the internal sphincter to rectal dilatation subsequently had either rectal biopsy or myectomy to confirm the diagnosis of Hirschsprung's disease.

Colonic motility was recorded using an open-ended multibore water-filled catheter calibrated to record at various levels 5 to 15 cm from the anal verge. The catheter was passed blindly into the rectum, as sig-
moidoscopy was found too disturbing, especially in very young patients. Pressure changes were transmitted through Statham transducers and recorded on a Devices multichannel recorder. Pressure changes were recorded as waves of amplitude over a range of 40 mm Hg at a speed of 2.5 cm/sec. A basal resting phase was followed by a measurement of response to food, and in a few patients responses to neostigmine were recorded.

Subjects
Records were obtained for 50 patients with an age range of 21/2-14 years. There were 40 boys and 10 girls. The sex ratio is in keeping with the male preponderance seen in Hirschsprung's disease.2 All 50 patients had been given laxatives, for various lengths of time. Preparations used depended mainly on personal preferences of referring physicians, but the anthracene group was the most common employed.

Results
Patients could be divided into three groups according to the type of basal motility tracing obtained. The largest group, 32, had tracings showing hypomotility: the rectal tracings generally showed the lowest wave amplitudes, and basal motility was sometimes zero (Fig. 1, left). This group contained the largest number of patients who subsequently were found to have Hirschsprung's disease. Three patients who had Hirschsprung's disease agreed to repeat motility testing after myectomy, and the tracing then showed return to a normal pattern (Fig. 1, right).

The second group consisted of eight patients who had a distinctive high-amplitude motility pattern (Fig. 2). Four of this group were subsequently found to have Hirschsprung's disease. Figure 2, left, was obtained from a 13-year-old boy who eventually needed resection for Hirschsprung's disease, which involved the rectum and distal sigmoid colon. A tracing obtained two years after operation shows a lower amplitude, approaching normal (Fig. 2, right). Two other patients in this group who had repeat tracings postoperatively showed more normal patterns.

In the third group of nine patients, a pattern that may be described as normal was seen (Fig. 3). No patient in this group had Hirschsprung's disease.

The responses to food and neostigmine in all three groups followed essentially the same trend, but with enhanced motility, that is, a higher motility index after each stimulus than had been obtained basally (Table 1).

Discussion
The predominant motility pattern seen in the present series was that of low amplitude, and in some cases, a featureless tracing. This finding is different from that found by others investigating children with constipation,1 3 and may reflect the method of testing, in that this was carried out before the patients had had any corrective treatment of their constipation. Several investigators have attributed a flat tracing to the adult to the prolonged use of laxatives.3 6 Although all children tested in the present series had taken laxatives, the periods were comparatively short.

The following explanation is suggested for the present findings. Many of these children had had episodes when their bowels had not emptied for many days. This resulted in the rectum's becoming dilated and elongated to form an inert reservoir. Thus, the tube at motility testing was placed in an enlarged rectum, in spite of having been passed for several centimeters. The rectal balloon at manometry in these subjects could be inflated to volumes of 150 ml of air without producing any sensation of awareness or discomfort.

A finding of hypomotility more often accompanied Hirschsprung's disease, the
Pre-Myectomy

<table>
<thead>
<tr>
<th>10 cm</th>
<th>Post-Myectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 cm H$_2$O</td>
<td></td>
</tr>
<tr>
<td>10 cm H$_2$O</td>
<td></td>
</tr>
<tr>
<td>0 cm H$_2$O</td>
<td></td>
</tr>
</tbody>
</table>

5 cm

---

Fig. 1. Left, pre-myectomy records from a patient with Hirschsprung's disease, showing lack of motility in cm H$_2$O pressure 5 and 10 cm from the anal verge (basal activity). Right, post-myectomy records at the same levels, showing contractile responses in the basal period of the test.

Pre-Myectomy

<table>
<thead>
<tr>
<th>15 cm</th>
<th>Post-Myectomy + Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 cm H$_2$O</td>
<td></td>
</tr>
<tr>
<td>10 cm H$_2$O</td>
<td></td>
</tr>
<tr>
<td>0 cm H$_2$O</td>
<td></td>
</tr>
</tbody>
</table>

10 cm

---

<table>
<thead>
<tr>
<th>5 cm</th>
<th></th>
</tr>
</thead>
</table>

Fig. 2. Left, pre-myectomy records from a patient with Hirschsprung's disease, showing hypermotility in cm H$_2$O pressure 5, 10 and 15 cm from the anal verge (basal activity). Right, post-myectomy basal records at the same levels. Those at 10 and 15 cm are reduced.
hypermotility definitely was present in a small number of patients. In the hypomotile groups the motor responses to food and to cholinergic stimulation fell short, in motility index terms, of the basal activity of the hypermotile patients.

Restoration of normal caliber, either by myectomy for Hirschsprung's disease or by repeated enemas or washouts in acquired megacolon, resulted in more normal motility patterns.

Swenson et al. found that activity in the contracted distal segment in Hirschsprung's disease was diminished or absent.

**Table 1. Motility Indices for Basal, Post-food and Cholinergic Activity**

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Food</th>
<th>Neostigmine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirschsprung's disease (common)</td>
<td>0</td>
<td>130 ± 58</td>
<td>220 ± 60</td>
</tr>
<tr>
<td>Hirschsprung's disease (less common)</td>
<td>380 ± 96</td>
<td>620 ± 114</td>
<td>960 ± 134</td>
</tr>
<tr>
<td>Megacolon</td>
<td>128 ± 38</td>
<td>464 ± 82</td>
<td>800 ± 96</td>
</tr>
</tbody>
</table>

* The common type of Hirschsprung's disease was associated with absence of basal activity. The other type of Hirschsprung's disease was associated with basal activity higher than that of the common type, even when it had been rendered active by food and neostigmine. The values recorded for megacolon generally fell between the other two sets of values.
In the present series, where the distal segments were mostly very short, it was not possible to correlate length with motility pattern. However, the teenaged boy with aganglionosis of the rectum and part of the sigmoid had a high-motility pattern (Fig. 2), which subsequently returned to normal following resection.

It is suggested that colonic motility is a useful adjunct to rectal manometry in investigating children who have constipation, and has value in assessing the success of medical and surgical management.

Summary

The predominant colonic motility pattern in constipated children with Hirschsprung’s disease was hypomotile; in a small subgroup there was hypermotility.

Normal motility was a feature of megacolon of other causation.

References

Comparison of bran, ispaghula, and lactulose on colon function in diverticular disease

M. A. EASTWOOD, A. N. SMITH, W. G. BRYDON, AND J. PRITCHARD

From the Wolfson Laboratories, Gastrointestinal Unit, Departments of Medicine and Clinical Surgery, University of Edinburgh, and Department of Clinical Chemistry, Western General Hospital, Edinburgh

SUMMARY Bran, ispaghula (Fybogel), and lactulose were given to three groups of patients with diverticular disease for four weeks. Faecal weights, bile acids, fat and electrolytes, transit time, and colonic motility were estimated before and after treatment. Stool weight increased, notably with Fybogel. Cereal bran had the greatest effect on the transit time, reducing it significantly. There were no changes in faecal bile acids, fat or electrolytes. Coarse bran reduced colonic motility and the number of high pressure waves after food; Fybogel increased the basal pressure and was without effect on the food-stimulated pressures; whereas lactulose influenced neither. All agents paradoxically equally alleviated symptoms.

The symptoms of diverticular disease arise in patients who have, in the main, a small stool weight, prolonged intestinal transit time, and a raised intracolonic pressure (Painter, 1975). The rational basis of the treatment of diverticular disease is principally to influence the raised intraluminal pressure. As the various agents used in therapy would be expected to share in promoting this, we have examined three compounds which can be used in the treatment of diverticular disease: wheat bran, Fybogel, an ispaghula hydrophilic colloid (Godding, 1976), and lactulose, which is a synthesised disaccharide unabsorbed in the small intestine and hydrolysed by bacteria in the caecum.

Methods

Thirty-one patients in all were studied. The mean age was 60 years, range 32-84 years. They were recruited either from the outpatient clinic or from the radiology department. All gave informed consent to a trial of the agents used in their management. The diagnosis of diverticular disease was established by the demonstration of diverticula by a barium enema preceded by sigmoidoscopy and clinical examination. The symptoms ranged in all patients from constipation to diarrhoea or pain, while in others the disease was asymptomatic and a chance finding.

Each patient was studied at home on his habitual diet. For one week stool was collected; at the start of the collection 40 barium impregnated markers were taken by mouth (Hinton et al., 1969). Such markers not only give a crude estimate of transit but act as indicators of the accuracy of stool collection. They also took polyethylene glycol: chromium sesquioxide (PEG: Cr2O3) capsules to mark the liquid and solid phases of the intestinal contents respectively (Findlay et al., 1974). The stool was collected from their homes and stored at -20°C, pooled, and freeze dried. Faecal wet weight, dry weight, bile acids (Evra rf and Janssen, 1968), fat (Varley 1967), sodium, potassium, calcium and magnesium (flame photometry and atomic absorption spectrophotometry after charring with nitric acid), and PEG (Malawi and Powell, 1967), and Cr2O3 (Bolin et al., 1951) were individually estimated. Colonic motility was studied in fasting patients with open-ended tubes, by means of which both basal measurement and the responses to food were measured in the distal colon and rectum. Measurements were taken at 15, 20, and 25 cm from the anal verge. The amplitude and frequency of the waves were calculated to give a motility index (Attisha and Smith, 1976).

An analysis of the occurrence of waves of different amplitudes in the range 50-90 cm was performed.

seven patients took the cereal bran—20 g/day, this was Prewitt's bran with a water-holding capacity of 5 g/g dry weight. Each day's allowance of bran preparation was provided packaged separately.

Table 1

<table>
<thead>
<tr>
<th>Stool weight (g/24 h)</th>
<th>Transit time (h)</th>
<th>Motility—basal</th>
<th>Motility—food</th>
<th>PEG/Cr ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Received for publication 3 July 1978
Comparison of bran, ispaghula, and lactulose on colon function in diverticular disease

1145

into individual plastic bags. Fourteen patients had the hydrophilic colloid agent Fybogel (ispaghula husk BPC), two sachets per day, and 10 patients were given the synthetic disaccharide laxative lactulose, 20-40 ml/day. The patients were seen at weekly intervals during their course to check that they were suffering no deleterious effects and that they were taking their medication. Each treatment course lasted four weeks and the patients were retested during the last week. Because of the range of results these are expressed as a median and the Wilcoxon test for pair differences has been used for statistical analysis.

Results

All the agents administered were observed to increase the stool weight; only patients with Fybogel, however, reached significance (p < 0.001) (Table). All patients expressed satisfaction at the increased stool production, but the patients on lactulose complained of excessive flatus. Cereal bran reduced the transit time from a median of 88 hours to 50 hours, which was significant (p < 0.02). The overall recovery of pellets was 89.5% with a range of 28 to 40 capsules returned. There was no effect of either bran, Fybogel, or lactulose on faecal bile acid fat, sodium, potassium, calcium, magnesium excretion, or on the PEG: Cr₃O₇ ratio. The effect of bran and lactulose on the basal motility was insignificant (Fig. 1). However, Fybogel increased the basal motility from a median of 1150 (range 284-2034) to 2100 (range 0-3309), which was significant by Wilcoxon test for pair difference (p < 0.001). Bran generally reduced the food-stimulated pressure (Fig. 2) but there was no significant effect of Fybogel or lactulose on the food-stimulated colonic motility.

Table  Effect on colonic function of treatment—median (range)

<table>
<thead>
<tr>
<th></th>
<th>Bran</th>
<th>Fybogel</th>
<th>Lactulose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>Before</td>
</tr>
<tr>
<td>Stool weight (g/24 h)</td>
<td>82 (50-150)</td>
<td>103 (50-188)</td>
<td>75 (52-169)</td>
</tr>
<tr>
<td>Transit time (h)</td>
<td>88</td>
<td>50 (53-160)</td>
<td>24-84</td>
</tr>
<tr>
<td>PEG/Cr ratio</td>
<td>—</td>
<td>—</td>
<td>0-79-1-71</td>
</tr>
<tr>
<td>Motility—basal</td>
<td>451</td>
<td>201 (369-1343)</td>
<td>35-3064</td>
</tr>
<tr>
<td>Motility—after food</td>
<td>878</td>
<td>539 (575-1685)</td>
<td>2050 (0-2605)</td>
</tr>
<tr>
<td>Fecal bile acids (mmol/24 h)</td>
<td>0-670</td>
<td>0-41 (0-438-1-37)</td>
<td>(0-238-1-82)</td>
</tr>
<tr>
<td>Fat (mmol/24 h)</td>
<td>—</td>
<td>—</td>
<td>0-2-22 (5-22-8)</td>
</tr>
<tr>
<td>Sodium (mmol/24 h)</td>
<td>—</td>
<td>—</td>
<td>0-48</td>
</tr>
<tr>
<td>Potassium (mmol/24 h)</td>
<td>—</td>
<td>—</td>
<td>6-12</td>
</tr>
<tr>
<td>Calcium (mmol/24 h)</td>
<td>12-9</td>
<td>12-1</td>
<td>(5-62-19-1)</td>
</tr>
<tr>
<td>Magnesium (mmol/24 h)</td>
<td>3-5</td>
<td>4-5</td>
<td>(1-75-6-64)</td>
</tr>
</tbody>
</table>

Fig. 1  Effect of bran, Fybogel, and lactulose on basal motility index, before and after treatment.
Changes in motility expressed as a 'motility index' may mask the nature of the underlying motor response, as this is a product of the wave amplitude and the duration of the motor effect. A common motility result could be arrived at by many smaller waves or less frequent large waves. Waves of greater amplitude might, however, be more damaging to the colon and responsible for some of the symptoms or of the pathology of diverticular disease. Furthermore, it could be argued that these are the ones which the effective agents should be abolishing. Counts of the waves (Fig. 3) in the amplitude range 50-90 cm $H_2O$ were made and the average number recorded per patient in each treatment group. On bran, the number of waves was reduced at each 10 cm level in a one hour period of activity after a food stimulus. Fybogel, on the contrary, raised the average number of waves, whereas lactulose had no effect. Since the effect of Fybogel in raising the basal motility and the number of high pressure waves present after food is contrary to what one expects of a bulk-acting agent, the experiment was repeated with four patients on four sachets of Fybogel per day. The stool weight was increased two to four times. The basal motility again increased but there was no constant change in the faecal sodium, potassium, calcium, and magnesium.

**Fig. 2** Effect of bran, Fybogel, and lactulose on post-food motility index before and after treatment.

**Fig. 3** Effect of bran (B), Fybogel (F), and lactulose (L) on post-cibal waves before (c) and after treatment (B,F, and L).

**Discussion**

It is now established that important bulk agents such as bran (Findlay et al., 1974), sterol (Srivastava et al., 1976), and methylcellulose (Hodgson, 1972) used in the treatment of bowel disease may be expected to lower the intraluminal pressure within the colon. The reason thought for this may be that the additional contents of the activity of the smooth muscle or increase pressure or intraluminal width. A change of viscosity may be contributory factor. Bulk-forming cereal fibre mainly consists of bran should lower pressure by one or other of these means; however, the problem is to determine with that part of bran fibre should be taken, as not all forms of bran consistently lower the luminal pressure. The fibre suggested is cereal fibre in the form of milk bran, but it is not clear what form of bran is suitable, nor is it known if other forms of bran from fruit and vegetable sources are equally effective. A rough form, Prewitt's, was found to be more effective at the same dose than a fine form (Allinson's), which had a reduced water-holding capacity and thus a lowering bulk-forming capacity (Kirwan et al., 1974). There are several approaches to the selection of fibre. On the one hand, con...
select a source of fibre by its chemical constituents, such as its content of cellulose, pectin, hemicellulose, and lignin (Cummings et al., 1978). This information is not readily available. Alternatively, a physicochemical approach can be applied using the waterholding capacity of the fibre, which is proportional to its bulk-acting or promoting properties, and, to a lesser extent, the cation exchange capacity (Kirwan et al., 1974). Such measurements, however, are provisional in their value in predicting their effect on bowel function, in that the fibre may be metabolised by faecal flora. This leads to the production of hydrolytic end products which may themselves be absorbed from the caecum or may have biological effects of their own (Eastwood, 1975).

The therapeutic agents which we tested might have been expected in general to decrease intracolonic pressure. The pretreatment pressures in the three groups differ in their range, though all the measurements were obtained using the same apparatus, the same technique, and the same technician; this type of result reflects the diversity which can be obtained in the manometry of diverticular disease (Eastwood et al., 1978). However, given raised pretreatment pressures, a reduction would be expected after successful therapy and not, as is found for Fybogel, an increase. Coarse bran has already been shown to exert a reduction in pressure (Kirwan et al., 1974). There is therefore no uniform relationship between the modification of symptoms and the efficacy of the compounds in lowering pressure, in the short term at least. This raises some doubt about the overall importance of 'features' of diverticular disease—that is, low stool weight, the prolonged transit time, and the raised intraluminal pressure—which were formerly thought to be hallmarks of this disease. Although two of the agents used here raised the intraluminal pressure or left it unchanged, both produced an equivalent symptomatic relief. The patients were mainly complaining of constipation, apart from abdominal pain and discomfort, and it is possible that part of the therapeutic effect is achieved by overcoming another factor such as stasis. Yet agents which raise or leave pressure unchanged may not in the long run be entirely free of the risk of producing further damage to the bowel in diverticular disease. Thus, we would have to conclude that bran remains the most efficacious agent by adding to the stool weight and lowering the intraluminal pressure in diverticular disease.

We gratefully acknowledge that this work was done during the tenure of grant SHERT 491 (to A.N.S.) and with assistance from Reckitts and Colman, Duphar Laboratories, and the Incorporated National Association of British and Irish Millers. Miss Elizabeth Drummond gave invaluable help with the recording of the motility data.

References


COLONIC FUNCTION IN PATIENTS WITH DIVERTICULAR DISEASE

M. A. EASTWOOD
W. G. BRYDON
A. N. SMITH
J. PITCHARD

Wolfson Laboratories, Gastrointestinal Unit, Departments of Medicine and Clinical Surgery, University of Edinburgh, and Department of Clinical Chemistry, Western General Hospital, Edinburgh

Summary
Diverticular disease is thought to be associated with prolonged intestinal transit-time, a reduced stool weight, and increased intracolonic pressure. Sixty patients with diverticular disease did not regularly show these features. Variation in colonic function was considerable in these patients and was similar to that in the general population from which the patients were recruited. Constipation may be a complication of diverticular disease and not necessarily part of its aetiology.

Introduction
The management of diverticular disease has changed radically. The rationale for the introduction of dietary fibre into the treatment regimen is based on observations that diverticular disease is characterised by a low stool weight, prolonged intestinal transit-time, and raised intracolonic pressure, all of which are thought to be the result of a reduced intake of dietary fibre. However, since it is not known whether these changes are always present, we investigated colonic function in sixty patients with diverticular disease.

Patients and Methods
Sixty patients with diverticular disease were investigated, but not all in the same detail. All the patients had been at home on their usual diet and were investigated as outpatients after consenting to inclusion in the study. The mean age was 60 years, range 32–84 years. Diagnosis was based on a barium-enema examination preceded by sigmoidoscopy and a clinical examination. Symptoms included constipation, diarrhoea, and pain. In some the disease was asymptomatic and diagnosis was the result of a chance finding. Sixty patients recorded their transintestinal transit-time by means of barium-labelled impregnated markers; such markers not only give a crude estimate of transit-time but indicate the accuracy of stool collection. Thirty patients took polyethylene glycol/chromium sesquioxide (P.E.G./Cr₂O₃) capsules to demonstrate gastrointestinal streaming. The stool was collected and stored at —20°C, pooled, and freeze dried. Faecal wet weight, bile acids, fat, sesquioxide (P.E.G./Cr₂O₃) capsules to demonstrate gastrointestinal transit-time but indicate the accuracy of stool collection; such markers not only give a crude estimate of transit-time but indicate the accuracy of stool collection. Patients and Methods
Sixty patients with diverticular disease were investigated, but not all in the same detail. All the patients had been at home on their usual diet and were investigated as outpatients after consenting to inclusion in the study. The mean age was 60 years, range 32–84 years. Diagnosis was based on a barium-enema examination preceded by sigmoidoscopy and a clinical examination. Symptoms included constipation, diarrhoea, and pain. In some the disease was asymptomatic and diagnosis was the result of a chance finding. Sixty patients recorded their transintestinal transit-time by means of barium-labelled impregnated markers; such markers not only give a crude estimate of transit-time but indicate the accuracy of stool collection. Thirty patients took polyethylene glycol/chromium sesquioxide (P.E.G./Cr₂O₃) capsules to demonstrate gastrointestinal streaming. The stool was collected and stored at —20°C, pooled, and freeze dried. Faecal wet weight, bile acids, fat, electrolytes, sodium, potassium, calcium, and magnesium (Automated Analyzer' after charring with nitric acid), and P.E.G. and Cr₂O₃ were estimated in fifty patients. In forty-one patients colonic motility was tested. Colonic motility was studied with open-ended tubes by means of which both basal measurements and response to food were measured in the distal colon and rectum. Measurements were taken 5, 15, and 25 cm from the anal verge. The amplitude and frequency of the waves were calculated to give the motility index. Inserted from 1 to 19 mmol/24 h (mean 8.0 mmol/24 h). Faecal bile-acid excretion ranged from 0.1 to 1.4 mmol/24 h (mean 0.5 mmol/24 h). The mean basal motility index in forty-one patients was 800 and the post-food motility index was 2200 (range 400–6800) (see accompanying figure).

Discussion
None of these patients had been on any kind of treatment before they were studied, and they may be regarded as being typical of patients coming to an outpatient department. Our results raise some doubts about the overall importance of the “features” of diverticular disease—i.e., low stool weight, prolonged transit-time, and raised intraluminal pressure—which were formerly thought to be characteristic of this disease. The stool weight and transit-time in our patients with untreated diverticular disease were in the same range as those in a normal population—80 g/24 h (range 20–280 g) and 72 h (range 24–186 h), respectively—derived from the same part of Edinburgh and aged 16–80 (unpublished). The motility index in the diverticular-disease patients...
also varied widely. In our patients the range of results for stool weight, transit-time, and colonic motility index was considerable. Thus, patients said to have had the hallmarks of diverticular disease—i.e., low stool weight, prolonged transit-time, and an increased motility index, may more correctly be said to have represented those with special features such as chronic colonic obstruction or constipation. It seems that only a proportion of patients have diverticular disease attributable to a motility disturbance. The pressure change and the transit disturbance may only become prominent at a certain stage in the disease process, such as when there is a degree of obstruction present. Some more subtle change in colonic function or in the strength or integrity of the wall of the bowel may have been present in the earlier stages of the disease.

Preliminary Communications

EXTENSIVE PROLONGATION OF RABBIT KIDNEY ALLOGRAFT SURVIVAL AFTER SHORT-TERM CYCLOSPORIN-A TREATMENT

COLIN J. GREEN ANTHONY C. ALLISON

Divisions of Comparative Medicine and Cell Pathology, M.R.C. Clinical Research Centre, Northwick Park, Harrow, Middlesex

Summary The fungal metabolite cyclosporin A has been administered daily at 25 mg/kg to nephrectomised rabbit recipients of a single renal allograft. After only 4 weeks of daily administration, rejection was prevented for long periods without the need for other immunosuppressive therapy. Renal function has been excellent in all cases, rejection episodes have not been encountered except in a small percentage of animals, and the surviving recipients are still in excellent health 3–6 months after transplantation. The possibility that clones of responding lymphocytes might be selectively killed by this agent was suggested from earlier experiments and prompted this study. If toxicity is not encountered in man cyclosporin A may prove valuable in preventing rejection of organ and bone-marrow allografts and might be useful in treating some leukaemias of lymphoid origin.

INTRODUCTION

Cyclosporin A, a fungal metabolite with potent anti-lymphocytic activity, has been evaluated as an immunosuppressive agent in animals. It inhibits humoral immunity by reducing plaque-forming cells and haemagglutination titres in mice, and suppresses cell-mediated immunity to skin allografts, graft-versus-host disease, and experimental allergic encephalomyelitis in rodents. The agent proved highly active in treating chronic inflammatory reactions but exerted only weak cytotoxicity for lymphoblasts of both T and B cell origin while leaving intact clones of lymphocytes later able to respond to a specific antigenic challenge (e.g., allogeneic cells) while leaving intact clones of lymphocytes later able to respond to other challenges such as virus infections. This in turn suggested that short periods of administration might be sufficient to prolong graft survival indefinitely, thus avoiding the problems of continuous therapy with steroids. We have done experiments with short periods of daily cyclosporin A in recipients of rabbit kidney allografts followed by withdrawal of all therapy.

MATERIALS AND METHODS

Animals Sandy Lop rabbits of either sex weighing 3–4 kg were used as donors. Both kidneys were removed, and one was allografted into each of two New Zealand White rabbits by end-to-end anastomosis. The recipient's contralateral kidney was removed at the same time. In every experiment the anaesthesia (fentanyl-fluanisone induction, nitrous-oxide/oxygen maintenance), fluid replacement, and postoperative supportive therapy were identical.

Assessment of Function

Post-graft renal function was assessed by observation of kidney colour and urine production; by blood-urea (urease method); by an index of renal function obtained by integrating the blood-urea with respect to time over the first 14 days (normal values 6.5±3.5 mg/dl in unoperated rabbits and 8.2±4.2 mg/dl in rabbits autografted with fresh, unstored kidneys); by serum-creatinine (alkaline-picrate method), normal values 6.5±3.5 mg/dl in unoperated rabbits and 8.2±4.2 mg/dl in rabbits autografted with fresh, unstored kidneys; by serum-creatinine (alkaline-picrate method), normal values 6.5±3.5 mg/dl in unoperated rabbits and 8.2±4.2 mg/dl in rabbits autografted with fresh, unstored kidneys; by clinical appearance, including weight and food and water intake; and by macroscopic and microscopic appearance of kidneys at necropsy (hematoxylin and eosin and periodic-acid/Schiff).

The day of operation was taken as day 0. The time of rejection was taken as that day in which the rabbit first showed symptoms of uraemia and was killed. Blood-samples were taken for full haematological investigation, and axillary and popliteal lymph-nodes were examined at necropsy.

Treatment

Cyclosporin A (Sandoz Ltd., Basle) was dissolved in olive oil at a concentration of 50 mg/ml and remained in solution so that it was administered daily for 4 weeks by intravenous injection (the dose being 50 mg/m2 of body surface area).

This work was done during the tenure of a grant SHERT 491 and with the assistance of Reckitt and Colman, Duphar Laboratories, and the Incorporated National Association of British and Irish Millers. Miss Elizabeth Drummond gave invaluable help with the recording of the motility data.

Requests for reprints should be addressed to M.A.E., Wolfson Gastrointestinal Laboratories, Western General Hospital, Edinburgh EH4 2XU.

REFERENCES


8. The Lancet, June 3, 1978
Effects of bile salts and prostaglandins on colonic motility in the rabbit

J. DIANE FALCONER, A. N. SMITH AND M. A. EASTWOOD

Following the ingestion of food there is an increase in motor activity throughout the gastrointestinal tract, originally attributed to a neural mechanism by Pavlov in 1910. The persistence of the phenomenon following the destruction of the spinal cord raises the possibility that a humoral mechanism might be involved. The intravenous injection of gastrin has been shown to stimulate small bowel and colonic motility. Similarly cholecystokinin has been shown to increase the intestinal transit rate. Both gastrin which has a choleretic action and cholecystokinin which empties the gall bladder could exert these effects through the agency of bile, which has been shown to stimulate intestinal motor activity. Exaggerated colonic motility is a feature of cholerhoeic enteropathy in patients in whom the output of bile acids is markedly elevated. Part of this response could be due to the secretory and the exudative effects known to be produced by bile salts from the colonic mucosa.

METHODS

In order to elucidate whether there is a direct action of bile acids on the motility of the colon a series of animal experiments were designed. These took the form of acute experiments in rabbits anaesthetized with a mixture of halothane and nitrous oxide. The abdomen was opened and the terminal ileum tied to prevent the further passage of bile into the colon. A pressure-recording tube was passed into the rectum to 15 cm. Motility was recorded from two sites 5 cm apart, at 15 and 10 cm from the anal verge. The results are expressed as a colonic motility index (MI), obtained by taking the mean of the peak heights in mmHg and multiplying it by the percentage of time of
wave activity. In the tests, 5 ml boluses of bile acids, sodium glycocholate and sodium deoxycholate were instilled into the bowel, in concentrations ranging from 3 to 30 mM respectively.

These are the main bile acids present in the rabbit gastrointestinal tract and represent primary and secondary bile acids respectively. In a separate series of experiments prostaglandin E₂ was infused into the sigmoid colon under similar conditions.

Comparisons of the action of bile acids were made with detergents of three main types, and with control volumes of normal saline and of water. Experiments were also performed in vitro on isolated rabbit large and small intestine. Tissue was suspended in a glass organ bath filled with warmed Tyrode solution (37 °C) and aerated with 95% O₂ + 5% CO₂. Isotonic contractions were recorded from the longitudinal and from the circular muscle layers of the rabbit gut respectively. Any mechanical displacement produced by the gut was recorded on a potentiometer via a mechanical transducer. The tissue was allowed to equilibrate for an hour before the application of any drug agents to the Tyrode solution; the tissue was then primed with the cholinergic drug carbachol until a reproducible dose-response relationship was established. Six-minute cycles were used for the addition and wash-out of various drugs under test.

RESULTS

The effects of sodium glycocholate (Na GC) infused into the sigmoid colon of the anaesthetized rabbit

Pre-infusion and post-infusion motility indexes were calculated after the administration of varying concentrations (9–24 mM) of the primary bile acid sodium glycocholate. From the results in Table 67.1, it is seen that sodium glycocholate produced only minimal changes in the motility of the sigmoid colon. The changes in the motility indexes did not differ significantly from those produced either by distilled deionized water or isotonic saline.

<table>
<thead>
<tr>
<th>Concentration (mM)</th>
<th>Pre-infusion MI</th>
<th>Post-infusion MI</th>
<th>Change in MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>363</td>
<td>446</td>
<td>83</td>
</tr>
<tr>
<td>15</td>
<td>113</td>
<td>98</td>
<td>-15</td>
</tr>
<tr>
<td>15</td>
<td>248</td>
<td>269</td>
<td>21</td>
</tr>
<tr>
<td>24</td>
<td>205</td>
<td>229</td>
<td>24</td>
</tr>
<tr>
<td>24</td>
<td>101</td>
<td>109</td>
<td>8</td>
</tr>
<tr>
<td>Mean</td>
<td>206 ± 107</td>
<td>230 ± 142</td>
<td>24 ± 36</td>
</tr>
</tbody>
</table>

5 ml water and isotonic saline (n = 6)

| Mean               | 84 ± 46         | 86 ± 57         | 2 ± 37       |

Not significant
The effects of sodium deoxycholate (Na DC) infused into the sigmoid colon of the anaesthetized rabbit

The post-infusion motility indexes resulting from the infusion of 5 ml of Na DC (3–30 mM) were significantly different from the pre-infusion motility indexes ($p < 0.001$). The changes in motility indexes produced by Na DC (mean 285 ± 211) were significantly different from those produced by control infusions of distilled deionized water or isotonic saline (mean 2 ± 37, $p < 0.01$). In every experiment, infusion of Na DC produced an increase in the motility index. The results of these experiments are shown in Table 67.2. The motor effect of Na DC occurred in 5.4 ± 2.9 min and had a duration of 2–3 h.

### Table 67.2 Infusion of 5 ml Na DC into the sigmoid colon of the rabbit

<table>
<thead>
<tr>
<th>Concentration (mM)</th>
<th>Pre-infusion MI</th>
<th>Post-infusion MI</th>
<th>Change in MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 ($n = 1$)</td>
<td>129</td>
<td>182</td>
<td>53</td>
</tr>
<tr>
<td>6 ($n = 4$)</td>
<td>313 ± 136</td>
<td>433 ± 211</td>
<td>120 ± 97</td>
</tr>
<tr>
<td>9 ($n = 1$)</td>
<td>152</td>
<td>185</td>
<td>32</td>
</tr>
<tr>
<td>12 ($n = 1$)</td>
<td>79</td>
<td>197</td>
<td>118</td>
</tr>
<tr>
<td>18 ($n = 1$)</td>
<td>234</td>
<td>354</td>
<td>120</td>
</tr>
<tr>
<td>24 ($n = 24$)</td>
<td>135 ± 104</td>
<td>488 ± 205</td>
<td>353 ± 205</td>
</tr>
<tr>
<td>30 ($n = 1$)</td>
<td>398</td>
<td>522</td>
<td>124</td>
</tr>
<tr>
<td>Mean</td>
<td>166 ± 123</td>
<td>451 ± 206</td>
<td>285 ± 211</td>
</tr>
</tbody>
</table>

Onset time: 1–10 min; mean 5.4 ± 2.9 min
Duration: 2–3 h

5 ml water and isotonic saline ($n = 6$)

| Mean | 84 ± 46 | 86 ± 57 | 2 ± 37 |

$p < 0.01$

### Effects of Na DC on the activity of isolated rabbit intestinal tissue

The effect of Na DC was tested on the spontaneous activity and on a cholinergic stimulus given to the rabbit intestine. The results are summarized in Table 67.3. Carbachol almost uniformly contracted jejunal and colonic tissue, and acted in a like manner on both longitudinal and circular muscle. Na DC concentration $2 \times 10^{-7}$ mM, relaxed the longitudinal muscle of the jejunum, and produced no effect on colonic tissue, whether longitudinal or circular muscle. Furthermore, it produced a partial inhibition of the carbachol response when applied to both jejunal and colonic muscle. This is seen in Figure 67.1 where the contractile effect of $8 \times 10^{-9}$ moles of carbachol was reduced by $19.2 \times 10^{-6}$ moles of Na DC. Following the administration of the Na DC, it required four successive administrations of carbachol before there was complete return of the contractile effect of this substance. Na DC was therefore without a direct motor action on the isolated rabbit colon.
Table 67.3 Effect of carbachol and Na DC on the activity of isolated rabbit tissue

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Carbachol</th>
<th>Na DC</th>
<th>Na DC + carbachol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jejunum (n = 15)</td>
<td>10^{-10} - 10^{-11} mM</td>
<td>2 × 10^{-7} mM</td>
<td>-</td>
</tr>
<tr>
<td>Longitudinal muscle</td>
<td>13 ↑</td>
<td>2 -</td>
<td>4 -</td>
</tr>
<tr>
<td>Jejunum (n = 2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Circular muscle</td>
<td>2 ↑</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Colon (n = 26)</td>
<td>24 ↑</td>
<td>10 -</td>
<td>8* 2 -</td>
</tr>
<tr>
<td>Longitudinal muscle</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Colon (n = 3)</td>
<td>3 ↑</td>
<td>3 -</td>
<td>2* 1 -</td>
</tr>
<tr>
<td>Circular muscle</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

↑ = Contraction; ↓ = relaxation; - = no effect; * = partial inhibition of carbachol

Nevertheless, it had been shown to be capable of stimulating the in vivo preparation. This suggested the possible intermediary release of an active agent in the wall of the bowel in vivo. Since Na DC actively antagonized cholinergic activity, it did not appear likely that the transmitter substance for this effect would be acetylcholine. Prostaglandins have been shown to be present in the intestinal tissue of many species. In view of the evidence that prostaglandins of the E series are capable of exhibiting a stimulatory action on isolated intestinal tissue of the guinea pig, rat and human, together with the theory that prostaglandins may play a role in maintaining smooth muscle tone of the rabbit isolated jejunum, it seemed possible that a prostaglandin could be...
the intermediary agent necessary for Na DC to produce stimulation of the rabbit colon in vivo.

The action of prostaglandin E₂ on the rabbit sigmoid colon was subsequently examined.

The effect of prostaglandin E₂ (PGE₂) infused into the sigmoid colon of the anaesthetized rabbit

Prostaglandin E₂ was infused into the lumen of the colon in the range 400-800 µg, and produced a marked increase of the motility index. The changes in MI produced by PGE₂ (mean 458 ± 238) differed significantly from those produced by control administrations of water and isotonic saline (mean 2 ± 37, p < 0.001) (Table 67.4). The onset time was 1-5 min, with a mean of 2.5 ± 1-8 min, and the average duration was 2 h.

Both PGE₂ and Na DC had a stimulatory action of long duration when infused into the sigmoid colon of the anaesthetized rabbit. The possibility that Na DC may act via the release of PGs was examined using the prostaglandin synthesis inhibitor, indomethacin. The action of Na DC was compared when given both before and after the intravenous administration of indomethacin (2 mg/kg) in individual rabbits.

Table 67.4 Infusion of PGE₂ into the sigmoid colon of the rabbit

<table>
<thead>
<tr>
<th>Dose infused (µg)</th>
<th>Pre-infusion MI</th>
<th>Post-infusion MI</th>
<th>Change in MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>0</td>
<td>450</td>
<td>450</td>
</tr>
<tr>
<td>400</td>
<td>0</td>
<td>214</td>
<td>214</td>
</tr>
<tr>
<td>100</td>
<td>0</td>
<td>380</td>
<td>380</td>
</tr>
<tr>
<td>200</td>
<td>206</td>
<td>680</td>
<td>474</td>
</tr>
<tr>
<td>800</td>
<td>28</td>
<td>354</td>
<td>326</td>
</tr>
<tr>
<td>100</td>
<td>137</td>
<td>1042</td>
<td>905</td>
</tr>
<tr>
<td>Mean</td>
<td>62 ± 88</td>
<td>520 ± 298</td>
<td>458 ± 238</td>
</tr>
</tbody>
</table>

Onset time: 1-5 min; mean 2.5 ± 1.8 min
Duration: 2 h

Water and isotonic saline (n = 6)

| Mean | 84 ± 46 | 86 ± 57 | 2 ± 37 |

p < 0.001

Pressure recordings before and after infusion of 24 mM Na DC into the sigmoid colon of the anaesthetized rabbit in relationship to indomethacin administration

Figure 67.2 shows a typical motility record from an animal whose basal motor activity (A) was stimulated by the administration of Na DC. The intravenous administration of indomethacin (B) in a dose of 2 mg/kg markedly reduced the effect of a further infusion of Na DC. Pre-treatment with
indomethacin therefore diminishes the stimulatory effect of the main faecal bile acid of the rabbit. This suggests that the stimulatory action of Na DC may be due to the release of prostaglandins in the wall of the colon.

**Figure 67.2** Intracolonic pressure recording from an anaesthetized rabbit showing: (A) basal pressure altered at arrow by the infusion of 5 ml of 24 mM Na DC into the sigmoid colon, producing stimulation of colonic motility; (B) after the return of basal conditions, indomethacin (2 mg/kg) was administered intravenously at arrow on the left-hand side, followed by a repeat infusion of Na DC as above. The motor stimulation was markedly reduced.

Effects of detergents on colonic motility

In view of the action of bile acids as detergents, and to determine what proportion of the above motor effects were related to this physical property, comparisons were made of the action of Na DC and the anionic, cationic and non-ionic surfactants listed in Table 67.5. All increased the motility index, with an onset time of 2–4 min and a duration of 1–2 h. The changes in M1 produced by these surfactants (mean 132 ± 85) differed significantly from those produced by control solutions of water and isotonic saline (mean 2 ± 37, \( p < 0.001 \)).

The stimulant effect of one of these, namely Tween 80, was examined and shown to be markedly reduced in animals which had been pre-treated with intravenous indomethacin (2 mg/kg).

**DISCUSSION**

The primary bile acid, Na GC, which is not normally present in the colon of
### Table 67.5 Infusion of surfactants and control solutions into the sigmoid colon of the rabbit

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Mean pre-infusion M1</th>
<th>Mean post-infusion M1</th>
<th>Mean change in M1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surfactants</strong> (n = 7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anionic, Cationic and Non-ionic*</td>
<td>120 ± 87</td>
<td>252 ± 124</td>
<td>132 ± 85</td>
</tr>
<tr>
<td><strong>Controls</strong> (n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Water and isotonic saline)</td>
<td>86 ± 46</td>
<td>84 ± 46</td>
<td>2 ± 37</td>
</tr>
</tbody>
</table>

p < 0.001

Onset time: 2-4 min; duration 1-2 h

*Anionic surfactant – Na-n-Octanoate (24 mM); cationic surfactant – cetylpyridinium chloride (24 mM); non-ionic surfactant – Tween 80 (1% solution)

the rabbit, was without effect when infused into the sigmoid colon of the anaesthetized rabbit.

In comparison, the secondary bile acid, Na DC, which is the main bile acid found to be present in the colon of normal rabbits (mean (n = 10) 0.119 ± 0.072 mMoles) stimulated colonic motility when infused into the sigmoid colon of anaesthetized rabbits. The infusion of 5 ml of 24 mM Na DC resulted in the instillation of 0.120 mMoles Na DC in the sigmoid colon, which would have been equivalent to the entire bile acid content of the large bowel entering the sigmoid colon.

However, when examined on in vitro preparations, Na DC did not have any effect on the spontaneous activity of the isolated colon, but did exhibit a partial inhibition of the contractile response produced by a cholinergic stimulus.

The disparity between the in vivo and in vitro effects suggested the existence and release by Na DC of a possible intermediary factor in vivo. PGE₂ was examined as a possible candidate for this role.

Intraluminal infusions of PGE₂ were found to produce a comparable stimulatory action on the motor activity of the sigmoid colon of the anaesthetized rabbit, with a latency and duration of action similar to that of Na DC.

The stimulatory action of Na DC was shown to be reduced after pretreatment of each animal with intravenous indomethacin which is known to block the synthesis of prostaglandins^{8–10}.

Intravenous indomethacin had no such effect on the stimulatory response following the infusion of exogenous PGE₂ into the sigmoid colon; so it is unlikely that indomethacin was having any direct effect on the muscle.

As indomethacin itself was without apparent effect on the pre-infusion resting motility, it was thought that this reduction in the increase of the motility response to Na DC was due to indomethacin preventing the response to Na DC, and not by acting via a reduction in the pre-infusion resting motility.
These results suggest the possible release, by Na DC, of prostaglandins in vivo, resulting in an increased motility of the sigmoid colon.

Whatever the precise mechanism of action of Na DC in eliciting this motility response, the possibility that the response was due to its surfactant properties was investigated.

When either of the surfactants, Na-n-octanoate (anionic), cetylpyridinium chloride (cationic) or Tween 80 (non-ionic), were infused into the sigmoid colon of the anaesthetized rabbit, an increase in colonic motility occurred with a latency and duration of action similar to that of Na DC. In addition the motility response produced by Tween 80 was reduced in animals which had been pre-treated with indomethacin, suggesting that this compound also exerts its action via prostaglandin release.

CONCLUSIONS

From the results it would appear that the secondary bile acid, Na DC, is capable of increasing the motility index of the rabbit sigmoid colon in vivo and that this effect may be due to its surfactant properties. These studies suggest that its mechanism of action may be via the secondary release of prostaglandins in the wall of the colon. A similar mechanism is postulated for the action of Tween 80.

Acknowledgement

This work was supported by SHERT Grant No. 491. This help is gratefully acknowledged.

References

BILE AND COLONIC MOTILITY


The Measurement of Intestinal Transit Time

Adam N. Smith and Martin A. Eastwood

1. INTRODUCTION

Intestinal transit is the phenomenon accomplished by what is at first food, later chyme, and still later feces in making the journey of about one or two days along the alimentary canal. Transit is an important function to study, first because of its relationship to the change from food to chyme; at this stage, digestion is the principal activity affecting intestinal transit, mainly in the small bowel. Second, transit is studied in relation to the production of the formed feces; the retention and the excretory functions of the gut are the activities then under examination. "Intestinal transit" is most often measured as the total intestinal transit time along the whole alimentary tract and as such is mainly a function of propulsion in the small and large intestine. Yet, since there are variable periods of delay in the stomach, cecum, and rectum, such total measurements may be rendered capricious. The contribution of the various sectors of the alimentary tract physiologically to gastrointestinal transit will be summarized first.
II. PHYSIOLOGICAL RELATIONSHIPS

The contribution of esophageal motility is in moving the bolus along the esophagus by peristalsis. On arrival at the stomach, the swallowed material is accommodated by receptive relaxation of the upper stomach. Constrictions invoked by a possible pacemaker in the body spread into the antral area and serve to reduce the food to a smaller particle size. The pylorus relaxes and allows food and H ions to enter the duodenum, but acid in the duodenum inhibits further gastric emptying until neutralization has taken place, when emptying resumes. It does so at the height of another antral wave when osmotic relationships and particle size have been adjusted and are synchronized with pyloric duodenal relaxation, the three components—the antrum, the pylorus, and the duodenum—acting as a unit.

Onward transmission in the duodenum and small intestine is both peristaltic and segmenting in nature. The former is now regarded as the rarer event; the latter mixes the contents to and fro. As a result of contractions that are of greater amplitude and frequency proximally than distally, segmentation drives the chyme downwards along the alimentary tract, though much more slowly than by peristalsis. Measurements of intestinal activity made by radio telemetering capsules show that movement is in abeyance for very long periods; this is true of recorded pressure waves as well. The factors controlling these periods of activity and inactivity are imperfectly understood. Bursts of electrical activity, the interdigestive spike potentials, are recorded between meals and are thought to represent the motor activity of the intestinal tract emptying itself of its contents: according to Code and Martlett—"the housekeeper sweeping the house clean." They are related to neural, parasympathetic activity and possibly also to motilin release. They are inhibited by the further intake of food.

Transmission of contents in the colon is achieved by mass peristalsis, but here also a fundamental role is played by segmentation. This motor activity is, however, more likely to facilitate the slow turnover of contents locally to aid water absorption and thus the conversion from liquid to solid or semisolid feces. It is not known how closely the solidification of the contents to form feces by segmentation and mass peristalsis are related. Mass peristalsis, which occurs mainly postprandially, after breakfast in the majority, leads to feces entering a zone of sensory awareness and to the desire for defecation. Mass peristalsis is also facilitated, it appears, by somatic activity. A relationship of the so-called gastrocolic reflex to hormone release has been sought, but the involvement of any particular hormone such as gastrin is as yet unconfirmed. However, it is classically well documented that food increases the segmenting motor activity and it has alternatively been postulated that a humoral material derived from the duodenum or upper small intestine may affect the sigmoid colon. Cholecystokinin stimulates motor activity of the sigmoid colon in man, whereas secretin and glucagon inhibit it.

Cecum
III. METHODS OF MEASURING GASTROINTESTINAL TRANSIT

A. Gastric Emptying Time

It is clear that the methods for measuring gastric emptying time will influence the emptying time. If the marker that is used to measure emptying time is a solid, the value obtained is quite distinct from one that measures the liquid phase. On the other hand, changes in gastric emptying time that result from enhancing the fiber content of the diet may affect liquid emptying time and solid emptying time. Thus, a complication is added to measurements of this particular phase of intestinal transit.

Studies of the rate at which refined and unrefined carbohydrates leave the stomach of normal subjects have produced conflicting results. McCance et al. measured the rate of emptying of barium sulfate given with food. But Grimes and Goddard used radioactive tracer techniques and were able to measure the rate at which both the solid and liquid components were emptied from the stomach. McCance and his colleagues had indicated that whole-meal bread left the stomach more rapidly than white bread, whereas Grimes and Goddard, using their technique, found no difference in the rates at which the solid phase of the gastric content left the stomach. Liquid left the stomach significantly more rapidly with white bread than with whole-meal bread. Furthermore, the amount of liquid leaving the stomach unaccompanied by solids was significantly greater with white bread than with whole-meal bread. Grimes and Goddard suggested that an interpretation of McCance et al.’s previous work on the barium image of the stomach (that the stomach outline after white bread was small and more concentrated than after whole-meal bread) suggested a more rapid emptying of liquid after white bread. Obviously, in analyzing the results of gastric emptying studies, it is essential to know precisely what is measured by each technique.

An alternative technique is to measure the gastric emptying time by the rate of absorption of some nutrient. Such a technique has been used by Haber and his colleagues. In this study, 10 normal subjects ingested test meals based on apples, each of which contained 60 g of available carbohydrate. The apples were given pulverized, as juice, or whole and intact. There was no significant difference in the rate of rise of plasma glucose or the time or amplitude of peak value.

B. Small-Intestinal Transit Time

Measuring transit time in the small intestine presents formidable problems. Essentially, this technique is the estimation of the mouth-to-cecum transit time. Such a transit time will be influenced by the period of residence within the stomach and therefore, to an extent, it represents duodenum-to-cecum transit. A variety of factors will affect this transit time. Solids, liquids,
and other materials pass along the gastrointestinal tract at differing rates. Another variable may be the intestinal contents; therefore, factors such as the osmolality of the intestinal contents could be important. Another factor is the presence or absence of fiber from the test meal or the habitual diet of the person being studied. A temptation is to measure intestinal transit time in patients with ileostomies\(^6,7\) and to assume that the appearance of markers in the ileostomy bag is representative of what would have happened in the intact person. Almost certainly, however, adaptive changes have occurred in the ileum of ileostomy patients so that to some extent ileal tissue is beginning to adopt some of the function of the removed colon. Therefore, extrapolation from the ileostomy situation to the intact individual may be invalid.

A method that is widely quoted and used in clinical practice uses the head of barium passing along the gastrointestinal tract to give some indication of transit time. However, this again has considerable errors. Barium is a material of substantial specific gravity and therefore merely indicates a facet of the diagnostic technique which perhaps has little physiological relevance.

Kirwan and Smith\(^8\) developed a transit-time method which incorporated an isotope capsule. Localization of the capsule, which contained\(^{131}\)I, was made possible by a portable collimated sodium iodide scintillation counter. The time for capsules to pass from mouth to cecum was always within 8 hr. The techniques used, however, are to an extent artificial. The consequence of the technique can be illustrated by the method developed by Bemair and his colleagues.\(^9\) They used an externally applied magnetic transducer, which senses the presence of an ingested ferromagnetic material as it passes along the small intestine. The mean transit time in a group of 20 normal subjects was found to be \(157 \pm 64\) min, much less than measurements obtained by capsules. It is of interest that the magnesium ferrite remained finely dispersed and did not clump together even after most of the meal was absorbed from the small intestine.

An alternative method of measuring mouth-to-cecum transit time is the utilization of the phenomenon of gas production by colonic bacteria. The three major gasses formed in the colon—hydrogen, carbon dioxide, and methane—are excreted predominantly in the breath. The hydrogen is normally produced almost solely in the colon, and the production depends on the presence of exogenously supplied fermentable substrate, primarily carbohydrate. Bond and Levitt\(^10\) found that variations in the dose of bran influenced their results, so that 10 g of bran had no effect on pulmonary hydrogen excretion, whereas 20 and 30 g of bran caused an increase in pulmonary hydrogen production, which came between 90 and 120 min after ingestion of the bran. On the other hand, they found that only 10 g of lactulose, with a transit time of only \(48 \pm 6\) min, gave a more vigorous response in terms of hydrogen production. Adding bran to lactulose did not significantly alter its rate of movement through the small bowel. The transit time of lactulose with and without bran averaged \(52 \pm 1\) min and \(58 \pm 14\) min (SEM), respectively. Jenkins and his colleagues\(^11\) made
sured the mouth-to-cecum transit time of a variety of fiber analogues: guar, gum tragacanth, pectin, and cholestyramine. They measured the point at which the breath hydrogen began to increase as reflecting the mouth-to-cecum transit time. In their control subjects, the mean transit time was between 90 and 120 min. Guar, gum tragacanth, pectin, and cholestyramine delayed transit time by 75, 30, 15, and 15 min, respectively. Methylcellulose had no effect on transit time, and bran reduced transit time by 45 min. The gums were related to the viscosity of a 1% solution at room temperature, guar having a viscosity of 1.3, gum tragacanth 0.2, pectin 0.21, and methylcellulose 0.07. There was a direct relationship between the mouth-to-cecum transit time and the viscosity ($r = 0.885; p < 0.02$).

The only problem with this technique is that the increase in breath hydrogen is reflecting the fermentation of the lactulose when it is given with the gum or cholestyramine or bran. The presence of the gums or bran could be influencing the onset of hydrolysis of the disaccharide.

The effect of these various polysaccharides on mouth-to-cecum transit time may be important in the enterohepatic circulation. The reduction in cycling frequency due to the presence of mucilaginous polysaccharides might be expected to reduce feedback inhibition of bile-acid synthesis and to increase the bile-acid pool size. This effect is relevant since cholelithiasis is commonly associated with a decreased pool of bile acids, perhaps because there is less bile acid in the gallbladder to dilute the more saturated bile secreted by the liver during an overnight fast. Therefore, altering small-intestinal transit time may cause various fibers to influence the bile-acid pool and the propensity for cholesterol gallstones.

C. Cecal Residence Time

Very few studies have been made that accurately establish the influence of fibers on the bile-acid pool. It is possible using barium enemata to show that there is a remarkable constancy in the sequence of colonic contractions. The initial contraction usually takes place immediately distal to the cecum. Not only is there segmentation with symmetrical contractions, but the whole cecum may rise up relative to the ascending colon. Frequently only part of the cecal contents are expressed, and mixing therefore occurs, a fact which may have considerable metabolic importance. A considerable clue to this has been given by feeding multiple markers on serial days for 1–3 days and estimating the appearance of the first and last of these in the feces. This gives an estimation of colonic turnover, from which a cecal emptying time can be calculated.

D. Total or Transintestinal Transit Time

The rate of passage of material from mouth to anus, total or transintestinal transit time, varies from person to person and even in individuals. Early
measurements were made with dyes and then with spheres, which were modified to plastic barium-impregnated pellets; this last refinement made observations more aesthetically acceptable by permitting collection of feces in plastic bags and X-raying them, rather than finding and counting the spheres! Early observations using the spheres indicated that those swallowed first were not always the first to be passed in the feces and that, to have a representation of gastrointestinal transit, it was necessary to have a whole series of “markers.” In the technique introduced by Hinton and his co-workers and widely followed, 40 markers are swallowed, and the time until 80% of these have been returned is taken as the “transit time.” The marker technique thus elaborated by Hinton et al. has been criticized by Eastwood et al. and Cummings. Eastwood et al. hold that individuals in the same trial might vary by as much as 46 hr, and Cummings pointed out how much transit measured by markers was dependent on the clearance of the last of the markers, which might merely reflect a delay in rectal emptying. A subject might be recorded as having a slow transit because of slow ejection, rather than a slow transit because of prolonged propulsion throughout the alimentary canal.

E. Modification by Fiber

Any effect of diet on transit has to be set against the great variability of the methods of estimation. Obviously, different sources of fiber influence intestinal transit time in different ways. Little information exists on the minimum effective dose of bran or on comparisons of different types of bran and transit time. Most studies have been conducted on individuals taking a self-selected diet rather than on carefully controlled populations.

Wyman and his colleagues have emphasized the variability of transit time in healthy subjects. In their study, 20 healthy subjects eating their habitual diets made repeated 5-day stool collections, the 10 females making their collections over 4–6 successive weeks. There were striking differences in transit time, the mean transit time in females being 82.4 ± 16.7 hr; however, the range for each individual was considerable, e.g., 47 and 123 hr in the same individual. There were no obvious changes related to the phases of the menstrual cycle. In males, the mean transit time was 65 ± 27 hr with a considerable range, though the study in these individuals was less detailed.

In another study, Wyman and his colleagues examined the effect of raw and cooked bran in different doses on intestinal transit and fecal bulk. The diet was essentially low fiber; details were not given, but all fiber-rich cereals and breads were omitted and fruits and vegetables were limited to six specified small portions per day. Significant changes from control values were achieved only with raw bran at 20 g/day. Cooked bran at either dosage had no significant effect on intestinal transit time. They suggested that the cereal manufacturing process alters wheat bran so that cooked bran has less effect on
intestine than does a comparable amount of raw bran. Other factors inherent in the fiber itself are also important. Kirwan et al.\textsuperscript{20} found that 20 g of a coarse bran accelerated slow transit, whereas the same amount of a fine bran had no effect. These effects were paralleled by pressure changes; there was a reduction of pressure by the coarse bran, no reduction or even an increase of intraluminal pressure with the fine bran. Thus, fiber supplements that increase transit speed may have different implications even though they share the common property of bulk expanders.

The effects of other sources of fiber are quite distinct. Kay and Truswell\textsuperscript{21} looked at the effect of 15 g/day of citrus pectin on transit time in a metabolically controlled situation. Pectin was consumed as a gel with fruit and sugar divided doses with meals. The mean intestinal transit time was not altered. Sugar cane fiber, bagasse, has also been studied in normal ambulant volunteers over a 9-month period.\textsuperscript{22} Though there was a significantly higher stool mass with bagasse supplements, the mean intestinal transit times for the radiopaque shapes used were lower but not of statistical significance. At the same time, they measured the mean carmine transit time; this showed that the bagasse biscuit supplement had a significantly lowering effect. This again emphasizes the problems of both diet and method of measuring transit time.

A study by Cummings et al.\textsuperscript{23} of the colonic response to fiber from cabbage, carrot, apple, and bran showed pronounced individual variation, but most of these materials did affect transit time. The effect of bran on the mean colonic transit time was profound, reducing it from 73 ± 24 hr to 43 ± 7.5 hr. The effects of cabbage and apple were less distinct. Cabbage decreased time from a control value of 80 ± 26 hr to 64 ± 20 hr and apple from 80 ± 21 hr to 43 ± 16 hr. The differences were significant at the 5% level, whereas carrot had no significant effect on transit time. These results underline the varying effects of different fiber sources on intestinal transit.

Walker\textsuperscript{24} has looked at the effect of a shorter transit time in South African Negro schoolchildren on a higher fiber regime. These children had a substantial excretion per day of fecal solids, nitrogen, fat, and other components. The average transit time on their habitual diet was about 9.5 hr. Supplements of fiber-rich food only slightly shortened the transit time to an average of about 8.5 hr, indicating that the daily intake of fiber of the children was acting maximally in respect of transit time. Walker was able to show that under conditions of high fiber intake, subsequent dietary supplementation with protein, fat, and carbohydrate had no effect on the fecal constituents, showing no malabsorption. Therefore, such a rapid transit time is not nutritionally disadvantageous.

Markers, being particulate, may not disperse throughout the fecal mass as particles they will not reflect the transit of the gut contents when these are liquid, as in diarrhea. Specific gravity is important in the measurement of transit time. Kirwan and Smith\textsuperscript{8} showed that a capsule with a specific gravity heavier or lighter than the gut contents travels faster than one more closely
related to the specific gravity of feces. The supposition was that, as the capsules were lighter or heavier, they would take up a position closer to the gut wall and be transported by its muscular action more readily. Kirwan and Smith suggested that the differential rate of particle transport through the gut may be one reason why bran, which is known to increase stool weight, can increase the rate of intestinal transit. They suggested, too, that other forms of vegetable fiber could alter the transit rate by altering the specific gravity of the colonic contents. There is also evidence that when fiber increases bulk and weight of feces excreted per day, the transit rate is increased; there is an exponential relationship, with short transit time being associated with high stool weight.21-24

F. Colonic Transit Time

Further studies by Kirwan and Smith27 and Waller28 have shown that there is little change in the small-bowel transit between normal subjects, those with constipation and those with diarrhea. Though Rosswick et al.29 have shown that considerable unexplained transit delay exists in the small intestine in ulcerative colitis, the greatest change in transit in subjects with constipation and diarrhea is in the colon; colon transit is also abnormal in diverticular disease.

The isotope capsule tracked by a hand-held monitor lends itself to this type of study because of the regular topography of the colon. It is fairly easy to follow the capsule from the right colon through the transverse to the left colon and past the pelvic loop to the rectosigmoid. Difficult areas of comparison leading to errors of postural estimation are mainly between a low-lying transverse colon and a long pelvic colon extending inward towards the midabdomen. Serial plots of the maximum radioactivity of the isotope (sodium iodide with 131I) sealed within the capsule allow subsequent correction of any false estimate of the localization of the emission source and thus the capsule site. It can be shown that in normal subjects, transit is slower in the left colon than in the right. In diverticular disease, it is relatively slower by a few hours in all zones when measured by isotope capsule. In contrast, the delay in constipation is mainly in the splenic flexures and rectosigmoid areas and especially in the latter zone, may be 10–20 hr or more greater than in normals, and in some dyschezic subjects, 50 hr or so. Waller28 has shown the slow rate of passage of the capsule in constipation and the correction of this by the administration of purgatives such as senna; and we have shown that bran accelerates the passage of the capsule in all the segments of the colon.27 Waller has also shown fast transit in postvagotomy diarrhea and its reduction by codeine.

Both Kirwan and Smith8 and Waller28 have compared the isotope capsule with Hinton markers, with similar results: the time of excretion of a capsule of specific gravity 1.1 corresponded statistically in the Kirwan and Smith series with excretion time of 81.8 ± 5.3% of the radiopaque pellets. (It is of interest to recall that this 81.8% is a mathematical constant attributed to the Hinton method of measuring transit times, and not the true transit time. In contrast, transit times determined by the capsule method are the actual transit times, i.e., the number of hours the capsule is in transit time. If you measure the transit time of a capsule, the error is only a few hours; if you measure the transit time of a marker, the error is a few days to a few weeks, depending on the method used. This is because the capsule method measures the actual transit time of the capsule, which is the same as the actual transit time of the feces, whereas the marker method measures the transit time of the markers, which is not the same as the transit time of the feces. The correct way to measure transit time is to measure the transit time of the capsule, not the marker. The capsule method is more accurate because it measures the actual transit time of the feces, and not the transit time of the markers.)
that a lighter capsule of specific gravity 0.53 gave a figure of 62.50% of radiopaque pellets, and a heavier one of specific gravity 1.35 gave an excretion time corresponding to 72.3 ± 7.8% of radiopaque pellets.) In constipation, there was a significant correlation between the two methods, the results falling about a line the regression coefficient of which is 0.99; but in diarrhea, the correlation between the methods did not reach statistical significance, as the isotope capsule tended to be excreted earlier than 80% of the radiopaque pellets.

C. Differential Colonic Transit Time

Colonic transit time can be recorded by estimating the passage of a radioisotope capsule along the length of the colon. This can be done by subtracting 8 hr from the time it takes to pass along the entire length of the gastrointestinal tract. Eight hours is the average time from mouth to cecum, and, according to Kirwan and Smith and to Waller, is relatively constant when measured by the radioisotope method. In 10 normal subjects, the estimated colonic transit time was 23 ± 8 hr, while the time measured directly was 25 ± 8 hr. In 5 constipated subjects, the estimated colonic transit time was 187 ± 85 hr, while the direct colonic measured time was 192 ± 92 hr. The time taken averaged 24 hr to pass the hepatic flexure, 78 hr to pass the splenic flexure, and a further 82 hr to pass the rectosigmoid. This was in contrast to 5 normal subjects in whom the capsule took an average of 10 hr to pass the splenic flexure and 20 hr to pass the rectosigmoid.30

H. Mean Transit Time

The most common technique for measuring transit time at the present is to record the passage of 80% of 40 swallowed radiopaque pellets.14 Repeated measurements in the same subjects show wide variations, the average coefficient of variation being about 30%, according to Cummings.16 The mean transit time (MTT) determined by repeated observations was shorter than the 80% transit time, which was 1.6 times the MTT.31 The 80% transit time, as has already been stated, is probably imprecise because it depends on collecting the total markers; this, in turn, is affected by the expulsion of the last of these in defecation, which varies depending on timing and clearance of the remaining markers. To overcome this and minimize the disadvantage of estimating transit at one point in time, a technique was evolved by Cummings and his co-workers to estimate a MTT by feeding small doses of markers over a period of weeks and estimating the turnover. A more accurate MTT could be obtained by reducing the day-to-day irregularities through the expression of the results as a 5-day running average.

This technique showed variations in MTT unrelated to the frequency of defecation, however, and it was deduced that there were other factors, probably
relating to diet. Studies to determine the influence of low and high fiber on MTT established that high fiber caused a fall in MTT. The changes obtained by the 5-day-average method and the 80%-transit-time method were made more statistically significant by combining with the low- and high-fiber tests. Yet the between-subject variation in MTT is still very great, e.g., 33–117 hr for normal subjects, and must reside in some individual or constitutional factor. Studies with Cummings’s MTT method in subjects on control diets and after added fiber showed that those with the slowest initial MTT show a more dramatic change than subjects with fast initial transit, who often show very minimal effects. Harvey et al. postulated that whereas fiber speeded the transit of those with a slow transit, this may be reversed in subjects with a fast transit, and thus the concept of a normalizing role for fiber in gut action was introduced.

The variation in the MTT cannot be reduced when the subjects take a constant diet; the only factor that appears to reduce the fluctuation in the MTT is the addition of fiber to the diet, which, by reducing the time of transit, appears to suppress the variation. The cause of the variation is unknown, though Cummings suggests that it may relate to the amount of exercise taken. Holdstock et al. found that exercise initiated motor activity. Brocklehurst and Khan and Eastwood suggested that lack of exercise might be one of the factors prolonging transit in the elderly and thus contributing to the constipation which they so often develop.

IV. TRANSIT IN RELATION TO OTHER FUNCTIONS

A. Relation to Pressure

The motility paradox of Connell was that diarrhea was associated with low-pressure and constipation with high-pressure waves. This may depend on the local conditions or the manner in which the motor phenomenon is being studied; e.g., a contraction spreading along an open length of bowel may lead to the equilibration of the pressure change throughout its length with little incremental effect. The physical nature of the contents is also important, since pressure will be more readily generated in the “spaces” near to solid fecal contents. The raised pressure of diverticular disease is further attributable to the subdivision of the bowel into small compartments by the excessive segmenting action of the circular muscle. This might imply delayed transit, but Kirwan and Smith found that in diverticular disease patients, pressure and transit were reciprocally related. Spriggs and Marxer and Manouso et al. further suggest that transit can be faster than normal in diverticular disease subjects who have, for example, an underfilled colon. They also found that the subject had distinctive patterns and that individuals varied greatly.
The increase in rate of transit caused by administration of wheat fiber might have nutritional consequences apart from any effects caused by binding or precipitation by phytates. Studies done at a time of enhanced transit showed an increased fecal fat nitrogen and calcium output. The output of volatile fatty acid was increased, as was that of the fecal bile acids. Colonic water content may be controlled by the VFA concentration. It has been mentioned that water content of the feces is kept as far as possible under control in the fecal lumen. Perhaps a factor such as this is inherent in the finding of Harvey et al. that "Bristol group," that wheat bran speeds transit when intestinal transit is slow, but also slows down fast transit.

B. Relation to Fecal Weight

Burkitt et al., Connel and Smith, Spiller et al., and Findlay et al. confirmed a reciprocal relationship between transit and fecal weight. Spiller et al. found that transit time decreased up to an output of 150 g/day, but beyond this there was no further decrease. The scatter of transit time was small (approximately ± 1 day) above a fecal weight of 140 to 150 g/day. This was so with lesser fecal outputs, when the variation could be ± 2 days or more. The colonic activity was more predictable (in terms of transit) at fecal outputs of 140 to 150 g when the transit averaged 2–3 days. They set the amount of fiber (or equivalent) for a standard diet as the amount that is required to produce a transit of not longer than 3 days and that will yield moist, formed, easily expelled feces, with a wet weight of no less than 140–150 g/day. At this level of fecal output, transit may be compared more uniformly in relation to other variables such as drug action and hormones.

C. Hormonal and Metabolic Influences

Almost all the hormones of the APUD series affect small-bowel motility and may affect colonic motor function as well. Several hormones have been investigated in regard to transit through the entire gastrointestinal tract. Gastrin has been studied in relation to the diarrhea of the Zollinger–Ellinson syndrome, and gastric inhibitory peptide (GIP) with possible release in the dumping syndrome. Motilin, which may affect gut transit, may act as a coordinator in the adjustment of motility to the delivery of nutrients at rates sufficient to fulfill calorie expenditure ratios. Secretin may have opposite functions, but whether these are part of a physiological mechanism of control is unknown. Prostaglandins, though not of the APUD series, have been related to the diarrhea of medullary carcinoma of the thyroid, and their effects on the intestinal transit have been directly studied. Prostaglandin E, increased the transit rate through the small intestine and the colon and produced abdominal colic and the passage of fluid and feces per rectum. Transit was examined in this study
using radioactive pellets; there was a concomitant increase of colonic pressure activity. Thyroxine is also said to increase transit rate, and this may be an explanation of the occasional diarrhea of thyrotoxicosis. Bile acids also cause clinical diarrhea, but motor activity of the intestinal tract has not been intensely studied in such patients, as it was hitherto believed that the main action of the bile salts in the causation of the diarrhea was on mucosal secretion. Motor activity has been shown to be excessive in the distal colon in patients with cholerrehe enteropathy, and it is likely that colonic transit at least is accelerated. Animal experiments have confirmed the motility change in rabbits and have shown that this is due mainly to the secondary bile acid, deoxycholic acid, with prostaglandin release as an intermediary mechanism.

In the colon, many of the changes in transit have been related to bacterial activity and the production of metabolites in response to stasis. Fecal ammonia levels measured by the dialysis bag technique of Wrong et al. were greater on a high-protein diet but less on a high-protein and high-fiber diet, which presumably reduced the transit time. Cummings quotes unpublished work by Bond, Hill, and himself who have also recorded a relationship between urinary phenol and transit, the higher values being associated with slow transit. Urinary sulfate and phenol are bacterial metabolites of dietary protein. It is of some interest that there is a relationship between urinary sulfate and transit in children which is also altered by the presence of fiber in the gut.

D. Changes in Colonic Disease

Differences in transit have been explored particularly in relation to theories of bowel carcinogenesis reviewed by Eastwood et al. In prolonged transit, the colon may harbor bile-acid-splitting organisms, particularly anaerobes of the NDH clostridial type. Short transit times have been recorded in Nigerians and Japanese who have a low bowel-cancer incidence; but when people of these nationalities migrate to the United States, their intestinal transit time increases significantly, to that of the indigenous American, and their incidence of bowel cancer increases. Attention has therefore been directed to the fecal flora and the bowel habits of other population groups that are considered “high” and “low risk” for colonic cancer. Two populations were compared in two areas of Denmark and Finland with a fourfold variation in colon cancer incidence. The relation to other known factors such as dietary fat, neutral or acid steroids and bacterial metabolites was inconclusive, but it appeared that there was a higher intake of dietary fiber in the low-incidence area, suggesting a possible protective role for fiber. Nevertheless, the mouth-to-anus transit times were unchanged in the two groups. The protective role of fiber may be more subtle than merely expediting the clearance from the colon of a hypothetical carcinogenic compound.
The irritable colon syndrome, which in incidence accounts for about 25% of hospital gastrointestinal outpatient attendance has, as one of its forms of clinical presentation, diarrhea rather than the more common symptom, abdominal pain. The transit time in this type is worthy of more complete investigation. In diverticular disease, motility changes and electrolyte shifts suggest some basic disturbance of Ca and Mg ions in the fecal output or perhaps in the wall of the bowel. This decreased electrolyte excretion in association with an enhanced colonic pressure may, however, merely reflect the amount of cation in the colon, as a result of the reduction in fiber and its cation-exchange properties. In diverticular disease, the classical view following the many studies by Painter, is that pressure increases in the distal bowel lumen, and this is the cause of the mucosal extrusion through the wall that becomes the diverticulum. Evidence has been presented in this review that, in diverticular disease, an isotope capsule passes through all the segments of the colon slowly and that it is expedited by bran; yet in other studies, pressure and transit were reciprocally related. Does this imply that there is in some patients an obstructive factor with a rise in pressure and thus a faster transit, and in others, perhaps with stasis, a more prolonged transit with a reduced intraluminal pressure? We have come to doubt that pressure change is the initial change in the diverticular disease state. It could depend on which patients are examined and at what time. Attisha and Smith measured the pressure in diverticular subjects, proceeding to myotomy, and found it to be invariably high preoperatively; yet Eastwood et al. found that the intraluminal pressure, the intestinal transit, and the stool weights were the same in 46 subjects with diverticular disease as in a normal population residing in the same part of Edinburgh. This must raise doubt as to the exclusiveness of some of the features of diverticular disease, such as low stool weight, prolonged transit, and high pressure, which could be more related to stasis in the distal bowel. These subjects may produce waves of larger amplitude at an early stage of the condition before moving into a later, more continuously maintained high-pressure phase of the disease and the full development of the characteristic “triad.” It is of interest that bran is more productive of transit change than fibogel or lactulose and was the only one of these compounds to influence consistently the high-pressure waves.

V. CONCLUSIONS

Published studies on intestinal transit times show that they are subject to great individual variation. Methods need standardization and improvement, not only in relation to transit as an aspect of gut motility, but also in refining the measurement of intestinal absorption, of which the rate of transit is but one variable. Measurement of intestinal transit has become of paramount
importance with the emergence of the study of dietary fiber in relation to gastrointestinal function. Alteration in transit time is one of the characteristic changes described as a response to the administration of cereal fiber. Refining the measurement of transit may enable us to detect abnormalities in diseases attributed to the lack of “roughage” in the Western diet.

REFERENCES


42. Falconer, J. D., A. N. Smith, and M. A. Eastwood. Effects of bile salts and prostaglandins


Faecal Characteristics and Colonic Intraluminal Pressure in Diverticular Disease

M.A. Eastwood, A.N. Smith, W.D. Mitchell and J.L. Pritchard

Wolfson Gastrointestinal Laboratories; Departments of Clinical Chemistry, Clinical Surgery and Medicine, Western General Hospital, and University of Edinburgh, Edinburgh

Key Words. Colon • Diverticular disease • Motility • Bile acids • Sodium • Potassium • Calcium • Magnesium

Abstract. Daily faecal calcium and magnesium outputs were inversely related to food-stimulated colonic intraluminal pressure in diverticular disease subjects. There was no relationship to sodium potassium and bile acid concentrations, nor to intestinal transit.

Diverticular disease of the sigmoid colon can be demonstrated in one-third of individuals over 65 years. Yet symptoms only occur in a small proportion of subjects. Pain is the commonest symptom and may well derive from increased colonic pressure (10). Increased colonic pressure may also be of great importance in the development of the disease. Knowing the mechanism of such an increase may help our understanding of the development of the disease and hence the management of this condition. The great success of fibre therapy of diverticular disease and the fact that fibre influences the gut contents by its bulking action suggests that the luminal contents may play some part in the expression of the diverticular state. The diverticula could however merely be extruded in a degenerative process, and an alternative possibility, then, is that the intestinal luminal contents may exert an effect on the colonic wall or change local conditions initially painless to the painful, fully symptomatic state. This in turn might be what the increased intake of fibre is reversing. We have examined various faecal constituents in diverticular disease to see whether they are related to raised colonic pressure. The measurements include faecal bile acids, faecal fat, cations and stool weight, together with intestinal transit time.

Patients, Materials and Methods

19 patients with diverticular disease (mean age 64 range 47–84 years, 8 males and 11 females) were studied at home whilst taking their habitual diet. The patients were recruited through the radiology department, having had diverticula shown on a barium enema during the previous 2–3 weeks. They had been referred for specialist opinion usually with the symptoms of a change of bowel habit or less commonly abdominal pain. 10 patients presenting with abdominal
pain and 9 with altered bowel habit predominantly, although most patients had both symptoms.

Colonic motility was measured using open tubes with a maintained patency in patients with diverticular disease. Intraluminal pressure was recorded using pressure-sensitive transducers registering on Devices recorders for a basal period of 30 min at 15, 20 and 25 cm from the anal verge. This was followed by a standard meal after which food-stimulated activity was recorded for a further 30 min, following which prostigmine (1 mg) was given intramuscularly and the motility recorded for another 45 min. The wave analysis was done using a D-mac wave analyser relaying to a computer which assessed the number of waves and their height. A motility index as a product of the average amplitude times the percentage activity was calculated for the basal period and for the motor activity induced by food and prostigmine. In no instance did the administration of food or drugs to elicit motility change induce painful responses which might in consequence have provoked or inhibited the response.

The intestinal transit time was measured by the method of Hinton (6). The recovery of markers was never less than 90% and was a reassuring indication of the completeness of the stool collections. Faeces were collected for 5–7 days, homogenised, freeze dried and analysed for bile acids (3), fat (9) and sodium and potassium by flame photometry and calcium and magnesium by atomic absorption spectrophotometry after nitric acid ashing. None of the subjects had been or were on any medication for their symptoms, nor were they on any therapy, e.g., anti-cholinergic therapy, liable to vitiate the results.

Results

Table I shows the results for the individual measurements, with their range which is considerable. The possibility of a relationship between faecal constituents and colonic pressure was examined by correlation coefficients (Table II). There was no correlation between the colonic motility index (basal, food-stimulated or prostigmine-stimulated) and intestinal transit time, stool weight, faecal bile acids or fat.

### Table I. Colonic function and faecal constituents (mean ± SD) in subjects with diverticular disease (n = 19)

<table>
<thead>
<tr>
<th></th>
<th>Intestinal transit time, h</th>
<th>Faecal weight, g/24 h</th>
<th>Total bile acids, mmol/24 h</th>
<th>Sodium</th>
<th>Potassium</th>
<th>Calcium</th>
<th>Magnesium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Wet</td>
<td>Dry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>73 ± 27</td>
<td>94 ± 35</td>
<td>2.4 ± 1.9</td>
<td>6.0 ± 2.9</td>
<td>15.4 ± 6.5</td>
<td>4.2 ± 2.3</td>
</tr>
</tbody>
</table>

### Table II. Correlations between the motility index and colonic function (for calcium and magnesium see figures 1 and 2)

<table>
<thead>
<tr>
<th></th>
<th>Post-food motility index</th>
<th>Post-prostigmine motility index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily stool weight/24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wet</td>
<td>-0.25</td>
<td>-0.31</td>
</tr>
<tr>
<td>Dry</td>
<td>-0.06</td>
<td>-0.18</td>
</tr>
<tr>
<td>Wet stool</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile acids, mM/kg</td>
<td>-0.35</td>
<td>-0.17</td>
</tr>
<tr>
<td>Sodium</td>
<td>-0.38</td>
<td>-0.06</td>
</tr>
<tr>
<td>Potassium</td>
<td>-0.39</td>
<td>-0.29</td>
</tr>
<tr>
<td>Dry weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile acids</td>
<td>-0.10</td>
<td>-0.06</td>
</tr>
<tr>
<td>Sodium</td>
<td>-0.05</td>
<td>-0.02</td>
</tr>
<tr>
<td>Potassium</td>
<td>-0.06</td>
<td>-0.15</td>
</tr>
<tr>
<td>Bile acids, mM/24 h</td>
<td>-0.14</td>
<td>-0.26</td>
</tr>
<tr>
<td>Sodium</td>
<td>-0.02</td>
<td>-0.06</td>
</tr>
<tr>
<td>Potassium</td>
<td>-0.11</td>
<td>-0.16</td>
</tr>
</tbody>
</table>

The statistical test used was a regression correlation test where the significance limits and the population correlation coefficient is zero.
There was a significant negative correlation (fig. 1, 2) between colonic motility stimulated by food and the daily faecal outputs of calcium (mmol/24 h) \( (r = -0.62; p < 0.025) \) and of magnesium (mmol/24 h) \( (r = -0.63; p < 0.01) \).

There was also a significant similar relationship between the concentrations of calcium and magnesium per kg wet weight (calcium \( r = -0.56; p < 0.05 \); magnesium \( r = -0.69; p < 0.01 \)) and motility. The stool dry weight concentrations varied, being significant for magnesium but not for calcium (magnesium \( r = -0.67; p < 0.01 \); calcium \( r = -0.42 \)).

**Discussion**

Over the last decade fundamental advances in our knowledge of the physiology and pathology of diverticular disease, in both the complicated and uncomplicated forms of the disease, have been achieved. A rational treatment based on cereal fibre such as millers' bran has apparently transformed the prognosis for this disease, in that few operations are being performed electively for diverticular disease in main surgical centres. This approach is thought to be based on changing the disturbed physiology (4).

An understanding of the mechanism of the enhanced colonic pressure may be used to help reduce the pressure in the patients with symptoms. The ingestion of different bulking agents — coarse and fine bran (7), ispaghula (2) and sterculia (11) — results, however, somewhat ambiguously in both decrease and increase in colonic pressures. So there remain questions to be answered. One is the relationship of pressure to the severity of the disease process. Originally our understanding of the pathophysiology of this condition was arrived at in patients with symptomatic disease who exhibited raised intraluminal colonic pressure, prolonged intestinal transit and a diminished faecal output (4). In contrast to this, patients in whom diverticular disease was found almost incidentally, by re-
recruitment from the radiology department as outpatients as in this study, do not inevitably show these features (1). Many of them lack the pressure criterion which above all seems to have become the *sine qua non* of the disease and which has been held to be fundamental for the extrusion of the diverticulum. We believe it is important to know why a symptom-free patient with diverticula showing some of these features becomes a symptomatic one, regularly exhibiting all of them. The converse is perhaps even more important in terms of therapy.

Our concept of a luminal factor causing spasm in diverticular disease resulted from observations that in patients with choleraeic enteropathy faecal bile acid excretion was many times greater than normal and this coincided with an increased colonic motility (8). We had anticipated that the faecal bile acids might be concentrated in the pellety stool of diverticular disease with an increased colonic intraluminal pressure. In the present study neither faecal bile acids, faecal fat, stool weight nor transit time correlated with colonic motility. Only diminished faecal calcium and magnesium did and the presence of calcium and magnesium in the faeces is largely dietary in origin. Since the correlation was a negative one it might suggest that local conditions in the colon such as the diminished presence of calcium and magnesium lead to pain *pari passu* with a rise in the motility. This further emphasises the importance of a dietary role in this disease. How this is mediated is not clear, but it may be that both factors, electrolyte concentration and motility change require reversal together by fibre.

Acknowledgement

We gratefully acknowledge that this work was done during the tenure of grant 491 from the Scottish Hospital Endowment Research Trust awarded to A.N. Smith.

References


Received: August 3, 1979
Received in revised form: November 19, 1979

A.N. Smith, Wolfson Gastrointestinal Laboratories, Edinburgh (Scotland)
A STUDY OF
BULKING AGENTS IN ELDERLY PATIENTS

R. G. SMITH1, M. J. ROWE2, A. N. SMITH1, M. A. EASTWOOD1,
ELIZABETH DRUMMOND1 AND W. G. BRYDON3

1University Department of Geriatric Medicine, City Hospital,
Greenbank Drive, Edinburgh EH10 5SB
2St Martin’s Hospital, Combe Down, Bath, Avon
3Wolfson Gastrointestinal Unit, Department of Medicine and Clinical Surgery,
Western General Hospital, Edinburgh

Summary
A study comparing the effects of bran and ispaghula in constipated elderly patients is described. Ispaghula and bran increased the wet and dry stool weight. There were no serious side-effects and no change in colonic pressures. The use of these bulking agents is shown to be better than the traditional use of laxatives in the elderly.

INTRODUCTION
In the elderly, constipation is a common problem which is often difficult to overcome. The introduction of bran into the management of constipation and diverticular disease has made for considerable relief of the distress caused by these conditions. However, in the elderly the use of bulk-providing agents has received minimal attention in clinical trials. This study describes a comparison of the effects of bran and ispaghula (Fybogel) in patients who were found to be constipated when coming into an assessment unit in a geriatric hospital.

Patients, Materials and Methods
Patients admitted for clinical assessment to the geriatric unit of the Royal Victoria Hospital, Edinburgh, were asked if they would participate in the study. The mean age of the patients was 81 years (range 65–96 years) and there were 18 males and 19 females. Each treatment group was strictly comparable in age-group distribution. The Ward Sister decided if the patient was able to co-operate before the patient was approached. Every patient was studied within a week of admission. On the first day a capsule containing 131I was given orally (Kirwan & Smith 1974). The course of the capsule along the intestine was followed with a Pitman Isotope Localisation Monitor 235. At the same time a stool collection was begun and continued over five days. Two capsules containing polyethylene glycol (PEG 4000, 125 mg) and chromium sesquioxide (125 mg) were given three times a day with meals throughout the collection (Findlay et al. 1974a). On the sixth night the bowel was prepared for manometry on the next day using a micro-enema—sodium citrate, sodium alkylsulphate and sorbic acid (‘Micralax’). Manometry involved the introduction of open-ended tubes to 25 cm from the anal margin. Pressures within the lumen of the sigmoid colon at 25 cm were recorded on a Devices single-channel pen-recorder through a Statham model P23 series pressure transducer (Attisha & Smith 1969).

The collected stool was frozen and stored at −20°C. Wet and dry weight were obtained by weighing before and after freeze-drying. The pooled collection was homogenized, freeze-dried

23
and analysed for bile acids (Evran & Janssen 1968), fat (Varley 1967), sodium and potassium by flame photometry, and calcium and magnesium by atomic-absorption spectrophotometry after nitric-acid ashing. None of the subjects was receiving any therapy, e.g. anticholinergic drugs liable to influence the colonic results.

For the next 28 days each patient was allocated to one of three treatment courses. One group was given one ispaghula sachet night and morning; or wheat bran (American Association of Cereal Chemists standardized bran) 10 g twice daily, given in the morning with milk and in the evening in soup. A control group was left to the customary practice of the Ward Sister: this treatment was confined to the use of laxatives if the nursing staff thought the patient was becoming uncomfortable due to constipation. Fifteen patients received ispaghula, 10 patients bran and 12 were control subjects.

At the end of three weeks of treatment the pre-treatment study was repeated in full whilst on treatment.

RESULTS

Thirty-seven patients completed the study. Ten others started but had to be withdrawn because of bed occupancy requirements, change in their medical status, or initial misconception of what was entailed. None of the subjects failed to complete the study because of the bulking agent being unacceptable.

In 17 patients the initial intestinal transit time exceeded five days whereas in only seven subjects did the transit time exceed five days after therapy. In the ispaghula-treated patients the transit time decreased in 13 of the 15 patients and in four of the bran-fed

| Table I. Mean stool weight and range (g/24 h) using ispaghula and bran |
|---------------------------------|---------------------|---------------------|---------------------|
|                                  | Ispaghula           | Bran                | Control             |
|                                  | (Fybogel)           | mean (range)/24 h   |                     |
| Stool weight (g)                 | Pre                 | During              | Pre                 | During              |
|                                 | 37                  | 75                  | 27                  | 62                  |
|                                 | (0.7-94)            | (7-170)             | (8-58)              | (12-83)             |
| Dry weight (g)                   | 10.2                | 20.2                | 7.9                 | 16.8                |
|                                 | (0.3-23)            | (6-54)              | (2-19)              | (3-29)              |
| Faecal bile acids (mM)          | 0.26                | 0.54                | 0.4                 | 0.54                |
|                                 | (0.06-0.72)         | (0.02-1.75)         | (0.03-0.6)          | (0.03-2.0)          |
| Faecal fat (mM)                  | 4.2                 | 7.9                 | 3.6                 | 4.8                 |
|                                 | (0.6-11.8)          | (0.7-18.4)          | (0.3-7.8)           | (1-11.3)            |
| Motility index                   | Basal               | Post food           |                     |
|                                 | 1345                | 0-2825              | 3165                |
|                                 | (2116)              | (0-6425)            | (3434)              |
|                                 | 1938                | (0-6525)            | 3231                |
|                                 | (1833)              | (0-6425)            | (3219)              |
|                                 | (300-6750)          | (1075-6850)         | (1425-5850)         |
| PEG/Cr ratio                     | 0.0                 | 0-3.8               | 0.84                |
|                                 | 1.1                 | 0-3.5               | 2.1                 |
|                                 | 1.44                | 0-4.9               | 0.6                 |
|                                 | 1.05                | 0-1.9               | 0.9                 |
| Sodium                           | 0.84                | 0-2.2               | 4.9                 |
|                                 | 2.1                 | 0.1-5.7             | 10.2                |
|                                 | 0.6                 | 0.2-1.1             | 3.5                 |
|                                 | 0.9                 | 0.1-2.5             | 7.7                 |
| Potassium                        | 4.9                 | 1-10.2              | 10.2                |
|                                 | 3.5                 | 0.5-23.4            | 1.3-10.4            |
|                                 | 7.7                 | 3.5                 | 1.6-10.9            |
| Magnesium                        | 2.7                 | 0.1-7.1             | 3.7                 |
|                                 | 1.6                 | 0.3-10.4            | 1.6                 |
|                                 | 4.0                 | 0.4-4.4             | 4.0                 |
| Calcium                          | 8.9                 | 0.5-19              | 13.3                |
|                                 | 1.6-29.7            | 0.3-10.4            | 7.8                 |
|                                 | 2.8-19.9            | 2.8-19.9            | 2.8-19.9            |
|                                 | 0-11.9              | 0-11.9              | 0-18.1              |
patients, but in eight of the control subjects there was also a material decrease in the transit time. The mean stool weight was initially small but was in general markedly increased by bran and ispaghula (Table I; Fig.). There was no change in the control group. The results were analysed using Wilcoxon’s matched-pairs signed rank test.

Fig. Wet stool weight (g/24 h).

There was a statistically significant increase in the wet stool weight \((P < 0.002)\) and dry weight \((P < 0.05)\) in the patients taking ispaghula. The change in stool weight did not reach significance for bran, and was unchanged in the control group. There was an enhanced excretion of faecal bile acids and fat in the patients receiving ispaghula \((P < 0.01\) and \(P < 0.05\), respectively). The colonic motility did not change significantly in the ispaghula group, the bran group or the control group. In many patients the initial stool output did not allow for the measurement of the chromium in the stool. However, in those where it was possible to measure PEG and chromium, there was a trend for the
ratio PEG/chromium to return to unity on hydrophilic colloid therapy. In control patients in both collections the stool was too small to allow for measurement of the PEG/chromium ratio.

Table II shows that the concentration of faecal constituents, bile acids, fat and electrolytes did not fall consistently. This reflects an enhanced excretion of the faecal contents along with the increased stool weight.

Table II. Concentration of faecal constituents [mM/kg wet weight stool: mean (range)]

<table>
<thead>
<tr>
<th></th>
<th>Ispaghula</th>
<th></th>
<th>Bran</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>During</td>
<td>Pre</td>
<td>During</td>
</tr>
<tr>
<td>Faecal bile acids</td>
<td>6.9 (2.0–10.8)</td>
<td>5.9 (0.68–10.9)</td>
<td>8.3 (1.9–15.5)</td>
<td>8.2 (2.1–26)</td>
</tr>
<tr>
<td>Faecal fat</td>
<td>109 (59–185)</td>
<td>106 (17–232)</td>
<td>142 (17–423)</td>
<td>92 (36–254)</td>
</tr>
<tr>
<td>Sodium</td>
<td>26.4 (5.8–69)</td>
<td>25.7 (1.3–51)</td>
<td>24 (6.2–50)</td>
<td>14.1 (1.1–19.4)</td>
</tr>
<tr>
<td>Potassium</td>
<td>133 (74–266)</td>
<td>123 (70–244)</td>
<td>116 (66–227)</td>
<td>131 (93–181)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>106 (30–529)</td>
<td>55 (20–168)</td>
<td>60.3 (21–95)</td>
<td>70 (47–98)</td>
</tr>
<tr>
<td>Calcium</td>
<td>294 (106–773)</td>
<td>180 (63–346)</td>
<td>326 (97–1242)</td>
<td>213 (109–360)</td>
</tr>
</tbody>
</table>

**Discussion**

Constipation in the elderly is one of the problems which can precipitate admission to hospital. On admission most of these patients were embarrassed by faecal impaction. In general, patients receiving either ispaghula or bran were not enthralled with these preparations. It should be recognized that these were elderly patients coming into hospital for assessment as they were not coping at home. Many, after the period of assessment, were returned to their homes and independence. It will be seen that the initial stool weight was very low with a mean value of between 28 and 37 g (range 0.7–94 g/24 h). This faecal output is substantially less than the initial stool weights for a previous study on patients with diverticular disease where the same faecal bulking agents were used (Eastwood et al. 1978). In that study the average age was 60 (range 32–84) and the mean initial stool weights were 75 to 95 (range 25 g–199 g). In the present study the output of faecal constituents, bile acids, fat and electrolytes was reduced (Eastwood et al. 1978); so these elderly subjects though excreting less faeces were not excreting a highly concentrated stool. This must imply a certain reduction in the output of substances normally excreted in the stool. This appears to be reversed by the use of ispaghula and bran.

The effect of ispaghula and bran was to increase considerably the wet and dry weight of stool, though only after ispaghula was the increase significant. The enhanced excretion of bile acids, fat and electrolytes kept the faecal concentration constant so that there was none of the dilution effect which has been shown for bran in the past (Findlay et al. 1974b). The failure of stool weight to increase on the control regime implies that the effects attributed to bran and ispaghula were not just due to coming into hospita.
Patients with diverticular disease treated with ispaghula had shown a significant increase in stool weight but there was no increase in faecal fat or bile acid excretion (Eastwood et al. 1978).

The basal motility indices were low. There was no effect of either compound on colonic pressure compared with controls, both for the basal period and also after stimulation by food. This is again in contrast to the diverticular disease study (Eastwood et al. 1978) where ispaghula increased the basal pressure but not the food-stimulated pressure and when bran regularly lowers the intracolonic pressure after food and prostigmine.

It is also noteworthy that whilst there were modest increases in the excretion of electrolytes these did not reach statistical significance. This suggests that the use of bran or ispaghula in the elderly is not associated with risks from an enhanced loss of important minerals.

The regular administration of bran or ispaghula would appear to have great advantages. Ispaghula has been shown to be free of side-effects and there was no undesirable increase in colonic pressure in this study in the constipated elderly subjects such as had been found previously in patients with diverticular disease. The use of bran and ispaghula as valuable bulk providers over a period of a month is a better ward practice than one in which laxatives are routinely given when the elderly patient is uncomfortable with severe constipation, and the availability of the two preparations offers a choice to the elderly patient.

ACKNOWLEDGEMENTS

This work is supported by Reckitt & Colman Ltd, the Incorporated National Association of British and Irish Flour Millers and S.H.E.R.T. Grant No. 491.

We are also grateful to the nursing staff at the Royal Victoria Hospital, Edinburgh, for their considerable help during this study and to the Consultants for allowing their patients to take part.

REFERENCES


The Effects of Bile Acids on Colonic Motility in the Rabbit

J. DIANE FALCONER, A. N. SMITH and M. A. EASTWOOD

From the Wolfson Gastrointestinal Laboratories, and Departments of Medicine and Clinical Surgery, Western General Hospital, Edinburgh EH4 2XU, and the University of Edinburgh, Scotland.

(RECEIVED FOR PUBLICATION 6 DECEMBER 1979)

The content of the rabbit colon has been examined and found to contain the secondary bile acid deoxycholate. Infusions of sodium deoxycholate stimulated colonic motor activity, but the infusion of the primary bile acid sodium glycocholate did not have this effect. Infusions of control amounts of distilled deionized water and isotonic saline were not followed by a significant change in motor activity. Histological damage was caused by 15 mmol l⁻¹ solutions but was not severe till above 24 mmol l⁻¹. The possibility that mucosal damage produced motor activity was discounted by the fact that this damage was also present in rabbits treated by sodium glycocholate with no observed motor response. It is postulated that the secondary bile acid, sodium deoxycholate, could have a role in the production of colonic motor activity in the rabbit.

The ingestion of food stimulates motor activity throughout the gastrointestinal tract, a phenomenon which was originally attributed to a neural mechanism by Pavlov in 1910. Motility persists, however, following destruction of the spinal cord and the possibility that a humoral mechanism might be involved was therefore raised. Various gastrointestinal hormones influence gut motility. Both gastrin, which has a choleretic action, and cholecystokinin, which stimulates the gall-bladder, could exert these effects through the agency of bile, which has been shown to stimulate intestinal motor activity [Kirwan, Smith, Mitchell, Falconer and Eastwood, 1975]: exaggerated colonic motility was, for example, a feature of cholerrhoeic enteropathy in patients in whom the faecal bile acids were markedly elevated. Part of this response could, however, have been due to the secretory effects known to be produced by bile salts in the colonic mucosa filling the lumen and indirectly leading to mechanical stimulation. The question of a direct motor action though referred to [Shiff, 1979] has not been fully explored. This has now been studied by examining the actions of primary and secondary bile acids on colonic motility in the rabbit, injecting amounts which were first established as relating to the concentration of faecal bile acids present in the colon in these animals.

Methods

Acute experiments were designed in which rabbits were anaesthetized with a mixture of halothane and nitrous oxide (final concentrations 33% O₂ 1-1₂%)
fluothane, 66% N₂O). The abdomen was opened and the terminal ileum tied to prevent the passage of further endogenous bile from the small bowel into the colon. A multi-lumen tube was passed into the rectum to 15 cm and changes in colonic pressure were recorded from 2 sites, 5 cm apart, 15 and 10 cm from the anal verge. The results are expressed as a colonic motility index (MI) obtained by taking the mean of the peak height in mm (Hg) and multiplying it by the percentage of activity time. Five millilitre boluses of sodium glycocholate and sodium deoxycholate were instilled as molar solutions into the bowel, through the lumen of the pressure tubing which opened at 15 cm from the anus. The concentrations of the bile acids administered ranged from 3–30 mmol.L⁻¹. The bile acids injected were the two main bile acids present in the rabbit gastrointestinal tract, and represent primary and secondary bile acids respectively.

To estimate the concentration of bile acid likely to be present in the colon of the rabbit, the intact colon was removed immediately after some of the experiments. Other rabbits were killed independently of any experiment and the entire bowel contents including the gall bladder removed. In each case the bowel was placed in a polythene bag and cut longitudinally: distilled water (500 ml) was placed in the bag, which was tied and shaken manually for several minutes. This was stored at 6°C overnight. The next day the bag was again shaken manually, the bowel removed and washed 5 times with 100 ml distilled water which was subsequently added to the bag. This technique resulted in a faecal-free bowel the contents of which had been mixed with 1 litre of distilled water. The mixture was then homogenized for several minutes using a stomacher 3500 (Colworth) and treated as follows: approximately 75 ml of homogenate were transferred to a 100 ml round bottom flask, and frozen around the surface of the flask by rotating the flask, in acetone cooled by a Cryo-cool instrument. The frozen homogenate was then freeze dried using a Chemlab instrument. The method of performing these is described by Mitchell and Eastwood [1972].

For the motility experiments, controls were performed by administering boluses of isotonic saline and deionized water in similar volume to the amount used with bile acids. Similar controls were made with Tris buffer. To diminish any additional effects relating to the possibility of mechanical stimulation through the secretory action of the bile salt, colonic material was allowed to drain via one of the channels of the multi-lumen pressure tubing. The histology examination were done according to routine laboratory procedures.

Results

1. Total bile acid concentration of the small bowel, large bowel and gall bladder

The bile acid content of the entire bowel, including the gall bladder, was investigated in three stock rabbits. The contents of the large bowel were all removed at the termination of 10 experiments (in none of which had exogenous bile been infused into the rabbits).

The results of bile acid analysis of the contents are shown in Tables I and I.
Table 1. The concentrations and amounts of bile acids found in the small bowel, large bowel and gallbladder of the rabbit.

<table>
<thead>
<tr>
<th>Rabbit weight</th>
<th>Wet weight of faeces</th>
<th>Dry weight of faeces</th>
<th>D.C.A. mg g⁻¹ dry faeces</th>
<th>L.C.A. mg g⁻¹ dry faeces</th>
<th>Total B.A. mg g⁻¹ dry faeces</th>
<th>D.C.A. total mgs</th>
<th>L.C.A. total mgs</th>
<th>Total B.A. total mmol</th>
<th>D.C.A. total mmol</th>
<th>L.C.A. total mmol</th>
<th>Total B.A. total mmol</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.55 kg</td>
<td>134 g</td>
<td>43.0 g</td>
<td>3.82</td>
<td>0.19</td>
<td>4.01</td>
<td>164.26</td>
<td>8.17</td>
<td>172.43</td>
<td>0.420</td>
<td>0.022</td>
<td>0.442</td>
</tr>
<tr>
<td>4.05 kg</td>
<td>208 g</td>
<td>63.49 g</td>
<td>2.82</td>
<td>0.15</td>
<td>2.97</td>
<td>179.04</td>
<td>9.52</td>
<td>188.56</td>
<td>0.458</td>
<td>0.025</td>
<td>0.483</td>
</tr>
<tr>
<td>5.82 kg</td>
<td>251 g</td>
<td>89.60 g</td>
<td>2.17</td>
<td>0.09</td>
<td>2.26</td>
<td>194.43</td>
<td>8.06</td>
<td>202.49</td>
<td>0.497</td>
<td>0.022</td>
<td>0.519</td>
</tr>
<tr>
<td>Mean (n=3)</td>
<td></td>
<td></td>
<td>2.94</td>
<td>0.14</td>
<td>3.08</td>
<td>179.24</td>
<td>8.58</td>
<td>187.83</td>
<td>0.458</td>
<td>0.023</td>
<td>0.481</td>
</tr>
</tbody>
</table>

D.C.A.—Deoxycholic Acid
L.C.A.—Lithocholic Acid
Total B.A.—Total Bile Acids

Methyl-ketone derivatives
The 3,12-di-keto-methyl ester derivative of deoxycholic acid (DCA) was the main bile acid derivative present in the bowel of the rabbit; a 3 keto-methyl ester derivative of lithocholic acid (LCA) was also found to a lesser extent. DCA derivatives constituted $95.2 \pm 0.53\%$ of the total bile acid content of the first set of animals and $90 \pm 5.30\%$ of the latter group of animals.

2. Comparison of the endogenous bile acid content of the rabbit colon and the amount of exogenous bile acid infused into the colon of the experimental rabbits

The infusion of 5 ml of 24 mmol l$^{-1}$ NaDC into the sigmoid colon resulted in the instillation of 0.120 mmol of NaDC within the sigmoid colon of the rabbit. This amount was within the normal range found to be present in the large bowel of the rabbit (DCA derivatives varied from 0.023 to 0.235 mmol) and shows a close correlation to the mean amount of DCA, $0.119 \pm 0.072$ mmol found to be present in the large bowel of the rabbits examined. There was considerable variation in the concentration (total bile acids 0.34 to 1.97 mean 1.35 ± 0.62 mg per gram dry faeces) and total amounts, (total bile acid 0.028 to 0.257 mean 0.129 ± 0.077 mmol) of bile acids found to be present in the large bowel of the rabbit. There was no significant relationship between the basal motility and the bile acid contents found in these rabbits respectively. Table II shows the basal motility occurring in relationship to the concentration and total amounts of bile acid found in the large bowel of the rabbit.

### Table II. The basal M.I., concentrations and total amounts of bile acid found in the large bowel of the rabbit.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>mg g$^{-1}$ dry faeces</td>
<td>mg g$^{-1}$ dry faeces</td>
<td>mg g$^{-1}$ dry faeces</td>
<td>total mmol</td>
<td>total mmol</td>
<td>total mmol</td>
</tr>
<tr>
<td>0.84</td>
<td>0.10</td>
<td>0.94</td>
<td>0.070</td>
<td>0.009</td>
<td>0.079</td>
</tr>
<tr>
<td>1.74</td>
<td>0.11</td>
<td>1.85</td>
<td>0.122</td>
<td>0.008</td>
<td>0.130</td>
</tr>
<tr>
<td>1.69</td>
<td>0.15</td>
<td>1.84</td>
<td>0.235</td>
<td>0.022</td>
<td>0.257</td>
</tr>
<tr>
<td>1.29</td>
<td>0.06</td>
<td>1.35</td>
<td>0.134</td>
<td>0.007</td>
<td>0.141</td>
</tr>
<tr>
<td>0.86</td>
<td>0.21</td>
<td>1.07</td>
<td>0.057</td>
<td>0.014</td>
<td>0.071</td>
</tr>
<tr>
<td>0.41</td>
<td>0.05</td>
<td>0.46</td>
<td>0.031</td>
<td>0.004</td>
<td>0.035</td>
</tr>
<tr>
<td>1.59</td>
<td>0.15</td>
<td>1.74</td>
<td>0.191</td>
<td>0.019</td>
<td>0.210</td>
</tr>
<tr>
<td>1.88</td>
<td>0.09</td>
<td>1.97</td>
<td>0.130</td>
<td>0.007</td>
<td>0.137</td>
</tr>
<tr>
<td>0.28</td>
<td>0.06</td>
<td>0.34</td>
<td>0.023</td>
<td>0.005</td>
<td>0.028</td>
</tr>
<tr>
<td>1.86</td>
<td>0.10</td>
<td>1.96</td>
<td>0.194</td>
<td>0.011</td>
<td>0.205</td>
</tr>
<tr>
<td>0.24</td>
<td>0.11</td>
<td>1.35</td>
<td>0.119</td>
<td>0.011</td>
<td>0.129</td>
</tr>
<tr>
<td>±0.50</td>
<td>±0.05</td>
<td>±0.62</td>
<td>±0.072</td>
<td>±0.0</td>
<td>±0.077</td>
</tr>
</tbody>
</table>

Mean (n = 10).
The effects of primary and secondary bile acid infusions into the sigmoid colon

(a) Control experiments. As the bile acids used were dissolved in distilled-deionized water and instilled in 5 ml volumes it was first necessary to examine the effect of distilled deionized water alone, before the bile acids themselves. There was no significant difference between the preinfusion and post-infusion MIs produced by either the infusion of 5 ml of distilled deionized water (pre-infusion MI = 93 ± 34, postinfusion was 88 ± 9, change in MI = −5 ± 42) or 5 ml of isotonic saline (pre-infusion MI = 93 ± 28, post-infusion MI = 128 ± 62, change in MI = 35 ± 65) into the sigmoid colon. The changes in MI produced by 5 ml of distilled deionized water were not significantly different from the changes in MI produced by 5 ml of isotonic saline. Therefore it appeared that both distilled deionized water and isotonic saline were without effect when 5 ml volumes were infused into the sigmoid colon of the rabbit.

The relationship between the volume of solution infused and the pressure changes produced was then examined. The differences between the preinfusion MI and the post-infusion MI's were only significant if 15 ml of distilled deionized water had been infused (pre-infusion MI = 69 ± 34, post-infusion MI = 128 ± 26, change in MI = 60 ± 10 P < 0.01). However, neither a 30 ml volume of distilled-deionized water nor any volume of isotonic saline which was tested produced a notable difference between the pre-infusion and the post-infusion MI's. Five to seventy-five millilitres of distilled deionized water produced a mean pre-infusion MI = 98 ± 56, post-infusion = 120 ± 57, change in MI = 22 ± 32, 5-50 ml of isotonic saline produced at pre-infusion MI = 109 ± 58, post-infusion MI = 115 ± 65, change in MI = 6 ± 39. It was therefore unlikely that there was any significant relationship between the volume of solution infused and the change in MI produced by either distilled deionized water in the range 5 to 75 ml of isotonic saline in the range 5–50 ml.

(b) Effects of sodium glyco-cholate. Pressure changes were recorded within the sigmoid colon, following the infusion of 5 ml volumes of varying concentrations (9–24 mmol l−1) of the primary bile acid sodium glyco-cholate infused into the sigmoid colon of anaesthetized rabbits. It is seen (Table III) that sodium glyco-cholate produced only minimal changes in the motility of the sigmoid colon. There was no significant difference between the preinfusion MI and the post-infusion MI produced by any concentration of NaGC (pre-

<table>
<thead>
<tr>
<th>Concentration of NaGC</th>
<th>Pre-infusion M.I.</th>
<th>Post-infusion M.I.</th>
<th>ΔM.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 mmol l−1</td>
<td>363</td>
<td>446</td>
<td>83</td>
</tr>
<tr>
<td>15 mmol l−1</td>
<td>113</td>
<td>98</td>
<td>−15</td>
</tr>
<tr>
<td>15 mmol l−1</td>
<td>248</td>
<td>269</td>
<td>21</td>
</tr>
<tr>
<td>24 mmol l−1</td>
<td>205</td>
<td>229</td>
<td>24</td>
</tr>
<tr>
<td>24 mmol l−1</td>
<td>101</td>
<td>109</td>
<td>8</td>
</tr>
<tr>
<td>Mean (n = 5)</td>
<td>206 ± 107</td>
<td>230 ± 142</td>
<td>24 ± 36</td>
</tr>
</tbody>
</table>

Table III. The change in M.I. produced, following the infusion of 5 ml of sodium glychocholate (NaGC) into the sigmoid colon of the anaesthetized rabbit.
infusion $MI = 206 \pm 107$, post-infusion $= 230 \pm 142$, change in $MI = 24 \pm 36$). Furthermore the changes in MI produced by NaGC did not differ significantly from those produced by either distilled deionized water or isotonic saline. It would appear that NaGC was inactive in altering the motility of the sigmoid colon over the range of concentrations tested.

(c) **Pressure change within the sigmoid colon following sodium deoxycholate.** The secondary bile acid, sodium deoxycholate, would normally be found in the colon of the rabbit, sodium glycocholate being more likely to have been re-absorbed in the terminal ileum or converted in the caecum to sodium deoxycholate.

Table IV shows the effects when 5 ml volumes of varying concentrations (3-30 mmol. l$^{-1}$) of secondary bile acid sodium deoxycholate were infused into the sigmoid colon of the anaesthetized rabbit. The post-infusion MI's resulting from

<table>
<thead>
<tr>
<th>Concentration of NaDC</th>
<th>Pre-infusion M.I.</th>
<th>Post-infusion M.I.</th>
<th>$\Delta$M.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mmol. l$^{-1}$ ($n=4$)</td>
<td>313 $\pm$ 137</td>
<td>433 $\pm$ 211</td>
<td>120 $\pm$ 96</td>
</tr>
<tr>
<td>3-18 mmol. l$^{-1}$ ($n=8$)</td>
<td>231 $\pm$ 132</td>
<td>331 $\pm$ 184</td>
<td>100 $\pm$ 73</td>
</tr>
<tr>
<td>24 mmol. l$^{-1}$ ($n=23$)</td>
<td>126 $\pm$ 95</td>
<td>490 $\pm$ 209</td>
<td>364 $\pm$ 202</td>
</tr>
<tr>
<td>24-30 mmol. l$^{-1}$ ($n=24$)</td>
<td>137 $\pm$ 109</td>
<td>491 $\pm$ 205</td>
<td>354 $\pm$ 204</td>
</tr>
<tr>
<td>3-30 mmol. l$^{-1}$ ($n=32$)</td>
<td>160 $\pm$ 120</td>
<td>451 $\pm$ 209</td>
<td>291 $\pm$ 211</td>
</tr>
</tbody>
</table>

the infusion of 5 ml volumes of NaDC (3-30 mmol. l$^{-1}$) were significantly different from the pre-infusion MI (pre-infusion $MI = 160 \pm 120$, post-infusion $MI = 291 \pm 211$ $P<0.001$). The changes in MI produced by NaDC were also significantly different from those produced by distilled deionized water (mean change in $MI = -5 \pm 42$, $P<0.025$) isotonic saline (mean change in the motility index $= 35 \pm 65$, $P<0.05$). In every experiment infusion of NaDC produced a positive increase in MI.

The regression line, relating with varying concentrations of NaDC to the changes in MI produced, shows a direct relationship between the concentration of NaDC and the change in the motility index produced ($P<0.01$). There were many more tests carried out using a 24 mmol. l$^{-1}$ solution of NaDC than with solutions in the lower range of concentrations, 3-18 mmol. l$^{-1}$. With such a large scatter of points at the level of 24 mmol l$^{-1}$, it is unlikely that this curve gives a total indication of the relationship. From Fig. 1 it can be deduced that there would be no significant difference between the changes in MI produced by the infusion of 5 ml of 6 mmol. l$^{-1}$ NaDC (mean change in motility index $= 12 \pm 96$) and the changes in MI produced by the infusion of either 5 ml of distilled deionized water (mean change in motility index $= 5 \pm 42$) or isotonic saline (mean change in motility index $= 35 \pm 65$); furthermore, there was no significant difference between pre-infusion MI and the post-infusion MI's produced by the infusion of 6 mmol. l$^{-1}$ NaDC (mean pre-infusion MI $= 313 \pm 137$, post-infusion MI $= 433 \pm 211$, changes in MI $= 120 \pm 96$).
However, the changes in the MI produced by 24 mmol.l. NaDC (mean change in motility index = 364 ± 202) were significantly different from the changes in MI produced by either distilled deionized water (mean change in MI = 5 ± 42, P < 0.005), or isotonic saline (mean change in MI = 35 ± 65, P < 0.02). Therefore the infusion of 5 ml of 24 mmol.l. NaDC into the sigmoid colon of the anaesthetized rabbit produced a positive change in the motility of the sigmoid colon in the region of 10-15 cm, proximal to the anal verge. The onset of the increased motility varied from 1-10 minutes after the infusions of NaDC (mean onset time 5.4 ± 2.9 minutes). Once this increased bowel activity had commenced it continued for 2-3 hours.

(d) Variability of the results. Figure 2 illustrates a wide variation in pre-infusion MI between individual rabbits. As there was no significant relationship between the pre-infusion MI and the change in MI produced by the infusion of 24 mmol.l. NaDC (n = 23), it appeared that the large scatter of post-infusion MI must be due to biological variation and not to resting basal mobility. The coefficient of variation for the results obtained 24 mmol.l. NaDC is 55.5% and for those obtained with 6 mmol.l. NaDC was 80%.
(c) Relationship between the pH of sodium deoxycholate infused and the pressure changes produced. The solutions of 24 mmol.1\(^{-1}\) NaDC infused in the sigmoid colon of the rabbit had a pH 9.2–9.6. The increased activity occurring following the infusion of 24 mmol.1\(^{-1}\) NaDC could have been a result of the high pH solution. However, a single infusion of 5 ml of Tris buffer of pH 9.1 into the sigmoid colon produced a comparatively minimal increase in the MI (change in MI = 54), whereas a single infusion of 5 ml of 24 mmol.1\(^{-1}\) NaDC dissolved in phosphate buffer (pH 7.3) produced a response (change in MI = 473) similar to that obtained when 24 mmol.1\(^{-1}\) NaDC was dissolved in distilled deionized water and when a pH 9.2–9.6 was used (change in MI = 36 ± 202). Table V illustrates the above relationship. It would appear that the increase in the motility of the sigmoid colon following infusion of 24 mmol.1\(^{-1}\) NaDC was not a result of the high pH of the solution.

(f) Histological changes of the sigmoid colon. Histological changes were apparent at concentrations greater than 15 mmol.1\(^{-1}\) and were those of mucosal damage only. Above 30 mmol.1\(^{-1}\) the changes became transmural and the fluid in the bowel could become haemorrhagic. These histological changes were
The change in M1 produced, following the infusion of 5 ml of three solutions into the sigmoid colon of the anaesthetized rabbit:

(i) NaDC (H2O) = sodium deoxycholate dissolved in distilled-deionized water, at pH 9.2-9.6,
(ii) NaDC (PO4) = sodium deoxycholate dissolved in phosphate buffer solution, at pH 7.3,
(iii) Tris buffer, pH 9.1.

<table>
<thead>
<tr>
<th>Concentration/solution</th>
<th>pH</th>
<th>Pre-infusion M1</th>
<th>Post-infusion M1</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 mmol.l⁻¹ Na DC (H2O)</td>
<td>9.2-9.6</td>
<td>126 ± 95</td>
<td>490 ± 209</td>
<td>364 ± 202</td>
</tr>
<tr>
<td>(n = 23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 mmol.l⁻¹ Na DC (PO4)</td>
<td>7.3</td>
<td>128</td>
<td>601</td>
<td>473</td>
</tr>
<tr>
<td>(n = 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tris Buffer</td>
<td>9.1</td>
<td>374</td>
<td>428</td>
<td>54</td>
</tr>
<tr>
<td>(n = 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

equally apparent using NaDC and NaGC. Since motility changes featured in NaDC experiments but not in the NaGC ones it would appear that the histological change, present after infusion of either compound, was not the factor stimulating the motor activity.

Discussion

The examination of bile acid content present in the small bowel, large bowel and gall bladder taken from pre- and post-experimental rabbits shows that DCA is the main bile acid present in the rabbit and verifies that the amounts used in the experimental procedures were within the physiological range in respect of the levels found in the colon of these animals [Falconer, Smith and Eastwood, 1977]. It was of interest that there was no significant relationship between the resting bile acid content and basal motility index. Furthermore the initial basal motility did not appear to have any bearing on the motility index following stimulation by exogenous bile acid. This may mean that the bile present in the colon had already elicited motor effects and that it is only when this is added to incrementally that a motility effect becomes apparent. If so, some adaptation must already exist because some animals had a plentiful local supply of bile. Nevertheless, as the infusion of additional increments of NaDC, the principal bile acid of the rabbit colon, produced additional motor activity, the results strikingly confirm that sodium deoxycholate has a motor action. This is in marked contra-distinction to the primary bile acid, sodium glycocholate, which has no such effect when tested on colonic motor activity; the relative inactivity of sodium glycocholic acid on the motility of the colon in the range of concentrations tested could, however, be partly the result of its greater insolubility. As a conjugated bile acid, NaGC would be almost completely reabsorbed in the terminal ileum and any remaining would be converted in the caecum to the secondary bile acid sodium deoxycholate by the process of bacterial deconjugation and 7 alpha-dehydroxylation. Greater bowel motility was produced by control amounts of isotonic saline or distilled deionized water than by the infusion of sodium glycocholate. If the motor activity following NaDC resulted from damage it might have been expected that
this phenomenon would be present in both groups of animals given NaGC and NaDC, but this was not the case.

It is of some interest that patients with bile acid problems may have motility stimulation associated with severe clinical diarrhoea [Kirwan et al., 1975]. The motor activity might be considered to have resulted from excessive secretion within the lumen of the colon. Care was taken, however, to aspirate additional lumen content during the conduct of the experiments. The motor activity would also have tended to increase with repeat tests of control solutions if this had been due to additional secretory material within the lumen. The fact that there was no significant relationship between the volume of control solutions infused and whether distilled deionized water or isotonic saline was used was of significance, but also in relationship to the possibility that by bulk action they might have stimulated motor activity.

It is of interest that bile acids have been shown recently to produce spiking on recording the electrical potentials from the smooth muscle of the colon [Flynn, Darby, Hammond, Hyland and Taylor, 1979], and that this follows the administration of the secondary bile acid deoxycholate but not the primary bile acid sodium glycocholate, a result in keeping with the present experiments.

References

Pressure changes after balloon distension of the colon wall in diverticular disease

A N SMITH, * J SHEPHERD, † AND M A EASTWOOD

From the Gastrointestinal Unit and Departments of Clinical Surgery and Medicine, University of Edinburgh and Western General Hospital, Edinburgh

Summary Balloon distension of the distal colon in diverticular disease does not produce the pressure change in response to increasing volumes that occurs in normal subjects. This phenomenon, though modified at first by resection, is not abolished by resection nor by myotomy or bran. This adaptive quality of the wall of the colon to balloon distension possibly reflects a structural change in its wall, as the phenomenon was present in the colon in diverticular disease in vitro as well as in vivo.

The muscle of the large intestine is capable of producing a raised intraluminal pressure in diverticular disease.1 2 The force created may have a critical role in extruding the diverticulum. Furthermore, the reduction of the pressure appears to be beneficial in that symptoms become less and complications may become fewer.3 A paradox exists, however, in that balloon distension of the colon in diverticular disease4 produces a premature relaxation of the colonic wall indicating that it has developed characteristics which suggest reduction in its inherent strength. This phenomenon has been examined in normal subjects and in patients with diverticular disease with and without symptoms. The effects of treatment by cereal fibre and operations such as resection or myotomy which lower the intraluminal pressure1 are also assessed.

Methods

Normal subjects and patients with diverticular disease before resection and myotomy were examined by passing an open-ended tube and large balloon system, similar to that of Parks,5 as far as the rectosigmoid junction. The balloon was attached to a triple lumen tube used for measuring intraluminal pressure and allowed inflation of the balloon. This was done in 20 ml increments over the range of 20–200 cm H2O pressure and the change in the balloon pressure was measured graphically by attachment to a pressure transducer activating a preamplifier and linked pen-writing system. The change in the inserted balloon pressure reflected the tension in the wall of the colon rather than the distensibility of the balloon itself. This could be deduced from pressure/volume curves for balloon distension in vitro to the point of rupture: a very low pressure was established in the balloon at first, which differed from the pressure curve established when the balloon was placed within the colon of normal subjects. The pressure in vitro later rose to become similar to those obtained in the colon of normal subjects over the range 120–180 ml H2O as the distending volume (Fig. 1). Above this figure (at 200 ml) the balloon finally ruptured in vitro, though not necessarily in vivo because of the support of the colonic wall. These observations suggested that, at the low or mid-part of the curve, the response of the balloon reflected the contribution of the muscle of the colon. As the reactions in diverticular disease show a failure to maintain pressure even in the 'normal range', this could be considered as representing a weak response of the supporting wall of the colon, as was observed by Parks and Connell.4 Measurement was made of the point where the graph plateaued and this was considered the critical point of pressure change. Each subject was studied in duplicate and his critical pressure derived from the average of the two tests.

Results

Figure 1 shows in graphical form how a critical point is reached in the balloon pressure in a normal
subject at 55 cm H₂O pressure and in diverticular disease at 30 cm H₂O pressure, beyond which on serial distension little or no further increment of pressure takes place, and how in diverticular disease the pressure within the distending balloon may even fall with ‘adaptation’. In Fig. 2 the mean critical pressure derived from such tracings is shown for 10 subjects with no symptoms (I) and 10 others (II) with no alimentary disease but with severe recent constipation; there was no significant difference in the critical pressure—that is, in the adaptation levels of the responses. In contrast 10 diverticular disease subjects (I) without symptoms (Fig. 2) and (II) 10 with pain and recent constipation had a significantly lower pressure at which the balloon pressure fell on distension by similar serial 20 ml volumes (p<0-001). Figure 3 shows the critical pressure in seven of the diverticular subjects who were to have resections performed. It will be seen that the critical pressure was the same when the subjects were examined in vivo and when their specimens were tested in vitro.

---

**Fig. 1** A pressure volume curve after balloon distension in the colon in a normal subject and in one with diverticular disease, relating the tension in the colon wall in cm H₂O to serial distending volumes. The effect of distending the balloon in vitro is also shown and was followed by balloon rupture at 200 ml.

**Fig. 2** Ten symptomless subjects (I) and a similar number (II) with constipation are compared with 10 symptomless (I) diverticular disease patients and 10 symptomatic (II) cases; the results are expressed as means of the critical pressure ± SE.

**Fig. 3** Tests repeated in the same subjects; the mean critical pressure in seven subjects with diverticular disease examined in vivo compared with the critical pressure determined in vitro on resected specimens from the same subjects and again in vivo one month after resection. This is also compared with three subjects in whom the colonic circular muscle had been divided by the operation of colomyotomy.
Pressure changes after balloon distension of the colon wall in diverticular disease

...post-operatively ($p<0.001$). When the same patients were examined a month after the resection, their critical pressure had risen to become similar to that of normal subjects. These responses were in marked contrast with three other subjects with diverticular disease who had had a myotomy performed, in whom the critical pressure remained low. When the same resection patients were tested at one year (Fig. 4) the critical pressure had fallen to the level of diverticular disease; there had been no change in the post-myotomy cases. Ten diverticular disease patients, both symptomatic and asymptomatic, and who had been treated with bran (Fig. 5), showed no significant change; nor did bran affect the properties of the colonic wall in normal subjects.

The responses to the distension at the rectal level were identical though less marked than at the rectosigmoid level.

![Diagram](image)

Fig. 4 The resection and myotomy studies were repeated one year later and are compared with the findings for normal subjects and for diverticular disease.

![Diagram](image)

Fig. 5 The low critical pressure of diverticular disease is seen to be uninfluenced by bran, whether the diverticular disease subjects have (I) or have not (II) got symptoms. The higher critical pressure of normal subjects was uninfluenced by bran.

**Discussion**

Colonic intraluminal pressure in diverticular disease is raised, but only 'consistently' in patients with low faecal outputs and a delayed transit.7 Parks and Connell4 and Parks6 showed, however, that the wall of the bowel in diverticular disease, though capable of generating the raised pressure, is remarkably adaptive to distension and demonstrated how it yielded prematurely to colonic balloon distension compared with normal subjects. We have confirmed this and have shown that the phenomenon is present in vitro as well as in vivo, as it is present in tests in excised specimens as well as in subjects in vivo.

Resection of the pelvic colon which removes the diverticula does not appear to change the ready tendency of the colonic wall to relax, other than temporarily in the first month after operation. Myotomy, which lowers the intraluminal pressure,3 did not change the relaxation of the wall nor did the administration of bran, which also reduced the intraluminal pressure.8 It is unlikely, therefore, that bran influences the painful motor action of the pelvic colon in diverticular disease by an easier emptying of the distal bowel through a relaxation of its wall, as this change is already present in diverticular disease.

The fact that the phenomenon of relaxation after distension is present in diverticular disease and is not influenced by in vivo or in vitro testing or by treatment—be it by division or resection of the
muscle or by bulk additives such as bran—suggests an intrinsic derangement of the arrangement of the collagen or muscle fibres of the colonic wall. Although a continually raised intraluminal pressure may be one factor which causes this change as well as extruding the diverticulum, it would appear that even if the pressure is reduced by treatment, the response to distension is not readily changed.

We are indebted to support from the Scottish Hospitals Endowment Research Trust Grant No. 418.

References


The effect of coarse and fine Canadian Red Spring Wheat and French Soft Wheat bran on colonic motility in patients with diverticular disease


ABSTRACT Bran from a Canadian Red Spring Wheat of both a coarse and fine type was compared with that from a French Soft Wheat, also with coarse and fine characteristics. The coarse type whether Canadian or French had the more significant effect on the stool weight, speeded the intestinal transit as measured by Hinton markers, and reduced intraluminal pressure in the colon more than did the fine types from the same sources in patients with diverticular disease. The texture of a bran may be important in relationship to its clinical efficacy.

KEY WORDS Diverticular disease, intraluminal pressure, transit, wheat bran

Introduction

Interest continues to be focussed on the manner in which the fiber residues behave in the gastrointestinal tract (1). It is now accepted that prolonged administration of fiber increases the stool bulk, speeds up transit, and reduces the intraluminal pressure in the colon (2). Coarse cereal fiber is (3) more efficacious than finely milled fiber, and it appears that the phenomenon is related to physicochemical properties which bind water, increase the fecal bulk, and influence colonic transit and pressure.

The question thus arises whether the action of fiber on the gut is a result of the physical character, e.g., the size, of the fiber particles alone, or is influenced by the chemical structure of the fiber source, given that fiber from different sources and countries may vary in composition. For this reason it was decided to investigate whether wheat from two different (Canadian and French) sources and of two varying physical characteristics (fine and coarse) possessed the same or differing effects on the function of the colon.

Methods

Patients were recruited from the outpatient clinics of the Gastrointestinal Unit, Western General Hospital, Edinburgh. Twenty-four patients successfully completed the protocol. The patients were not receiving any medication.

All the patients were studied for a control week on their normal dietary intake during which they collected stool, and on completion their intestinal transit time was measured by the method of Hinton et al. (4), in which the time taken for a series of plastic shapes to pass through the alimentary tract was estimated radiologically. Pressures in the rectosigmoid region were registered intraluminally, in the sigmoid colon, rectosigmoid, and rectum, from an open-ended multilumen tube connected to a series of transducers, and the pressure changes at each level were displayed as wave forms on a standard recording device after amplification. The number and height of the waves was counted on a waveform analyzer. A motility index was derived as an indication of motor activity from the combined wave frequency and magnitude by expressing these as a percentage product of both parameters (5). In this way a representation of the bowel response was obtained. The records obtained for the sigmoid, rectosigmoid, and rectum were comparable, and only those of the sigmoid colon are quoted herein. Pressure was registered in the basal state and after a stimulus such as food, given as a cup of...
tea, toast, and marmalade, after an overnight fast. The purpose of the light meal was to trigger gastrocolic activity and although the caffeine content may have had an effect of its own, this was a constant factor in this and other studies (2).

Patients were randomly allocated into one of four treatment groups each of which took 20 g of bran a day for 1 month either as Canadian Red Spring Wheat Bran or French Soft Wheat Bran, either in a coarse or fine form as obtained from Chancelot Mills, Leith. The chemistry of the brans and their water holding capacity are shown in Table 1. The protein was measured as N × 5.7 and the fat by acid hydrolysis. The carbohydrate analyses were based on the method of Southgate (6). Various differences in the chemistry were noticeable mainly for starch, hemicellulose, and cellulose. The water holding capacities were measured by soaking in water overnight, and represented the water held after centrifugation at 6000 × g for 15 min. The water holding capacity was greater for both types of coarse bran than for the fine brans. Further periods of collection came at the end of the treatment period and were the same as in the control study.

Results

The effects on the stool weight and transit times of Canadian Red Spring and French Soft Wheat, for both fine and coarse varieties, are shown in Table 2. The coarse bran significantly decreased the transit time from whatever source and also significantly increased the stool weight. The effects of bran on motility index are shown in Table 3. Neither coarse nor fine Canadian Red Spring wheat nor French Soft Wheat whether coarse or fine, individually gave significant changes in motility index using parametric or nonparametric analyses. However, pooling the coarse bran results for the entire Canadian Red Spring and French Soft wheat groups showed a significant effect on the postfood motility index (p < 0.05 Mann-Whitney test). This effect was not found in the case of the fine varieties of bran similarly pooled together.

### TABLE 1

**Chemical analyses of bran**

<table>
<thead>
<tr>
<th></th>
<th>Canadian Red Spring Wheat</th>
<th>French Soft Wheat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coarse</td>
<td>Fine</td>
</tr>
<tr>
<td>Protein (g/dry wt)</td>
<td>14.8</td>
<td>15.8</td>
</tr>
<tr>
<td>Fat (g/dry wt)</td>
<td>6.4</td>
<td>6.75</td>
</tr>
<tr>
<td>Starch (g/dry wt)</td>
<td>17.5</td>
<td>25.7</td>
</tr>
<tr>
<td>Pectic substance (g/dry wt)</td>
<td>0.44</td>
<td>0.35</td>
</tr>
<tr>
<td>Hemicellulose (g/dry wt)</td>
<td>22.8</td>
<td>16.3</td>
</tr>
<tr>
<td>Cellulose (g/dry wt)</td>
<td>9.7</td>
<td>8.2</td>
</tr>
<tr>
<td>Lignin (g/dry wt)</td>
<td>4.7</td>
<td>4.0</td>
</tr>
<tr>
<td>Moisture (%)</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Water holding capacity (g water/g fiber)</td>
<td>8.5</td>
<td>6.5</td>
</tr>
</tbody>
</table>

### TABLE 2

**Effects of bran of different sources and type on transit time and stool weight**

<table>
<thead>
<tr>
<th></th>
<th>Canadian Red Spring Wheat</th>
<th>French Soft Wheat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coarse</td>
<td>Fine</td>
</tr>
<tr>
<td>Transit time (h)</td>
<td>56 ± 26</td>
<td>61 ± 16</td>
</tr>
<tr>
<td>(NS)</td>
<td>(&lt; 0.005)</td>
<td>(NS)</td>
</tr>
<tr>
<td>Wt (g)</td>
<td>80 ± 16</td>
<td>96 ± 16</td>
</tr>
<tr>
<td>(NS)</td>
<td>(&lt; 0.01)</td>
<td>(NS)</td>
</tr>
</tbody>
</table>

### TABLE 3

**Effects of bran of different sources and type on motility indices (MI)**

<table>
<thead>
<tr>
<th></th>
<th>Canadian Red Spring Wheat</th>
<th>French Soft Wheat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coarse</td>
<td>Fine</td>
</tr>
<tr>
<td>Basal MI Before</td>
<td>621*</td>
<td>708</td>
</tr>
<tr>
<td>After</td>
<td>384</td>
<td>1022</td>
</tr>
<tr>
<td>Postfood MI Before</td>
<td>1815</td>
<td>967</td>
</tr>
<tr>
<td>After</td>
<td>1563</td>
<td>1563</td>
</tr>
</tbody>
</table>

* Median.
† Range.
Discussion

A diet that is rich in plant fiber is believed by some to be a factor in the prevention of diseases such as diverticular disease. It was as a corollary to this that increasing the dietary fiber content of the diet was introduced to ameliorate the symptoms of diverticular disease (7). It is believed by increasing stool weight that it is possible to abolish the symptoms of pain on the left and right side of the colon. The addition of fiber to the diet of individuals with diverticular disease produces changes in colonic physiology which can be measured, such as an increased fecal bulk, an accelerated rate of transit, and a lowering of intraluminal pressure (8). Feces are approximately 75% water. The fecal dry material is a complex mixture of 40% microorganisms and 40% dietary fiber residue (9). The increased bulk after the ingestion of a cereal fiber intake is believed to be a result of the fiber binding water (10). Other fiber sources are believed to increase stool bulk by a proliferation of bacteria (11).

Fiber acts as a physicochemical influence along the gut, but its physical properties can be modified in the colon by bacteria (11). Cereal bran, however, because of its chemical and physical structure, passes through the gut minimally affected by bacteria (12).

The problem facing the clinician prescribing an enhanced fiber content to the diet is to obtain a predictable response. A vegetable fruit gum or mucilage source of fiber which acts substantially by increasing bacterial bulk is not predictable. It has been shown that the greater the water holding capacity the greater the effect of bran on stool weight (13) or in producing a decrease in intracolonic pressure (3). Cooking or baking the bran reduces or modifies the water holding capacity (14).

It will be seen from the experiments recorded herein that the type of wheat, hard or soft, or the chemistry, is less important than physical factors such as the water holding capacity, either as a predictor of stool bulking function or in reducing intracolonic pressure. The amount of protein and fat are of the same order in the various types of bran. There is less starch in the coarse Canadian Wheat Bran than in the other sources. Similarly in the finely ground wheats (Canadian Red Spring and French Soft Wheat) there is less cellulose present. Overall, the chemical differences are small and are unlikely to account for the differing actions.

The stool also stimulates the motor function of the gut since it appears that stool bulk and time of transit are inversely related (2). The greater the water holding capacity, regardless of origin, the more efficacious is the bran. It would appear that the water holding capacity of cereal bran could be a good and inexpensive indicator of clinical efficacy but the same, however, may not be true of other sources of fiber if they lack this property. Coarse bran is thought to lead to the adsorption of water into the greater inter- and intraparticulate spaces in the fiber particles (15) and in this way it augments the stool bulk and produces a greater change in colonic pressure and intestinal transit. The texture of a bran may, as a result, be more important than any variation in its composition according to its source and this may determine the efficacy when a cereal bran is used to alter the function of the gastrointestinal tract.

The chemical analysis of each type of bran was made through the kindness of Dr. Fisher of Chorleywood.

References

CHAPTER 6

Hydrophilic Colloids in Colonic Motility

M.A. EASTWOOD and A.N. SMITH

A. Introduction

Colonic motor activity has been shown to be of clinical importance in diverticular disease, the irritable bowel syndrome and the patient with colitis who is constipated. A decrease in colonic intraluminal pressure may be obtained by pharmacological agents but increasing stool weight may also decrease colonic pressure.

A curious paradox exists in which a relaxation of the colonic musculature is achieved by an increased bolus of stool. The easiest way to produce an increase in stool weight is by dietary fibre or hydrophilic colloids, either as cereal bran, fruit, and vegetables, or the gums developed by the pharmaceutical industry. The effect of these hydrophilic colloids both on stool weight and colonic pressure is variable. In an attempt to lay a logical basis for treatment regimes, we have discussed the different types of dietary fibre and the problems associated with identifying their physiological properties and their effects on colonic physiology, especially colonic pressure.

The treatment and the theories associated with diverticular disease changed as a result of the work of Painter (1974) who, in defiance of previous concepts, suggested that an increased bulk content of the diet and the faeces might result in a decrease in the pressure of the sigmoid colon. (His hypothesis was that, in parallel with the increase in bulk content of the diet and the decrease in the motility index, there would be an increase in stool weight.) Painter originally emphasised the role of wheat bran as possibly inducing such changes and described its effect on stool weight and intestinal transit. However, the use of dietary fibre in altering stool weight and colonic motility was extended beyond wheat bran, in part because bran is not universally acceptable. It was also recognised that fruit and vegetables can influence stool weight. However, the use of different sources of fruit and vegetables introduced unknown variables and furthermore, the shelf-life of fruit and vegetables is quite short. Therefore in order to meet the demands of contemporary marketing and culinary practice, the food industry has had to provide means of preserving fruit and vegetables, e.g., freezing, canning, and dehydration. In order to extend the shelf-life of fruit and vegetables as sources of dietary fibre it is attractive to use fibre concentrates. In making fibre concentrates, changes occur in the biological properties of the fibre. It is important therefore to develop some logic to anticipate the biological effect of these fibre concentrates along the gastrointestinal tract.

The spectrum of fibre sources is as large as the plant kingdom. There are of course chemical and physicochemical differences between fruit and vegetables. The age, species and anatomy vary; the site and the climatic conditions where the plant
is grown influence the properties of the fibre. The mode of cooking and preparation may make important changes, so that even the relatively simple cereal bran is more complex than appears at first. For example, the varieties of wheat grown in North America and Europe are chemically and physically distinct, and the chemistry and physical properties of each bran are further affected by the particular milling process used and at what milling stage the bran is obtained.

The commonly used hydrophilic colloids provided by the pharmaceutical industry are a quite distinct group of plant materials. These are gums which exude from trees, often grown in arid desert areas. These plants are of immense importance in the ecology of a region, stabilising uncertain water areas. Some of the gums leak from the plant when there is injury and therefore they have a protective role. Others, e.g. ispaghula, are derived from the coats of seeds which grow in desert areas; these become hydrated and hold the available water so as to allow germination to take place.

B. The Nature of Stool Bulk and How it is Provided

There is a considerable variation in colonic function both between subjects and from day to day in healthy subjects. WYMAN et al. (1978) demonstrated the extent of the variability between individual faecal wet and dry weights, the faecal volume and the frequency of defecation. The size of individual stools varied over a ten-fold range. There was no significant difference between males and females. This variation in the weight of individual stools indicates the importance of collecting stools for several days. However, it is not known how long it is necessary to collect stools in order to measure accurately the constituents of the stool and to calculate an accurate daily output. There is little variation in the water content of the stool which has a value of 75% ± 4%.

It is possible that the variability in colonic function is a function of the segmenting activity of the colon. It is known that when the caecum contracts during a barium enema, and the barium is expressed along the colon, some barium remains in the filled caecum (MCLAREN et al. 1955). It has also been suggested in the past by ELLIOTT and BARCLAY-SMITH (1904) that antiperistaltic waves drive the fluid contents of the colon towards the caecum, the antiperistaltic waves being replaced from time to time by peristaltic waves. This type of movement, though it may occur anywhere in the colon, is usually confined to the proximal colon so that the liquid chyme newly received from the ileum is passed to and fro on the surface of the colon for absorption to occur. It is therefore possible that the nature of the contractions makes it impossible for the colon to produce stools of a regular size each day. On the other hand it is conceivable that it is the constituents of the stool, either in concentration or in daily output which dictate faecal excretion. It is also recognised that water-soluble markers of stool content, e.g. PEG 4000 and insoluble markers, e.g. chromium sesquisoxide, may pass along the intestine at differing rates (MITCHELL and EASTWOOD 1976). Such stratification of flow along the intestine does not facilitate our understanding of the events which occur in the transformation of liquid ileal effluent into the normal stool.

There has long been an interest, however, in the manner in which food controls the bulk of faeces. WILLIAMS and OLMSTED in 1936 reviewed the causes of constipation. They stated that both clinicians and physiologists agreed that the indig-
tible carbohydrates of food have a greater effect on stool volume than protein, fat, and carbohydrate. They believed that, of the three classes of carbohydrates which most markedly increased stool weight, hemicellulose was the most efficacious and cellulose in its natural state was somewhat less effective. They suspected that the highly hygroscopic carbohydrates were the most effective. Lignin-containing residues were costive.

They thought that the effectiveness of indigestible residues was not due primarily to the mechanical stimulus of swollen fibre but rather to the chemical stimuli of compounds arising from the effect of intestinal flora on hemicelluloses and celluloses, with the generation in particular of short chain volatile fatty acids. However, it should be noted that in these experiments, as in others, concentrates of fibre isolated from widely differing sources were fed and, as will be explained later, this is not the same as feeding raw vegetables. In more recent experiments Cummings et al. (1978a) showed that enhancing the fat content of the diet from 62 to 152 g/day under metabolic ward conditions did not alter stool wet or dry weight or mean transit time; however, the faecal bile acid excretion increased from 140 ± 63 mg/day on 62 g fat to 320 ± 120 mg/day on 152 g fat. The average faecal fat excretion also increased from 1.14 to 3.1 g/day. Therefore, dietary fat had no effect on overall colonic function. Williams and Olmsted’s concept, however, of short chain fatty acids being important in determining stool weight (1936) has to be reevaluated by the demonstration by McNeil et al. (1978) that the colon readily absorbs short chain fatty acids. They calculated that from a daily intake of 20 g fibre, 10–15 g would be broken down with the production of at least 100 mmol short chain fatty acids. Only approximately 5–20 mmol short chain fatty acids are excreted in the faeces so that 80% of fatty acids must be absorbed. Therefore the role of short chain fatty acids in faecal bulking remains unclear.

I. Water

There is little doubt that water is the most important single component of stool, and represents approximately 75% of the stool weight. The ability of the human colon to absorb fluid is immense, but estimates of the capacity of the large intestine to absorb dietary and secretory fluids vary. The calculation of amounts absorbed depends on the method of study used; whether this be a comparison of ileostomy effluent with normal stools, a comparison of ileal content and faecal output in normal volunteers ingesting their usual diet, or studies of colonic perfusion. From these methods the estimate of absorption capacity varies from 0.5 to 3.1 per day. The studies claiming to represent physiological conditions have tended to examine the absorption of water alone instead of the normal conditions of absorption of water from a gel or sludge. DeBongnie and Phillips (1978) have calculated that the normal colon is capable of absorbing 61/day water and 800 mequiv./day sodium. There is a relationship between absorption, total flow and the rate at which the fluid enters the colon. These authors have speculated that the sudden arrival in the caecum of a large bolus of fluid might cause acute diarrhoea. Unabsorbed solute, e.g. bile acids, possibly fatty acids and carbohydrates, may impair the absorption of water. Notwithstanding this, the stool weight varies between 10 and 500 g in the normal subject, and therefore there must be a factor or factors altering the residual water in the stool.
II. Bacteria

Faeces are complex mixtures of microorganisms, undigested food residues, excreted organic compounds, ions, and water. Whilst there are many studies on the faecal microbial flora, the faecal chemical composition and metabolism, these studies have almost without exception considered the faecal mass as a homogeneous mixture from which chemicals and bacteria can be isolated for study. This holistic view is reasonable in the identification of pathogenic bacteria by the pathologist, but it gives little insight into the role of bacteria in the normal stool. It is perhaps important to know the manner in which particles of fibre interact with microorganisms and other faecal components. Such a study was initiated by Williams et al. (1978) when they examined several specimens of stool by light and scanning electron microscopy. The matrix of faeces contained a large number of bacteria intermingled with smaller amorphous particles of food residue. Many aleurone cells of bran appeared to be intact. In general the various bacterial types were randomly mixed. However, occasional colonies of Gram-positive bacteria and yeast cells could be seen. By scanning electron microscopy, the matrix of fibre residues appeared to be surrounded by the amorphous mass. There are plant hairs and fibres in the stools and bran residues were seen to be undigested. The mass of bacteria consisted of a densely packed mixture of bacteria of quite diverse morphology, i.e. cocci and rods. There were also yeast bodies present. Although some particles of food residues were intermingled with the bacteria, the latter appeared to comprise most of the interfibre substance. Clearly at the interface between the plant residues and bacterial mass there is contact and plant fibres have bacteria on their surfaces. Bacteria are also seen with areas of damage on the outer seed coat of bran residue and other fibre, suggesting that extra cellular bacterial enzymes may be responsible for production of changes within the fibre.

The role of bacteria in the faecal mass has been extended further by Stephens and Cummings (1980), who have used the methods developed by ruminant physiologists to separate fibrous material and bacteria by centrifugation and filtering techniques. They have shown that the stool is made up of 50%-60% bacteria.

III. Fibre

Of the dietary constituents, it would appear that vegetable dietary fibre is a significant contributor to stool weight. From here, problems arise. Dietary fibre has yet to be adequately defined. The chemistry and biological effects of plants vary with their source, the age of the plant and the anatomy of the plant. Cooking and processing add complications to the manner in which the fibre behaves along the gastrointestinal tract.

The definition of the term “dietary fibre” has been the subject of considerable discussion (Trowell et al. 1978). Although of crucial importance, a major stumbling block to a definition of dietary fibre is the function of dietary fibre. Once a definition has been elaborated then, to an extent, thinking becomes less flexible and future ideas on fibre immediately become hidebound by that definition. It would be more appropriate to look at the biological effects of various sources of fibre and thereafter define fibre within that scope. To an extent the term dietary fibre is abs...
Hydropphilic Colloids in Colonic Motility

Table 1. Constituents of dietary fibre

<table>
<thead>
<tr>
<th>Reserve polysaccharides</th>
<th>Starches, e.g. amylose, amylopectin, dextrins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glycogen</td>
</tr>
<tr>
<td></td>
<td>Fructans</td>
</tr>
<tr>
<td></td>
<td>Galactomannans, e.g. guar gum</td>
</tr>
<tr>
<td>Structural polysaccharides</td>
<td>Cellulose</td>
</tr>
<tr>
<td></td>
<td>Peptic substances</td>
</tr>
<tr>
<td></td>
<td>Hemicelluloses</td>
</tr>
<tr>
<td>Nonstructural polysaccharides</td>
<td>Gums</td>
</tr>
<tr>
<td></td>
<td>Mucilages</td>
</tr>
<tr>
<td></td>
<td>Pectin</td>
</tr>
<tr>
<td>Algal polysaccharides</td>
<td>Sulphated, e.g. carrageenan, agar</td>
</tr>
<tr>
<td></td>
<td>Unsulphated, alginate</td>
</tr>
</tbody>
</table>

equately covered by the term “plant cell wall material.” There are those who would like the definition to include the difficult term “indigestible.” In this it is implied that enzymes of the human gastrointestinal tract do not hydrolyse the major skeleton of the polysaccharide material. On the other hand, bacteria in the colon extensively digest dietary fibre in the caecum. If a physicochemical approach is adopted to explain the biological role of dietary fibre, then it must be recognised that there may well be changes in the physical properties as a result of exposure to enzymes and solutions of different osmotic pressure and pH. A working definition is that dietary fibre is the amalgam of lignin and polysaccharides that are not digested by the endogenous secretion of the human digestive tract (SOUTHGATE et al. 1978). TROWELL et al. (1978) have argued that the term dietary fibre should be applied only to structural materials of the plant cell wall and indigestible storage polysaccharides in the body of the plant cell. This may well be the best definition that is available and perhaps the most useful.

Dietary fibre is a mixture of polymers derived in the main from the plant cell walls. SOUTHGATE (1976) has done a great deal to clarify and define what had previously been a confused, even contentious, subject. The polysaccharides and lignins are intimately intermeshed within the plant anatomy, being different in the cell wall, xylem, phloem, and seed coat and this clearly will be affected by the age of the plant. Table 1 indicates some of the constituents of dietary fibre. Amylose and amylopectins, the starches, are major components of the diet, whereas dextrins, glycogen, fructans, galactomannans, pectic substances, hemicelluloses, gums, mucilages, pectins, and polysaccharides are minor or trace constituents of the diet.

The starches, i.e. the α-glucans, are hydrolysed by the mammalian digestive enzymes so that both the α (1–4) and (1–6) glycoside linkages can be hydrolysed. It is believed that there are no endogenous enzymes capable of hydrolysing cellulose β (1–3, 1–4) – glucans, pectic substances, and hemicelluloses, gums and mucopolysaccharides. These polysaccharides are present in plant structure in a variety of structural forms so that it is possible for cellulose occasionally to have a degree of polymerisation with sugars present other than glucose. By and large, cellulose is a highly ordered structure, capable of strong intermolecular hydrogen bonding. It is insoluble in water, and is resistant to chemical and enzymatic attack. It may
be polymerised in a microcrystalline form which can be used in the food industry
as a stable aqueous suspension to be used as an emulsifier. On the other hand, if
the cellulose is made into an ether, i.e. carboxymethyl or methylethylcellulose, then the
result is a gel which is used to control the physical properties of food.

The β-glucans have a considerable degree of branching and degree of poly-
merisation. These form water-soluble materials which are gummy in texture. The
pectic substances are important in the immature cell wall and consist of rhamno-
galacturonans which are α(1-4)-d-galacturonans, with rhamnosyl insertions, and
a variable proportion of carboxyl-carrying methoxyl groups. The water-soluble
pectins form gels when combined with divalent ions. The methoxyl groups on
uronic acid residues affect the gelling properties. Arabinogalactans, i.e. β(1-4) or
(1-3)-d-galactopyranosides with arabinose side chains found in most plants are wa-
ter insoluble. The hemicelluloses are classified as galactomannans, i.e. β(1-4)-d-
mannopyranosides with galactose side chains. Xylans are β(1-4)-d-xylopyranosyl
chains with branching (1-3) with arabinose and 4-O-methylglucuronyl side chains and
xyloglucan an, i.e. β(1-4)-d-glucans with xylo side chains. These are found in many
cell walls. They may form the storage forms in many seeds.

The plant gums which are used extensively pharmaceutically are the galactan
(gum arabic), glucuronomannan (gum ghatti), galactomannan (tragacanthic acid
gums, locust bean gum, and guar gum), xylan (sapote gum) and
xyloglucan (tamarind). These consist of a core structure with side chains which give
rise to the complex physical properties of these substances. Often these gums are
important for giving protection to the plant or holding water in seed coats. There
are also algal polysaccharides which are used in foods such as agar, carrageens, and
alginites. Again these are highly complex polymers in which the intermeshing of
side chains are of paramount importance (SOUTHGATE 1976).

However, there are problems associated with regarding fibre as a chemical
structure. The analogy with enzyme kinetics is perhaps a useful one. Imagine the
amino acid sequence of chymotrypsin and urease being elucidated before the con-
cept of Michaelis-Menten kinetics. Clearly the structural analysis of enzymes is of
great importance, in the biological sense. Similarly, the nutritional value of vita-
mins preceded their chemical elucidation. There should thus be merit in seeking the
role of fibre along the gastrointestinal tract. One such approach is to regard fibre
as a physicochemical structure, passing like a sponge along the gastrointestinal
tract. Such physicochemical properties include water-holding capacity, cation-ex-
change capacity, adsorption, matrix provision, and gel formation (EASTWOOD and
MITCHELL 1976). It is only when the biological effects of fibre are understood that
the complexities of the chemical analysis can be fully realised and the work of the
analysts bear full fruition.

The problems of the analysis of dietary fibre are many. SOUTHGATE (1976) has
elaborated a useful procedure for the analysis of dietary fibre. However, all
methods are dogged by the presence of starch. These may cause certain restrictions
on the quality of the results obtained. While the importance of the chemical clas-
sification of fibre is clearly recognised, few laboratories are capable of the met-
tulous attention required for the analysis. It is also assumed that the cultivars of
fruit and vegetables from different countries grown under different circumstances
all have the same chemical constitution, but the particular plant example analysed
may not be typical of its type. All the fruit and vegetables which we now eat have changed through the ages (EASTWOOD and ROBERTSON 1978). The carrot is a good example. Originally this was a purple tap root, first described in Afghanistan in the sixth century. It reappeared in Holland in the seventeenth century as a white carrot for cattle food and an orange or modern carrot for human consumption. Until fairly recently carrots had a hard yellow core with an orange outer layer. This has been replaced by a cultivar which has an even appearance. The carrots which are now developed are often used for canning or freezing, so that the developmental work by the horticultural industry has been directed towards the requirements of the food industry rather than the fibre content of the carrot.

Table 2. Physicochemical properties and gastrointestinal effects of dietary fibre

<table>
<thead>
<tr>
<th>Physicochemical properties</th>
<th>Type of fibre</th>
<th>Modifying</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gel formation</td>
<td>Pectin</td>
<td>Gastric emptying</td>
</tr>
<tr>
<td></td>
<td>Mucilages</td>
<td>Mouth-to-caecum transit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small intestinal absorption</td>
</tr>
<tr>
<td>Water-holding capacity</td>
<td>Polysaccharides</td>
<td>Mouth-to-rectum transit</td>
</tr>
<tr>
<td></td>
<td>Lignins</td>
<td>Faecal weight</td>
</tr>
<tr>
<td>Matrix formation</td>
<td>Lignin</td>
<td>Intraluminal pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Faecal electrolytes</td>
</tr>
<tr>
<td>Bile acid adsorption</td>
<td>Lignin</td>
<td>Caecal bacterial metabolism</td>
</tr>
<tr>
<td></td>
<td>Pectin</td>
<td>Faecal steroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cholesterol turnover</td>
</tr>
<tr>
<td>Cation exchange</td>
<td>Acidic polysaccharides</td>
<td>Faecal minerals</td>
</tr>
<tr>
<td></td>
<td>Lignin</td>
<td></td>
</tr>
<tr>
<td>Antioxidant</td>
<td>Lignin</td>
<td>Free radical formation and action</td>
</tr>
</tbody>
</table>

Although vegetable dietary fibre may be regarded as a physicochemical bolus passing along the gastrointestinal tract, it may alter gastric emptying time and absorption from the small intestine (EASTWOOD and MITCHELL 1976). Furthermore, vegetable dietary fibre may also function in the colon. Here it forms a supporting matrix and provides surfaces upon which bacteria and intestinal contents can react. The principal physical properties of the matrix include water absorption, cation exchange and bile acid adsorption. Table 2 summarises the various physicochemical properties of dietary fibre and the effect of these along the gastrointestinal tract (EASTWOOD and KAY 1979). However, such a description of fibre is deceptive in that physical properties will, in the first instance, be influenced by the origin of the fibre and how it is prepared.

The physical properties, if they are analogous to, say, chromatography material, will be dictated by the capillary structure or ability to form gels. Therefore, a fibre source which has not been dried will behave quite distinctly from one which has been dried. The manner of drying, whether this be by air, freeze-drying or heat, will also affect the collapse of the capillaries and hence the ability to rehydrate. Straightforward evaporation of water from the gel collapses the gel to a nonporous solid. Another reaction which can cause problems in the heating of fibre sources
in a nonenzymic browning called a Maillard reaction which alters the surface structure of the fibre. Such properties have been studied by paper industry chemists (Stone and Scallon 1968) and also by ruminant physiologists (Osborn et al. 1976). In the conversion of wood to pulp for paper-making there is an excess of water present and the pulp production involves a constant modification of the lignocellulose gel as chemical and mechanical treatment removes materials from within the gel or ruptures the bonds which hold the matrix together. To some extent the processes of cooking or the production of fibre concentrates from fruit and vegetables are similar modifying processes. Again in the rumen, forage crops exist in the water-swollen state and the digestibility of the cellulose in the cell wall of these plants is almost certainly a function of the accessibility of the swollen wall to cellulose enzymes. A similar situation may well exist in the human colon.

Different types of structures are shown in Fig. 1a which shows a structure of a seed coat, e.g. bran; a cross-section of a stem (Fig. 1b); and the effect of drying that stem to a varying extent (Fig. 1c, d). It is clear that the manner in which these fibres behave as they pass along the gastrointestinal tract will be different. The ability of water to infiltrate, expand and hence influence the sponge performance along the gut will be dictated by the space available to it within the plant cell wall.

Various sources of dietary fibre bind bile acids in vitro (Eastwood and Hamilton 1968; Birkner and Kerns 1974; Story and Kritchevsky 1976), and it has been shown that different lignins adsorb bile acids to a varying extent. Lignin is a complex polymer consisting of oxygenated phenylpropane units and obviously each polymer will have its own properties, Kay et al. (1979), have demonstrated that lignins vary in their capacity to bind bile acids. Autohydrolysis extraction conditions were maintained to produce lignins of known chemical composition, free from contaminants. The most effective lignin preparations in their studies were intermediate in their methoxyl content. This material demonstrated a preferential a-
finity for the unconjugated dihydroxy bile acids such as are formed by bacterial action in the colon. The possible adsorption mechanism may be through hydrophobic bonds.

IV. Gas

A further important physical phase along the length of the gastrointestinal tract is gas. Anaerobic bacteria in the gastrointestinal tract produce partially degraded low molecular weight carbon compounds, e.g. volatile fatty acids and a number of gases (Prins 1977). Of these gases the major ones are carbon dioxide, hydrogen, and methane. The formation of hydrogen and methane is unique to anaerobic bacteria since no higher animal cells are known to produce these gases (Calloway 1978; Levitt and Bond 1970).

V. Bulking Agents

It is clear therefore that in evaluating the effects of bulking agents along the gut it is necessary to know the chemical structure, the physicochemical properties, the accessibility to bacterial degradation in the caecum and the consequence of this degradation, whether it be absorbable organic materials or volatile gases. This is not information that is readily available for any of the hydrophilic colloids either dietary or therapeutic. In discussing the effect of different fibres on colonic motility it is also important to recognise the effect of different fibre sources acting on the gastrointestinal tract. There are many contradictory experiments reported in the literature, which are often a function of the type and preparation of the fibre and the technique used to measure events along the gut rather than inherent differences between different experiments. Grimes and Goddard (1977) showed that there was no difference in the rate at which the solid phase of the gastric contents left the stomach after ingestion of wholemeal or white bread. Furthermore, the amount of liquid leaving the stomach unaccompanied, and therefore unbuffered by solid, was significantly greater after ingestion of white bread than wholemeal bread.

Gums and natural and synthetic particulate materials with quite different physical properties and chemical structures all affect the glucose tolerance curve. Jenkins et al. (1978) showed that the most important physical property is the viscosity and this has a considerable effect on absorption and transit time. Guar, the most viscous substance, was the most effective in decreasing postprandial glucose and insulin concentrations. Similarly, xylose excretion tended to be less than that of a control experiment. This suggests that there is slower absorption in the presence of these gels. The mouth-to-caecum transit time was related to the viscosity of the materials given. The action of viscous agents may be at two points, delaying gastric emptying and the absorption of glucose from the small intestinal lumen. The latter would result from a barrier to diffusion caused by an increased viscosity and the holding of materials within the gel.

The effect of various brans on stool weight in normal subjects and in patients with diverticular disease has been well explored. However, there are certain anomalies in the literature. For example, it was shown by Fantus et al. (1941) that the size and shape of bran particles are factors in the laxative action of bran. They
Table 3. Effect of wheat bran on stool weight

<table>
<thead>
<tr>
<th>Weight of Bran (g)</th>
<th>Period (weeks)</th>
<th>Stool weight (g)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>56</td>
<td>30</td>
<td>170</td>
<td>171</td>
</tr>
<tr>
<td>16</td>
<td>3</td>
<td>128±212</td>
<td>125–215</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>107±44</td>
<td>174±51</td>
</tr>
<tr>
<td>12&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
<td>120±18</td>
<td>183±22</td>
</tr>
<tr>
<td>20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
<td>131±17</td>
<td>140±9</td>
</tr>
<tr>
<td>17–45</td>
<td>3</td>
<td>79±1</td>
<td>228±30</td>
</tr>
<tr>
<td>23–35</td>
<td>3</td>
<td>125 (59–194)</td>
<td>225 (154–290)</td>
</tr>
<tr>
<td>38</td>
<td>1</td>
<td>93±10</td>
<td>166±15</td>
</tr>
<tr>
<td>84</td>
<td>3</td>
<td>103±40</td>
<td>266±90</td>
</tr>
<tr>
<td>20</td>
<td>3</td>
<td>140</td>
<td>320&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3</td>
<td>95</td>
<td>197</td>
</tr>
<tr>
<td>36</td>
<td>3</td>
<td>71±6.2</td>
<td>217±12</td>
</tr>
</tbody>
</table>

<sup>a</sup> Cooked bran; <sup>b</sup> raw bran; <sup>c</sup> coarse bran; <sup>d</sup> fine bran

used bran of different particle size which had previously been through the processes employed in the manufacture of a commercial bran breakfast cereal. They found that there was no correlation between the particle size of bran and the laxative action when measured by the effect on stool weight. Crude fibre prepared from bran also showed laxative effects, and so crude fibre itself appeared to be the active principle of bran. However, BRODRIBB and GROVES (1978) showed that wheat bran, when taken as large particulate material, or after milling to small particles, had differing effects on the stool weight. After ingestion of coarse bran, the stool weight (219 g/day) was significantly greater than after ingestion of fine bran (199 g/day). The reason for the differing effect is that the coarse bran they used had a greater water-holding capacity: 7.3 g water for 1 g coarse bran, compared with 3.9 g water for 1 g fine bran.

Some important experiments by CUMMINGS et al. (1978b) showed that fibre concentrates from different sources had a variable effect on stool weight. It must be emphasised, however, that these experiments used fibre concentrates, not fresh plant material. The concentrates represented fibre which had been dried and concentrated 20–40 times, although the fibre concentrate had a similar chemical composition to that of fresh carrot, cabbage and apple fibre. This suggested to them that processing had not altered the fibre to any extent chemically. Groups of six subjects took apple, carrot, cabbage, and bran and the increase in stool weight varied for the different concentrates. The faecal weight changes correlated with the amount of the pentose fraction of the noncellulose polysaccharides. The hexose and pentose contents of noncellulose polysaccharides are usually inversely related. There are individual variations in response to a given fibre intake, and such individual responses could not be ascribed to the intake of pentose-containing polysaccharide.
Table 4. Comparison of effects of fruit and vegetable fibre sources

<table>
<thead>
<tr>
<th>Fibre source</th>
<th>Weight (g)</th>
<th>Period (days)</th>
<th>Stool weight (g)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carrot concentrate</td>
<td>20</td>
<td>21</td>
<td>117</td>
<td>189</td>
</tr>
<tr>
<td>Cabbage concentrate</td>
<td>20</td>
<td>21</td>
<td>88</td>
<td>143</td>
</tr>
<tr>
<td>Apple concentrate</td>
<td>20</td>
<td>21</td>
<td>141</td>
<td>203</td>
</tr>
<tr>
<td>Guar concentrate</td>
<td>20</td>
<td>21</td>
<td>120</td>
<td>139</td>
</tr>
<tr>
<td>Plant fibre</td>
<td>60</td>
<td>28</td>
<td>177±40</td>
<td>240±35</td>
</tr>
<tr>
<td>Fruit and vegetable fibre</td>
<td>20</td>
<td>26</td>
<td>89±9</td>
<td>208±9</td>
</tr>
<tr>
<td>Citrus pectin</td>
<td>15</td>
<td>21</td>
<td>140</td>
<td>168</td>
</tr>
<tr>
<td>Pectin</td>
<td>6</td>
<td>21</td>
<td>150±10</td>
<td>186±15</td>
</tr>
<tr>
<td>Fruit, vegetables 50%, bran 50%</td>
<td>20</td>
<td>21</td>
<td>69±50</td>
<td>184±75</td>
</tr>
<tr>
<td>Cellulose</td>
<td>16</td>
<td>21</td>
<td>152±32</td>
<td>221±58</td>
</tr>
</tbody>
</table>

In humans, all fractions of dietary fibre, except lignin, are digested to some extent by colonic microflora. Such digestion may alter the water-holding capacity. The extent of digestion of the fibre could determine individual responses to a given fibre. The digestion of dietary fibre fractions was underlined by HOLLOWAY et al. (1978), who compared two groups of subjects: healthy subjects with an ileostomy and normal subjects. Both groups were given a regulated diet of known cellulose, hemicellulose and lignin content. The fibre content of the faeces was measured by the acid and neutral detergent method. Some 85% of the ingested cellulose was excreted intact by the ileostomy subjects. Where the colon was intact in normal subjects only 22% of ingested cellulose was excreted, indicating that approximately 80% of the cellulose was digested in normal subjects. Of the water-insoluble hemicellulose ingested, 28% was excreted from the small bowel, 4% from normal subjects. This represents approximately 96% digestion of the hemicellulose in normal subjects.

However, the large unknown is the role of bacteria in influencing stool weight. STEPHENS and CUMMINGS (1980) take the view that a factor in changing the stool weight is an increase in the bacterial content of the stool. This is more likely to apply with fruit and vegetables than with bran which appears to pass through the gastrointestinal tract unchanged by the presence of bacteria. Tables 3 and 5 summarise a number of papers in which the effects of bran and fruit and vegetables on stool weight have been examined. It will be seen that there is a wide range of responses. Whether or not the fibre is hydrolysed by bacteria in the caecum, bran appears not to be hydrolysed and other fruit and vegetables appear to be extensively hydrolysed. Pentose-containing noncellulose polysaccharides appear to be the most resistant to hydrolysis by bacteria. However, highly hydrated fibre sources with large water-holding capacity may well be the most vulnerable to bacterial attack and therefore compression of fibre and collapse of capillary structure may be another important factor.
C. Actions of Fibre and of Operations on the Colon Muscle in Diverticular Disease

Pari passu with the fibre studies already described, fundamental advances were being achieved in the physiopathology of diverticular disease and its management. Three important advances were made. First, the recognition that the disease is characterised by marked thickening of the large bowel muscle in the region of the sigmoid colon. The muscle abnormality is often the main abnormality, rather than any inflammatory change. The diverticula are sometimes difficult to show in resected specimens and even their demonstration in radiographs may occasionally be difficult. Second, the thickened muscle produces a high intraluminal pressure, as the thickened circular muscle, plus the overlying crescent folds of mucosa, occludes the lumen, producing localised “chambers” within which the high pressure is created. These high pressures have been described by AFWIDSSON (1964), PAINTER and TRUELOVE (1964), ATTISHA and SMITH (1969) and others, and are thought to be the principal reason for the herniation of the mucosa. The third, most recent advance has been the clinical finding that cereal fibre produced clinical improvement in patients with constipation and diverticular disease. When this was introduced as a clinical regimen there was no correlation with the other two factors. It had already been argued on epidemiological grounds that because of the low fibre content of Western diet, and perhaps with its higher content of refined absorbable products, the faeces were low in bulk and became further diminished or dehydrated as a result of prolonged transit in the large intestine. It was thus envisaged that it would be more difficult for the faecal bolus to pass through the sigmoid colon and enter the rectum. In this process the mechanical difficulties of onward transmission of pellety faecal contents were seen as leading to smooth muscle thickening. Thus the emphasis swung away from the diverticulum to the abnormal muscle function of the large bowel. It is in the alteration of this sequence that the importance of fibre lies.

Fibre has been further implicated in colonic disease by the contrasting states of Africa and Asia on the one hand and the Western World on the other: in the former there is minimal diverticular disease, a high fibre diet and bulky faeces and a fast intestinal transit - changed in each detail in the West to a high incidence of diverticular disease, a low fibre intake, pellety stools and an intestinal transit time prolonged several days more than that of the African and the Asian. Yet if this hypothesis were true the dietary abnormality must operate for a very long period of time before overt disease is produced since the incidence of the defect (colonic diverticulosis) does not become appreciable until the fifth decade of life.

In view of the clinical improvement generally recorded with cereal fibre it appeared important to document the action of this substance on the intraluminal pressure, seen according to the “pressure theory” as the established main factor. But first, proof was required that pressure was high. The operation of longitudinal colomyotomy had been introduced by REILLY in 1966 and afforded the opportunity not only to assess the efficacy of the operation in relationship to how far it is possible to lower the intraluminal pressure by this means, but also to analyse the role of the colonic muscle in this condition. If excessive intraluminal pressure were
the important factor in the genesis of diverticular disease, operations for diverticular disease should be judged on their ability to reduce this. If the action of fibre were to reduce the pressure and were this a valid treatment, operations would have to withstand comparison with this. Moreover, possible beneficial effects of operations could easily lapse if patients continued to be exposed after operation to the same conditions of fibre deficiency as preoperatively, and this could be counteracted, perhaps simply by increasing the fibre content of the diet.

It therefore seemed important: (1) to define the effect of the common operations performed for diverticular disease on the muscle on the intraluminal pressure, i.e. motility terms; (2) to determine how long the effects of operation last in patients left on their original diet compared with others given bran supplements postoperatively; (3) to define the effect, compared with (1), of added dietary fibre alone; and (4) to determine the changes produced by the bulk-producing agents such as bran ispaghula, lactulose, and sterculia. (For details of methods see Smith et al. 1974.)

I. Changes Induced by Operation

There was no difference in basal motility between normal subjects and diverticular disease patients before and after the operation of myotomy. Colonic activity was significantly increased after all forms of stimulation in diverticular disease, the effect being greatest after administration of prostigmine (Attisha and Smith 1969). These responses in diverticular disease patients were reduced to normal levels by myotomy and the patients were rendered symptom free. Myotomy thus confirmed the importance of the smooth muscle and of the pressure theory in diverticular disease.

Resection of the sigmoid colon was performed in a group comparable to the myotomy patients, i.e. with local obstructive features, high intraluminal pressure and a thick bowel muscle at operation. The motility index, high initially, remained raised after operation compared with normal subjects. Thus local resection of the pelvic colon (this was all that was carried out) did not restore to normal the inherent abnormality of the large bowel muscle, which must be more generalised than in the sigmoid area. Myotomy and resection patients were then followed for more than 3 years. A fall in the mean motility index (shown for prostigmine stimulation only) occurred during the first year following myotomy but over the subsequent 3-year period there was a considerable return in the mean pressure activity, and by 5 years this had risen to the same high preoperative level. In contrast, the motility index after colonic resection rose to levels very slightly above those recorded before operation. Furthermore, many of these patients still had symptoms. All the myotomy patients had a recurrence of their original symptoms at 3–5 years but with less severity than formerly.

The mean motility indices in patients after resection and myotomy were also contrasted with a comparable group of patients who were given 20 g unprocessed bran daily postoperatively. It has already been recorded that the mean motility indices after resection rose; this level was markedly lower in resection patients maintained on bran postoperatively. The mean motility indices after myotomy fell at
first, but by 5 years this trend had reversed (Fig. 2). However, when myotomy patients took bran postoperatively they showed a fall in pressure which was held at a much lower level than in comparable patients with uncomplicated diverticular disease treated by operation without bran.

II. Changes Induced by Cereal Fibre

The weight of faeces produced by Africans has been shown in field studies by Burkitt et al. (1972) to contrast markedly with the European output. When bran was given to normal British subjects it significantly increased the stool weight and this can be shown to be due to an increase in its water content. The increase in stool

Fig. 2. a Mean motility index for 5 years after resection; lower values in patients taking bran. Numbers of patients shown in parentheses. b Mean motility index lowered by myotomy but partial recovery in 3 years, complete by 5 years, lower values in patients taking bran. Numbers of patients shown in parentheses (Smith et al. 1974)
weight is less apparent in diverticular disease, probably because it starts from a lower value (FINDLAY et al. 1974). Relative changes in weight can be shown by marking the liquids and solids. The intestinal liquids are marked by the water-soluble PEG 4000, the solids by chromium sesquioxide. Both are injected at the same time and mix well with their respective phases. After equilibration of markers of the two phases, both are reduced in concentration after bran consumption. This suggests that, whatever the increase in solids as a result of bran intake, dilution occurs in the colon and that the effect of bran is mainly due to water binding. This is in keeping with the observed alteration to a more gelatinous stool consistency after ingestion of bran.

Africans also have a reduced transit time. Several observations have now shown that the intestinal transit is prolonged in symptomatic diverticular disease compared with normal subjects and that it is significantly shortened by bran, more so than in normal subjects. There is an interesting reciprocal relationship apparent in the graph of Fig. 3. In normal subjects, a change in stool weight induced by bran may not be accompanied by much change in transit time, since it occurs where the curve has flattened off; whereas in symptomatic diverticular disease, transit time may be significantly accelerated with very little change in the faecal weight, since with lower faecal weights the curve is steeper. In general, therefore, little change in the output of faeces is necessary to provide an expeditious transit in diverticular disease and can thus correct both "anomalies." Slow transit was evident throughout the various segments of the colon; in both symptomatic diverticular disease and idiopathic constipation the acceleration produced by bran occurred in all segments (KIRWAN and SMITH 1977).
Table 5. Mean motility indices (± standard errors) in 13 patients with diverticular disease before and after 4 weeks treatment with coarse bran

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>After food</th>
<th>After neostigmine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before coarse bran</td>
<td>878 ± 192</td>
<td>1,812 ± 391</td>
<td>2,758 ± 514</td>
</tr>
<tr>
<td>After coarse bran</td>
<td>335 ± 108</td>
<td>733 ± 237</td>
<td>1,545 ± 355</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

The motility paradox of CONNELL (1962) is well known: that raised intracolonic pressures accompany constipation and that pressures are low in diarrhoea. Partly this is explicable by the local conditions which accompany the pressure change-spasmodic contraction may produce a long “open” length of gut in which there is little measurable pressure change. The sigmoid intraluminal pressure in diverticular disease has generally been found to be raised (AREFWIDSSON 1964; PAINTER and TRUELOVE 1964; ATTISHA and SMITH 1969) but to be lowered by the administration of bran. The high pressure of diverticular disease is also lowered by severing the colonic muscle in the operation of myotomy (ATTISHA and SMITH 1969). Bran may exert its action like myotomy; both may affect the muscle by diminishing its segmenting activity, but both could also act by creating a bowel with a wider lumen which would automatically, on physical grounds, lead to a reduced pressure or tension acting on the wall.

The transit time was only significantly reduced in diverticular disease patients on bran. The stool weight was increased by an average of 63 g in normal subjects but not significantly in diverticular disease patients (17 g; FINDLAY et al. 1974).

In 13 patients with diverticular disease, basal motility was reduced by bran therapy but the response to food fell below basal levels; the response to cholinergic stimulation (prostigmine) fell by 50% after ingestion of bran (Table 5). The main findings in regard to bran and diverticular disease are thus in agreement with the hypothesis that this agent, known to be capable of relieving the symptoms, also lowers the intraluminal pressure, increases the bulk of the faeces and speeds the transit. TAYLOR and DUTHIE (1978) have also described pressure reduction and have added the observation that the rapid electrical rhythm which is characteristic of diverticular disease is abolished by bran. BRODRIBB and HUMPHREYS (1976) reinforce this by adding the finding that the counts of waves were greatly reduced in the sigmoid colon in 40 patients treated with bran for a longer period of 6 months.

The mechanism of the action of bran on the colon muscle has been further elucidated in a study of the respective actions of coarse and fine bran in diverticular diseases (KIRWAN et al. 1974). The former was much more effective than the latter in reducing the intraluminal colonic pressure and the transit time. That one bran was coarser than the other was shown by shaking the two brans for 90 min in test sieves of increasing aperture. The flour from each bran which passed through the mesh was weighed. Less of the coarse bran passed through the sieves of small pore size.

The water-binding capacity was more marked for the coarse bran. Coarse and fine bran respectively held 6.0 and 2.4 g water for 1 g bran. The acid detergent fibre
**Table 6. Comparison of the effects on colonic motility of fine and coarse bran taken separately and consecutively**

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>After food</th>
<th>After neostigmine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Coarse and fine bran motility index taken separately</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before coarse bran</td>
<td>892 ± 196</td>
<td>1,513 ± 456</td>
<td>2,120 ± 405</td>
</tr>
<tr>
<td>After coarse bran</td>
<td>648.7 ± 339</td>
<td>446.1 ± 130</td>
<td>1,216.8 ± 398</td>
</tr>
<tr>
<td>( P ) n.s.</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Before fine bran</td>
<td>1,181 ± 489</td>
<td>1,429 ± 405</td>
<td>4,075 ± 873</td>
</tr>
<tr>
<td>After fine bran</td>
<td>1,269 ± 468</td>
<td>2,534 ± 653</td>
<td>4,661 ± 410</td>
</tr>
<tr>
<td>( P ) n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td><strong>B. Fine bran followed by coarse bran</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After fine bran</td>
<td>1,202 ± 596</td>
<td>2,369 ± 811</td>
<td>4,726 ± 522</td>
</tr>
<tr>
<td>Followed by coarse bran</td>
<td>303 ± 168</td>
<td>1,459 ± 637</td>
<td>2,746 ± 749</td>
</tr>
<tr>
<td>( P ) &lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td><strong>Comparison of motility change</strong></td>
<td>n.s.</td>
<td>&lt;0.005</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

\( \text{n.s. = not significant} \)

Content was 15.1% and 9.7% with a higher lignin content for the coarse (4.1%) than the fine (2.6%) bran. After milling both brans to a particle size of <1 mm in the laboratory, the water-holding capacities were approximately equal, although the fibre content remained the same. Our observations suggest that bran with coarse particles binds more water and thus provides more bulk in the stool than does bran with finer particles. The marked difference in the effect of the two brans on bowel function was unexpected. Fine bran failed completely, unlike coarse bran, to reduce the colonic motility index (Table 6) and the gastrointestinal transit time. The beneficial effect of coarse bran is probably related to its water-holding effect which gives rise to a soft bulky stool which is easily passed. The change in the motility index resulting from ingestion of bran may also depend upon the bulk provided, since intraluminal pressure depends not only on the force exerted by the colonic muscle, but also upon the diameter of the bowel lumen and the viscosity of its contents. These results indicate that particle size could be of fundamental importance in determining not only the water-holding capacity but also the clinical efficacy of bran. It is possible, however, that if fine bran were given in a large dose, there would be sufficient large particles with a water-holding capacity to improve bowel function; but fine bran also contains a considerable amount of absorbable carbohydrate and the dose used might result in unacceptable weight gain.

### III. Other Agents

The symptoms of diverticular disease arise in patients who have, in the main, a small stool weight, prolonged intestinal transit and a raised intracolonic pressure (Painten 1975). The rational basis of the treatment of diverticular disease is prin-
Fig. 4a, b. Mean motility indices after treatment with bran, Fybogel and lactulose; change in the basal motility index a and also after food b, with each agent. Open circles, lactulose; full circles, bran; crosses, Fybogel.

Fig. 5. Changes in motility expressed as "motility index" could mask the nature of the underlying motor response, as this index is a product of the wave amplitude and the duration of the motor effect. For example, a common "motility" result could be arrived at by many smaller waves or less frequent large waves. Waves of greater amplitude might, however, be more damaging to the colon and responsible for some of the symptoms of diverticular disease. Furthermore, it could be argued that these are the ones which the effective agents should be abolishing. Counts of the waves (Fig. 5) in the amplitude range 50–80 cm H₂O were made and the average number of waves recorded per patient in each treatment group. On bran, the number of waves was reduced at each 10 cm H₂O pressure level in a 1-h period of activity examined after a food stimulus. Fybogel, on the contrary, raised the average number of waves whereas lactulose had no effect. Since the effect of Fybogel in raising the basal motility and the number of high pressure waves present after ingestion of food is contrary to what one expects of a bulk-acting agent, the experiment was repeated with four patients on a double dose of Fybogel per day. The stool weight and the basal motility were again increased but without further significant changes.
Fig. 5a-d. Effect of bran B, Fybogel F, and Lactulose L on postprandial waves before C and after treatment B, F, L. Pressures (in cmH₂O) are 80 a; 70 b; 60 c; 50 d. Vertical axis shows average number of waves per patient (EASTWOOD et al. 1978)

This type of result reflects the diversity which can be obtained in the manometry of diverticular disease (EASTWOOD et al. 1978). The therapeutic agents which we tested might have been expected to decrease intracolonic pressure since they equally relieved the symptoms of diverticular disease. Given raised pretreatment pressures, a reduction would be expected after successful therapy, not, as is found for Fybogel, an increase. Coarse bran has already been shown to exert a reduction in pressure (KIRWAN et al. 1974). There is no uniform relationship between the modification of symptoms and the efficacy of the compounds in lowering pressure, in the short term at least. This raises some doubt about the overall importance of "features" of diverticular disease - low stool weight, the prolonged transit time, and the raised intraluminal pressure - normally considered to be hallmarks of this disease. Although two of the agents used here raised the intraluminal pressure or left it unchanged, both produced an equivalent symptomatic relief. The patients were mainly complaining of constipation, apart from abdominal pain and discomfort, and it is possible that part of the therapeutic effect is achieved by overcoming factors such as stasis. Yet agents which raise or leave pressure unchanged, even though they relieve symptoms, may not in the long run be entirely free of the risk of producing further damage to the bowel in diverticular disease. Thus we would have to draw a distinction between what constitutes a truly efficacious agent and what does not; and conclude that coarse bran remains the most efficacious agent, not only by reducing symptoms but by adding to the stool weight and lowering the intraluminal pressure in diverticular disease.
D. Actions in Other Colonic Diseases

The muscle abnormality in the irritable bowel syndrome has certain similarities with early diverticular disease. The main points of differentiation appear to be the increased basal pressure, probably derived from muscle spasm. In diverticular disease the resting pressure is not elevated although the muscle is thick and hypertrophic, and the intraluminal pressure is increased only after stimulation by food and cholinergic drugs. Another significant difference is the presence of fast waves in the irritable bowel of a type not seen in diverticular disease. On the basis of the raised motility index present after stimuli such as the gastrocolic reflex one could make a case for the use of cereal fibre or hydrophilic colloids in the “spastic” type of irritable bowel syndrome. Even in diverticular disease WEINRICH (1977) has suggested that a “colicky sigmoid syndrome” and diverticula might occur independently in the population. The probability of coincidence increased with age since the presence of diverticula is age dependent. The action of bulk additives might lower the incidence of the colicky sigmoid syndrome, but on this basis might not necessarily lower the incidence of diverticula. One has to differentiate between an action on the muscle which may induce relief of symptoms and actions which may influence the aetiology of the disease. Another means whereby hydrophilic colloid agents might find a role in the irritable colon syndrome is in the management of the form associated with diarrhoea rather than constipation. HEATON and his colleagues have described how bran may “normalise” the intestinal transit; paradoxically, the addition of bulking agents to the diet can influence constipation, but may just as readily by water and electrolyte absorption influence the diarrhoeal state (PAYLER et al. 1975). Clinical trials in these aspects of the irritable colon syndrome are lacking and are of course needed.

Bulk agents may be used in ulcerative colitis on similar grounds. DAVIES and RHODES (1978) attempted to study this and compared a high fibre diet and sulphasalazine to determine whether fibre could replace sulphasalazine in keeping ulcerative colitis patients in remission. Only 25% of patients with ulcerative colitis could satisfactorily take the high fibre diet instead of sulphasalazine. A greater application may be in patients liable to develop colonic stasis, the so-called constipated colitics who may occasionally have diverticular disease but who may have a condition like diverticular disease with high intraluminal pressure in the left or distal colon and who may develop dilatation of the right or proximal colon.

There is no record of patients with carcinoma of the colon having elevated intraluminal pressures in the distal colon, yet their intestinal transit is in general prolonged, as befits differences between the Western World and Africa and Asia, described so well by BURKITT et al. (1972). HILL et al. (1975) gave point to the Burkitt hypothesis by describing a mechanism whereby delayed colonic transit and the action of organisms, particularly nuclear dehydrogenating (NDH) clostridia, might conspire to allow the degradation of the bile acids to a carcinogenic form within the colon. Confirmatory evidence of this is as yet lacking. In the long term, studies are required of groups who are prepared voluntarily to speed up their own intestinal transit by fibre and other agents. They would after all only be following the example of the population of doctors, now an interesting group, who abandoned
smoking 20 years ago. It would be interesting to know in the long term if the experiences of such a group would change the incidence of carcinoma of the colon in high risk countries such as Scotland.

E. Clinical Application of Fibre and Hydrophilic Colloid Additives

Experience with the therapeutic use of dietary fibre has resulted in the formulation of the following general principles (Brodbi 1978):

1) A precise diagnosis, with routine examination by sigmoidoscopy and barium enema, should be made before starting a high fibre diet. The use of bran as a diagnostic test is strongly deprecated.

2) Fibre intake should be increased in stages over a 3–4-week period to reduce the sensations of abdominal distension and discomfort associated with a sudden change in colonic filling.

3) It may be helpful to give an antispasmodic agent as well for the first few months.

4) It is probably best to use cereal fibre. An increase of 5–20 g/day in dietary fibre may be required. This can be given as bran or high fibre products such as wholemeal bread, bran biscuits, and high fibre breakfast cereals. The increased fibre intake should be taken regularly each day. The aim should be to establish a new dietary regime that can be maintained for a lifetime. A dietician is usually best qualified to achieve this.

5) Patients should be warned that a maximal therapeutic response will probably take at least 3 months from the time a high fibre diet is started, and that a dramatic, rapid effect is not to be anticipated.

6) Even if a high fibre diet has been established, 10%–20% of subjects may have persistent symptoms. This may have a number of causes. Undiagnosed inflammatory complications such as chronic pericolic abscess or stricture may be present. Many patients in our studies had other diseases such as gallstones, peptic ulcers or hiatus hernias and the symptoms may be due to these. Severe neuroses may be associated with a very low pain threshold, so that normal abdominal sensations appear as symptoms. Corry (1963) described a group of patients with diverticular disease who improved with a milk-free diet, and screening for hypolactasia should be considered. The possibility that a carcinoma of the colon or other colonic lesion had been missed initially should always be considered.

The value of dietary fibre in the treatment of uncomplicated diverticular disease has now been established. It appears to be more effective even than ablative surgery and no other treatment has been shown to give a better therapeutic response.

References


Durrington PN, Manning AP, Boston CH et al. (1976) Effects on serum lipids and lipoproteins, whole gut transit time and stool weight. Lancet 2:394–396
Elliott TR, Barclay-Smith E (1904) Antiperistalsis and other muscular activities of the colon. J Physiol (Lond) 31:272–304


Stone JE, Scallan AM (1968) A structural model for the cell wall of water swollen wood pulp fibres based on their accessibility to macromolecules, cellulose, chemistry, and technology. 2:343–358
Williams RD, Olmsted WH (1936) The manner in which bran controls the bulk of the feces. Ann Intern Med 10:717-727
6

Diverticular Disease — Is it a Motility Disorder?

M. A. EASTWOOD
D. A. K. WATTERS
A. N. SMITH

In our understanding of colonic diverticula, nomenclature has been a constant source of confusion. The first descriptive names used were diverticulosis and diverticulitis. Diverticulosis described asymptomatic diverticula of the colon. By contrast diverticulitis was associated with pain, thought to be due to inflammation. When it was appreciated that this distinction was not sustained by histological evidence, the term diverticular disease was introduced to include the whole range of states from symptom-free colonic diverticula to any of a spectrum of complications associated with the presence of diverticula. The concept of asymptomatic and symptomatic diverticular disease has developed from this.

It has yet to be resolved whether diverticular disease is a disorder of colonic muscle or a disease of the diverticula, or indeed whether the development of diverticula is a normal concomitant of ageing.

Morson (1975) has described diverticula as being of the pulsion type, consisting of a pouch of mucus membrane, including the muscularis mucosae which projects beyond the circular muscle layers of the bowel wall, coming to lie in the pericolic fat and appendices epiploicae. The majority of diverticula pass through the bowel at weak points in the circular muscle layer through which the main blood vessels pass to supply the colonic mucosa. It is usual to find two rows of diverticula on each side of the bowel wall, between the mesenteric and antimesenteric taenia (Slack, 1962). The condition occurs most commonly in the sigmoid and descending colon, but the rectum is never involved. It is suggested that muscle abnormalities are the most consistent and important feature of diverticular disease of the sigmoid colon (Morson, 1963; Hughes, 1969).

The taeniae coli are thickened to an almost cartilagenous consistency and the circular muscle is also thickened, leading to a corrugated appearance. Taeniae coli are involved in shortening the colon, acting not only as shortening bands for the colon but also as a fulcrum against which the circular fibres contract.

Diverticular disease of the colon is an increasingly common condition in European and North American communities.
The natural history of diverticular disease is extremely difficult to describe. This is because the true prevalence is not available as the condition may be relatively symptomless, diagnosis requiring a barium enema. Clues to the prevalence of the condition are given by two studies, postmortem (Hughes, 1969) and radiological (Manousos, Truelove and Lumsden, 1967). Hughes, in an autopsy study (1969) in Australia, found that diverticular disease was rare before 30 years of age, but after the eighth and ninth decade of life 50 per cent of colons had diverticula. Radiological surveys, particularly that of Manousos et al in Oxford (1967), confirmed this figure. Most of the published studies, however, have been based on hospital clinical practice rather than on population studies.

In a study by Eastwood et al (1977) the rate of positive diagnosis of diverticular diseases was 23 per cent in all patients undergoing barium enema investigation in Edinburgh hospitals. Even within the Electoral Wards of Edinburgh there was a considerable variation, with the annual incidence ranging from 0.92 to 2.04 per 1000 adult population. There were striking similarities in the incidence rates for adjacent areas, the highest incidences coming from the oldest part of the City in two socially quite dissimilar districts. The annual incidence also varied with age, ranging from 0.17 per 1000 for age 15 to 45 years, to 1.3 per 1000 for age 45 to 59 years, 3.88 per 1000 for ages 60 to 74 years and 5.74 per 1000 for those aged over 75 years.

Accounts of the prevalence of diverticular disease vary. The type of hospital or clinic and the speciality of the clinician determine the varying estimates of the prevalence of diverticular disease. Thus the spectrum of complications seen by the surgeon will be quite distinct from that seen by physicians or geriatricians.

Kyle and Davidson (1975) in the North East of Scotland, Podesta and Pace (1975) in Malta and Parks (1975) in Belfast all concluded that diverticular disease is associated with an ageing population, though factors other than age seem to determine the progression of the disease.

The rarity of diverticular disease in Africans in contrast to Europeans and North Americans could be due in part to differences in longevity. It is of interest that in Britain in 1981 there were 2800 centenarians, compared with only 140 in 1951 (Guardian, January 7th, 1982).

Painter has described diverticular disease of the colon as a 20th century problem. Painter (1963) and Arfwidsson (1964) showed that the sigmoid colon of patients with diverticular disease under resting conditions generated a pressure which was indistinguishable from that of normal subjects. The colonic pressure produced by the segmenting action of the colon stimulated by food or neostigmine is greater in individuals with diverticular disease than in normals. Higher than normal pressures were obtained in patients said to be in a pre-diverticular state, suggesting that the muscle changes and alterations in pressure precede the manifestation of symptomatic diverticular disease. Diverticula are the outward evidence of an inward disturbance of colonic motility.

There has developed the concept that diverticular disease is characterized by a history of pain relieved by defaecation, a reduced stool weight, a
DIVERTICULAR DISEASE

prolonged transit time and an increase in the motility index in response to a stimulus, whether this is food or neostigmine (Painter, 1975).

It would appear that a significant proportion of the normal population of Europe and North America have colonic diverticula, though only a small proportion of these seem to present to their medical practitioner with symptoms. Thus, the distinction has to be drawn between simply the presence of diverticula in the colon and symptomatic diverticular disease. Diverticula are a normal concomitant of the ageing process, but constipation may be a complication relieved by an increase in the fibre content of the diet.

The considerable contribution of Painter was to show that a high-fibre diet given to 70 patients with symptomatic diverticular disease resulted in an abolition of their symptoms. Two tablespoons of bran three times a day relieved the symptoms of the disease (Painter, Almeida and Colburn, 1972).

INDICATORS OF A MOTILITY DISORDER

Pain
The assumption is that it is an enhancement of segmentation in the colon leading to increased colonic pressure which causes the colicky lower abdominal pain in diverticular disease. Weinreich and Andersen (1976) measured sigmoid pressure in patients with well defined clinical symptoms. They showed that while a history of lower abdominal colic was significantly correlated with a high motility index, no such correlation was found between the mere presence of diverticula and high pressure activity. The demonstration of diverticula was significantly age-related, though no such relationship was found for either increased sigmoid pressure or lower abdominal colic. A group, 7.9 per cent of the population, regardless of age, were found to have longstanding abdominal colic but barium follow-through failed to show an increased prevalence of colonic diverticula.

Stool weight
Much interest has been directed to the bulk and consistency of faeces in diverticular disease. The dietary fibre hypothesis (Burkitt and Trowell, 1975) suggests that colonic diseases such as diverticular disease and colonic cancer arise from a life-long reduced faecal output, secondary to dietary fibre deficiency (Painter, 1975). There is a possibility that the patient with symptomatic diverticular disease may have a reduced faecal output, but spasm in the colon leading to pain may be associated with a reduced faecal bulk passing along the distal large intestine.

Table 1 shows reported data for stool weight in healthy individuals and subjects with diverticular disease, with no significant difference occurring between the groups. It is possible that the patients with diverticular disease were not symptomatic at the time of the study or that the normals were in fact individuals with a potential for, or who actually had, presymptomatic diverticular disease. The age range of this group is approximately the same as that of the recorded cases of diverticular disease.
Table 1. Stool weight and transit time in healthy subjects and patients with diverticular disease

<table>
<thead>
<tr>
<th>Healthy subjects (age range 18-80 years)</th>
<th>Stool weight(^a) (g/24 h)</th>
<th>Transit time(^b) (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edinburgh (Eastwood et al, 1981 unpublished results)</td>
<td>33 males 98 ± 49</td>
<td>72 ± 36</td>
</tr>
<tr>
<td></td>
<td>29 females 74 ± 34</td>
<td>86 ± 43</td>
</tr>
<tr>
<td>Bristol (Whyman et al, 1970)</td>
<td>10 males 131 ± 54</td>
<td>66 ± 27</td>
</tr>
<tr>
<td></td>
<td>10 females 126 ± 26</td>
<td>82 ± 28</td>
</tr>
<tr>
<td>Liverpool (Flynn et al, 1980)</td>
<td>17 subjects 103 ± 35</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diverticular disease (age range 30-84 years)</th>
<th>Stool weight(^a) (g/24 h)</th>
<th>Transit time(^b) (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belfast (Parks, 1980)</td>
<td>24 patients 96</td>
<td>44</td>
</tr>
<tr>
<td>Edinburgh (Findlay et al, 1974b)</td>
<td>7 patients 84 ± 14</td>
<td>93 ± 14</td>
</tr>
<tr>
<td>Liverpool (Hyland et al, 1980)</td>
<td>20 patients 171 ± 39</td>
<td>52 ± 9</td>
</tr>
<tr>
<td>Edinburgh (Eastwood et al, 1978a)</td>
<td>60 patients 98</td>
<td>(20-190) (24-190)</td>
</tr>
<tr>
<td></td>
<td>10 patients 215 ± 28</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elderly patients</th>
<th>Stool weight(^a) (g/24 h)</th>
<th>Transit time(^b) (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edinburgh (Smith et al, 1980)</td>
<td>median age 81 years (65-96)</td>
<td>37 patients 31</td>
</tr>
</tbody>
</table>

\(^a\)Mean ± s.d. or median (range).
\(^b\)n.d. = no data.

It is also of interest that the elderly coming for assessment to a geriatric unit who are frail and needing care or assessment have a significantly reduced faecal output (Smith et al, 1980). However, the active independent elderly person has a faecal output not significantly different from that of younger neighbours (Eastwood et al, 1981 unpublished results).

There is an immense variability of colonic function in healthy subjects. Whyman and his colleagues (1978) have shown wide variation of average faecal wet and dry weight. The size of individual stools varies, often over a tenfold range. The only constant feature of the stool is the faecal water content (71 to 79 per cent of the wet weight). Figure 1 shows similar results for individuals recruited from the north of Edinburgh. Stools were collected for seven days and the vertical line shows the range from the least to the greatest of stool weights excreted in that period. It is debatable how stool weight reflects colonic motility, though the two may be related.
DIVERTICULAR DISEASE

Intestinal transit time

If in diverticular disease there is an enhanced segmentation, retardation of colonic contents would be expected in any area where this is more pronounced. It could be predicted that any slowing of transit time would be in the distal colon but this is not so (Kirwan and Smith, 1977) and it will be seen from Table 1 that the transit time in patients with colonic diverticular disease is not different from, or is even faster than, that observed in studies of healthy asymptomatic subjects. Again Whyman and his colleagues (1978) underlined the problems of measuring intestinal transit times, showing wide variation not only between individuals but also when measurements were repeated for the same individuals. They suggested that this variability is a biological variation. The difficulty of estimating transit time in diverticular disease is shown when water-soluble and insoluble markers are given synchronously. A marker of the solid phase of the intestinal contents is chromium sesquioxide and polyethylene glycol 4000 (PEG) marks the water-soluble phase. In normal individuals the two markers appear in the stool synchronously. However, in diverticular disease it has been shown that the liquid phase marker passed more slowly than the solid phase markers (Findlay et al, 1974a). This was felt to reflect the effect of colonic hypersegmentation on the relative transit of liquid and solid phases. By the completion of studies on 30 subjects with diverticular disease who took PEG and chromium capsules, it was found that the ratio of the two markers in the stools range from 0.2 to 1.7 with a mean of 0.85. Overall, the solid
phase passes through the intestine more quickly than the liquid phase though there may be individual variations within the group (Eastwood et al., 1978b).

**Motility studies**

Studies on motility are the basis of our understanding of diverticular disease and perhaps more importantly lead to contemporary treatment patterns. Nevertheless, motility studies of the colon are of little use in clinical practice (Connell, 1978). The problem is in part the interpretation and the transformation of the recordings into figures to obtain a systematic analysis of motility records. There is also the matter of wide individual variation (Connell, Texter and Van Trappen, 1965). The original and important work on diverticular disease came from Arfwidsson (1964) and Painter (1963). Painter and Truelove (1964) found that patients with diverticular disease did not differ from the normal under resting conditions. Those segments of the colon containing diverticula contracted excessively in response to such pharmacological stimuli as prostigmine and morphine (Painter, 1964). Painter suggested that naturally occurring stimuli might produce an exaggerated response, resulting in the herniation of colonic mucosa. Such observations have important consequences for treatment. Since that time the use of morphine in the treatment of the pain of diverticular disease has not been recommended. Arfwidsson (1964) showed that the segmentation in the sigmoid colon with diverticular disease was greater than that for normal subjects under resting conditions, following a meal and after the injection of prostigmine. He suggested that the muscle in diverticular disease was generally overactive. Painter (1975) also combined simultaneous radiography with pressure recordings and described the mechanisms by which he believed diverticular were produced. Parks and Connell (1969) used open-ended tubes and found an exaggerated colonic motility response to food in diverticular disease patients. Under basal conditions the sigmoid motility activity was slightly greater in patients with diverticular disease than in the control group, though the strength of the contraction was greater in diverticular disease. Since then it has been possible through the use of transducers, amplifiers and analogue digital converters to calculate motility index which facilitates comparison of results, though studies using such an index confirm the earlier work (Attisha and Smith, 1968; Srivastava, Smith and Painter, 1976; Weinreich and Andersen, 1976). It will be seen from Table 2 that there is considerable variation in the motility indices recorded. Weinreich and Andersen (1976) studied motility in normal individuals and patients in whom the diverticular disease was an incidental finding and also in patients with chronic diverticular disease experiencing frequent symptoms. Symptomatic patients with diverticular disease recorded an increased motility index. In our experience (Eastwood et al., 1978b) with 60 patients with diverticular disease there was a considerable variation in results for both basal and stimulated motility indices. The motility index varied from normal in patients in whom the diagnosis of diverticular disease was an incidental finding, to an increased index in patients with symptoms of diarrhoea and pain.
### Table 2. Motility indices recorded in healthy subjects and patients with diverticular disease

<table>
<thead>
<tr>
<th></th>
<th>Basal recording</th>
<th>Stimulated recording</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 subjects</td>
<td>528</td>
<td>927 (food)</td>
</tr>
<tr>
<td>Diverticular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 patients</td>
<td>470</td>
<td>820 (food)</td>
</tr>
<tr>
<td>(Parks and Connell, 1969b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diverticular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 patients</td>
<td>892 ± 196</td>
<td>1512 ± 456 (food)</td>
</tr>
<tr>
<td>(Smith et al, 1974)</td>
<td></td>
<td>2120 ± 405 (prostigmine)</td>
</tr>
<tr>
<td>Diverticular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 patients</td>
<td>200</td>
<td>480 (food)</td>
</tr>
<tr>
<td>(Srivastava et al, 1976)</td>
<td>(75 - 600)</td>
<td>(90 - 800)</td>
</tr>
<tr>
<td>Normal subjects</td>
<td></td>
<td>597 (neostigmine)</td>
</tr>
<tr>
<td>12 subjects</td>
<td></td>
<td>(217 - 915)</td>
</tr>
<tr>
<td>Chronic diverticular disease</td>
<td></td>
<td>1996 (neostigmine)</td>
</tr>
<tr>
<td>62 patients</td>
<td></td>
<td>(201 - 7176)</td>
</tr>
<tr>
<td>Colonic diverticulosis</td>
<td></td>
<td>526 (neostigmine)</td>
</tr>
<tr>
<td>15 patients</td>
<td></td>
<td>(393 - 650)</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>1815 (neostigmine)</td>
</tr>
<tr>
<td>15 patients</td>
<td></td>
<td>(352 - 2103)</td>
</tr>
<tr>
<td>(Weinreich and Andersen, 1976)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diverticular disease</td>
<td></td>
<td>800 (food)</td>
</tr>
<tr>
<td>60 patients</td>
<td>(0 - 3800)</td>
<td>2200 (food)</td>
</tr>
<tr>
<td>(Eastwood et al, 1978b)</td>
<td></td>
<td>(400 - 6800)</td>
</tr>
<tr>
<td>Normal subjects</td>
<td></td>
<td>151 (food)</td>
</tr>
<tr>
<td>9 subjects</td>
<td></td>
<td>263 (food)</td>
</tr>
<tr>
<td>Diverticular disease</td>
<td></td>
<td>343 (food)</td>
</tr>
<tr>
<td>29 untreated patients</td>
<td></td>
<td>740 (food)</td>
</tr>
<tr>
<td>(Attisha and Smith, 1969)</td>
<td></td>
<td>2856 (prostigmine)</td>
</tr>
<tr>
<td>Myoelectrical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diverticular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flynn et al (1980)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-9 c/min</td>
<td>77.5 ± 3</td>
<td>60.4 ± 4</td>
</tr>
<tr>
<td>1-4 c/min</td>
<td>45.5 ± 6</td>
<td>53.0 ± 5</td>
</tr>
<tr>
<td>12-18 c/min</td>
<td>—</td>
<td>53.0 ± 5</td>
</tr>
</tbody>
</table>

Figures are mean ± s.d. or median (range).

Weinreich, Moller and Anderson (1977) sought a relationship between haustral pattern and intraluminal sigmoid pressure activity but found no correlation.

### THE STRUCTURE OF THE COLONIC WALL

The obvious muscle thickening and the demonstration on occasion of high intraluminal pressure have inspired many to regard diverticular disease as a disorder of smooth muscle function. The structure of the bowel wall has been somewhat neglected, although Painter (1975) described some of the factors which may predispose to a structural disorder, including obesity,
ischaemia and the site of entry of the blood vessels. The relationship of diverticula to the site of entry of blood vessels in the bowel wall is well recognized (Drummond, 1916), but there is little evidence to support the relevance of obesity and ischaemia.

A diverticulum, as a mucosal hernia through the wall of the colon, might be expected to occur at a point of weakness, possibly encouraged by high intraluminal pressure. In order to delineate the area of weakness in the bowel wall, the bowel has been distended with water (Beer, 1904) or air (Burt, 1931). The frequent finding, recently confirmed by Pace (1966), is that the rupture usually occurs through taenia rather than between the mesenteric and antimesenteric taenia, where diverticula are most commonly found. Parks and Connell (1969b) and Smith, Shepherd and Eastwood (1981) have studied the pressure/volume curves obtained with experimental distension of the distal colon by a balloon in diverticular disease. Such distension did not produce pressure changes in response to increase in volumes which occur in normal subjects and this phenomenon was temporarily altered by surgical resection, and not at all by myotomy or treatment with bran (Smith, Shepherd and Eastwood, 1981). This suggests that in diverticular disease there is a structural change throughout the distal colon.

Preliminary mechanical tests on postmortem bowel have shown a decline in tensile strength with age in all regions of the colon (Figure 2) (Yamada, 1970). The tensile strength is lowest in the distal colon, where diverticula are

![Ultimate Tensile Strength](image)

Figure 2. The ultimate tensile strength of colonic muscle from the ascending, descending colon and rectum in individuals aged from 4.5 to 79.5 years (drawn from data Iwasaki quoted by Yamada, 1970).
most commonly found. In both longitudinal and circular directions the tensile strength is greatest in the first decade of life but declines to 38 per cent in the 70 to 89 age group.

Pace (1966) examined the effects of ageing on colonic musculature and connective tissue. Table 3 shows that the thickness of both the circular and longitudinal muscle coats increases with age. Pace also found a progressive increase in the amount of collagen, elastin and reticular tissue with increasing age, though the amount of connective tissue between the two muscle coats declines from the age of 10 years. In the oldest age groups the connective tissue appears less regular and shows sign of wear. Considering Pace’s work in conjunction with the mechanical study of Iwasaki cited by Yamada (1970) one must conclude that the qualitative decline with age in the mechanical integrity of the colonic wall more than offsets the effect of the increase in the quantity of muscle or connective tissue.

The effect of age on the mechanical properties of tissue has been studied in more detail in skin. Daly and Oddland (1979) showed a loss of elasticity with increasing age. Similar changes in the stress/strain curves were obtained if elastin was removed enzymatically, suggesting that the age-related effect is due to changes in elastin. This ageing effect may be also achieved by fragmentation of the elastin. Pace (1966) noted that elastin became fragmented in the colonic wall in extreme old age, and Iwasaki’s work (Yamada, 1970) suggested that the colon becomes less expansive with increasing age. The colonic wall is a composite structure of smooth muscle, collagen, elastin, reticular fibres, cellular and nerve elements all embedded in a matrix. The mechanical properties of such a composite structure depend both on the strength, stiffness and toughness of the individual elements, and on their juxtaposition and interaction.

<table>
<thead>
<tr>
<th>Age</th>
<th>Anterior taenia (millimetres)</th>
<th>Circular muscle (millimetres)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 months' gestation</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>7 months' gestation</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>5 years</td>
<td>3.3</td>
<td>2.6</td>
</tr>
<tr>
<td>43 years</td>
<td>5.3</td>
<td>3.6</td>
</tr>
<tr>
<td>85 years</td>
<td>9</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Mechanical considerations relevant to the development of diverticula

The stress/strain curve of a homogenous engineering material such as steel is linear, indicating that the ratio of stress to strain is constant (Hooke’s Law) and may be expressed as an elastic or Young’s modulus, which enables a numerical figure to be given to the stiffness of the material. Elasticity is a property which implies that when a stress is removed the material returns to its original shape and dimension. Materials used in engineering are by and large elastic but biological materials are not. If a strip of human colon is stressed almost to breaking point and the stress then removed the strip only recovers 48 per cent (cited by Yamada, 1970). The stress/strain curve for
such biological tissues is shown in Figure 3, there being no constant elastic modulus. For biological tissues, there is no clearly defined elastic limit, i.e. that stress beyond which full recovery will not take place once the stress is removed. This inability to recover dimensions fully on removal of a stress is termed viscous behaviour. Because biological tissues tend to behave in part like a viscous liquid and in part like an elastic solid they are called viscoelastic (Fung, 1981). Viscoelastic materials show time-dependent properties so that if a constant stress is applied over a period of time the substance will continue to elongate, a property which is termed creep. If a constant strain is maintained then the amount of stress registered in the tissue will decline. This is known as stress relaxation and enables lower stresses to be accommodated when the bowel is distended. The advantages of viscoelastic design include the combination of properties such as expansibility, strength, load dissipation and maintenance of shape.

By considering the individual elements in the bowel wall it is possible to build up a simplistic picture of the reactions of a composite structure. Elastin in pure form as obtained from the ligamentum nuchae of ungulates appears to be truly elastic, with an elastic modulus of $3 \times 10^5$ Nm$^{-2}$ (Wainwright et al, 1976). Collagen is much stiffer than elastin and can only be extended reversibly by three to four per cent (the elastic limit). Its elastic modulus is of the order of $10^9$ Nm$^{-2}$, over 1000 times stiffer than elastin and smooth muscle, which has an elastic modulus of $1 \times 10^5$ Nm$^{-2}$ when relaxed, increasing to $2 \times 10^6$ Nm$^{-2}$ when active (Caro et al, 1978). Ground substance is viscoelastic, with a low modulus of the order of $1-10$ Nm$^{-2}$ (Wainwright et al, 1976).

A composite structure such as the bowel is capable of expanding to approximately 150 per cent of its original diameter. Collagen is the strongest material in the bowel wall, but it is also stiff and must therefore be arranged in a criss-cross arrangement like a fishnet in order for the whole structure to be expandable. This arrangement allows the combination of strong stiff fibres within a readily expandable matrix of ground substance and elastin. Examining the stress/strain curve three phases may be identified (Figure 3). Initially all the collagen fibres are slack (area A), then some fibres begin to take up the stress (area B) and then they all become taut (area C). A criss-cross arrangement would not be readily expandable if

![Figure 3. A typical stress/strain curve for biological tissue. Initially (A) all the tissue is slack, then (B) some fibres take up strain and finally (C) they all become taut.](image-url)
DIVERTICULAR DISEASE 555

Consisted of a matrix of continuous fibres, but the collagen in a biological tissue such as the bowel is almost certainly arranged in the form of a discontinuous network. A light microscopic study of individual layers of bowel wall supports the theory of such an arrangement of collagen bundles (Cavarligo, 1973).

A further factor limiting the distensibility of the bowel is the angle between individual collagen fibres. When the angle is acute stretching results in the fibres becoming taut rapidly (areas B and C, Figure 3) and so registering a higher stress at a lower strain than if the angle were more obtuse. The angle between the collagen fibres becomes more acute from the serosal to the mucosal side (i.e. acute in relation to the transverse axis of the organ) (Cavarligo, 1973). Thus on distending the bowel one would expect the layers to rupture from the mucosa to serosa since those layers with the most acute angle bear stress first. This was not the finding of Burt (1931), who found that the mucosal layer was the last to perforate. One explanation for this is that the mucosal layer is possibly more elastic than the other layers. This would explain why, if diverticular disease were related to a defect in the bowel wall, the stiffer external layers break and allow the elastic mucosa to herniate through, forming a diverticulum.

In a static tubular structure the circumferential stress in the wall is twice the stress in the longitudinal direction (Gordon, 1978). Thus if a cylindrical tube is distended the split formed when it ruptures is longitudinal. The wall breaks as a consequence of the circumferential, not the longitudinal, stress. This happens when one fries a sausage and the stuffing swells, and the sausage bursts; it also happens when the bowel is distended with air (Burt, 1931).

It is possible that the increased incidence of diverticular disease in the aged is related to a decline in mechanical integrity of the colonic wall with age. This possibility is further underlined by studies of the tensile strength of the colon in animals (Yamada, 1970). The colons of dogs, cats, cows and even domestic fowl have greater tensile strengths than the rabbit, an animal in which it has been possible to induce diverticula (Hodgson and Johnson, 1975). The only other animal in which diverticula have been reported is the rat (Wierda, 1943; Carlson and Hoezel, 1949), but the tensile strength of its colon has not been studied.

FIBRE AND DIVERTICULAR DISEASE

It has been suggested (Painter, 1975) that a depletion of dietary fibre in the diet is responsible for the genesis of the colonic diverticula. Painter (1975) has argued that a hypersegmentation of the colonic muscles associated with the propulsion of a small stool bulk strains the colonic mucosa, with subsequent development of diverticula. This is not inconsistent with a weakening of the wall associated with age. It is also possible that a high-fibre diet such as is eaten in African countries is in some way of value in maintaining the mechanical properties of the colon. It has been shown earlier that the faecal output in individuals with or without symptoms of diverticular disease do not differ significantly. It has been shown in Figure 1...
that there is a wide variation of stool weight in the normal population for each individual. Colicky abdominal pain was not recorded by the individuals when they passed small stools during the study (Eastwood et al, 1981 unpublished results).

It is possible that the colon with diverticula, on giving rise to symptoms, contracts as the result of some intraluminal spasmogen which would be present in high concentration if the stool were small perhaps with lack of sufficient dietary fibre. The effect of fibre is to increase the stool bulk by holding water within the faecal mass, either as a result of the direct water-holding capacity of the fibre or the intracellular water of bacteria which have proliferated as a result of the metabolism of fibre in the caecum (Stephens and Cummings, 1980).

**FAECAL BILE ACIDS AS COLONIC SPASMGENS**

Bile salts have been said to stimulate motility (Horral, 1938; Haney, Roley and Cole, 1939) and the introduction of bile into the colon and rectum results in defaecation (Hallion and Nepper, 1907; Schupbach, 1908). However, the lack of purity of some of the bile acid preparations available to these authors must limit the conclusions drawn from experiments. Experiments with purified bile acids (Kirwan et al, 1975) demonstrated that colonic motor activity was initiated by infusion of bile salts into the caecum or rectum of the anaesthetized rabbit. Primary bile acids produced a marked motor response throughout the colon. Deoxycholic acid, which results from bacterial action on cholic acid in the colon, was much less active than cholic acid conjugates in the rabbit. Patients with diarrhoea following ileal resection and who excrete primary bile acids in their faeces have a significantly greater motility index than patients with diarrhoea who only excrete secondary bile acids. This suggests that only primary bile acids are responsible for the production of the abnormal motility.

In the rabbit no significant relationship was found between the resting bile acid content of the colon and basal motility. The value for the initial basal motility did not determine the motility response following stimulation by exogenous bile acids (Falconer, Smith and Eastwood, 1980).

Table 4 shows the total daily faecal bile acid excretion and faecal bile acid concentration in several studies. Tarpila et al (1978) showed a higher average daily faecal bile acid excretion in diverticular disease patients than in controls. Administration of bran over a period of 12 months resulted in a reduction of the faecal bile acid excretion to values more nearly those of control subjects. Flynn et al (1980) found the daily deoxycholic acid and lithocholic acid excretion to be significantly lower in patients with diverticular disease than in normal subjects. They also reported a significant correlation between the faecal lithocholic acid and the incidence of 12-18 c/min myoelectrical activity and the deoxycholic excretion and the incidence of 6-9 c/min myoelectrical rhythm. After a year of bran treatment they showed that the incidence of 12-18 c/min activity fell significantly, whereas concentrations of lithocholic acid and deoxycholic acid were unchanged. Eastwood et al (1978b) in a study of 60 patients with
Table 4. Faecal bile acid excretion in healthy subjects and patients with diverticular disease

<table>
<thead>
<tr>
<th>Normal subjects</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Edinburgh (Eastwood et al, 1980)</td>
<td>Total bile acids</td>
<td>Deoxycholic acid</td>
<td>Lithocholic acid</td>
</tr>
<tr>
<td>33 males (mmol/24h)</td>
<td>0.71 ± 0.31</td>
<td>0.39 ± 0.19</td>
<td>0.26 ± 0.12</td>
</tr>
<tr>
<td>29 females (mmol/24h)</td>
<td>0.56 ± 0.35</td>
<td>0.31 ± 0.21</td>
<td>0.20 ± 0.11</td>
</tr>
<tr>
<td>33 males (mmol/kg w.f.)</td>
<td>8.0 ± 4.2</td>
<td>4.4 ± 2.1</td>
<td>2.9 ± 1.3</td>
</tr>
<tr>
<td>29 females (mmol/kg w.f.)</td>
<td>7.8 ± 3.3</td>
<td>4.3 ± 2.9</td>
<td>2.8 ± 1.5</td>
</tr>
<tr>
<td>Helsinki (Tarpila et al, 1978)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol/24h)</td>
<td>0.62 ± 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol/kg w.f.)</td>
<td>9.8 ± 5.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liverpool (Flynn et al, 1980)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 controls (mmol/24h)</td>
<td>0.91 ± 0.1</td>
<td>0.59 ± 0.1</td>
<td>0.32 ± 0.05</td>
</tr>
<tr>
<td>17 controls (mmol/kg w.f.)</td>
<td>8.9 ± 1.0</td>
<td>5.7 ± 1.0</td>
<td>3.2 ± 0.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diverticular disease</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Edinburgh (Eastwood et al, 1978)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 patients (mmol/24h)</td>
<td>0.5e</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0.1 - 1.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helsinki (Tarpila et al, 1978)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 patients (mmol/24h)</td>
<td>1.04 ± 0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edinburgh (Findlay et al, 1974b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 patients (mmol/24h)</td>
<td>0.71 ± 0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 patients (mmol/kg w.f.)</td>
<td>9.5 ± 2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 patients (mmol/24h)</td>
<td>0.58 ± 0.07</td>
<td>0.34 ± 0.04</td>
<td>0.24 ± 0.03</td>
</tr>
<tr>
<td>Liverpool (Flynn et al, 1980)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 patients (mmol/kg w.f.)</td>
<td>4.1 ± 0.4</td>
<td>2.5 ± 0.3</td>
<td>1.6 ± 0.2</td>
</tr>
</tbody>
</table>

mmol/kg w.f. = millimoles per kilogram wet faeces.

*Median and range.

diverticular disease reported a range of faecal bile acid excretion of between 0.1-1.4 mmol/24 h with a mean value of 0.5 mmol, which was in the normal limits for the same laboratory (Eastwood, 1981).

**CALCIUM AS AN INFLUENCE ON COLONIC MOTILITY**

Eastwood (1981) measured faecal excretion of electrolytes in patients with diverticular disease and showed that there was an inverse relationship between the faecal calcium and magnesium and colonic motility activity. Sodium and potassium were not so related.

These results suggest that there is a relationship between intestinal contents and colonic motility. It remains speculative whether faecal bile acids and faecal calcium reflect the fibre content of the diet or are of themselves stimulants or relaxants of the colonic musculature.

**THE HORMONAL ROLE IN STIMULATION OF COLONIC MOTILITY**

Following the ingestion of food there is an increase in motor activity throughout the gastrointestinal tract. The intravenous injection of gastrin (Hogg and Smith, 1966) or cholecystokinin (Harvey and Read, 1973) has been shown to stimulate small bowel and colonic motility and increase
intestinal transit time (Levant et al., 1974). As previously suggested, bile acids may be excreted to the colon in response to the choleretic action of gastrin or because of the emptying of the gallbladder in response to cholecystokinin. Postprandial serum gastrin concentrations are associated with two peaks of colonic motility. The initial motility peak occurs 10 minutes before the peak in serum gastrin (Kirwan and Smith, 1976), consistent with autonomic nervous control of the postprandial gastrocolic motor activity. While the serum gastrin remained elevated at 90 per cent above the basal concentration for at least 90 minutes the colonic motor activity fell briskly from its initial peak, though there was a later second rise. While the residual colonic motility after the initial peak may be the result of a raised serum gastrin concentration a group of further peptides may be released during the postprandial phase. The release of such hormones has yet to be studied in diverticular disease.

THE EFFECTS OF TREATMENT AS SUPPORT FOR THE CONCEPT OF DIVERTICULAR DISEASE AS A MOTILITY DISORDER

Symptomatic diverticular disease is characterized by a low stool weight, prolonged transit time, variable appearance of abnormal faecal bile acids and calcium and an increased motility index. By adding fibre to the diet Painter was able to show symptomatic improvement in the majority of his patients with diverticular disease.

Brodribb and Humphries (1976) have since shown that there is also a substantial placebo effect in the treatment of diverticular disease. Reassurance to patients that they do not have cancer is frequently associated with improvement.

Coarse bran has been shown to reduce the motility index with a concomitant increase in stool weight and return of the transit time to normal (Findlay et al., 1974b). If the coarse bran was then rendered fine the water-holding capacity was reduced and the effect on colonic motility was also reduced (Kirwan et al., 1974). If bran cooked and compressed into a palatable biscuit is used then the treatment is relatively ineffective (Ornstein et al., 1981). Faecal bile acids are restored to normal either by dilution (Findlay et al., 1974b) or by reduction (Tarpila, Miettinen and Metsaranta, 1978). Myoelectric abnormalities found in association with a low deoxycholic and lithocholic content of the stool disappeared after a year of successful treatment (Flynn et al., 1980), though the faecal bile acid excretion was unchanged. Following treatment, the calcium content of the stool increases as a result of the cation exchange capacity of the bran (Eastwood and Mitchell, 1976). All of these changes are consistent with the suggestion that symptomatic diverticular disease is a motility disorder. Sterculia and ispaghula gums, however, when used in the treatment of diverticular disease, increase stool weight and abolish symptoms and yet are associated with an increase in motility index (Srivastava, Smith and Painter, 1976; Eastwood et al., 1978a). This is contrary to the concept that diminished stool weight, increased motility and the presence of symptoms always run in parallel.
Diverticular disease is a condition prevalent among communities eating a Western diet. It is a condition associated with changes in the mechanical properties of the ageing bowel. The condition may remain symptomless throughout life. The tendency to have symptoms and to have a motility disorder increases with age and may be reversed by augmenting the intake of dietary fibre.

REFERENCES


Wiers, J. L. (1943) Diverticula of the colon in rats fed on a high fat diet. *Archives of Pathology*, 36, 621-626.

Diverticular Disease of the Colon in Scottish Hospitals over a Decade

Kathleen Chalmers*
Research Assistant
JM Wilson†
Senior Research Fellow
Information Services Division, Scottish Health Service
Common Services Agency
Trinity Park House, Edinburgh EH5 3SE
AN Smith
Consultant Surgeon and Reader in Surgery
MA Eastwood
Consultant Physician and Senior Lecturer
Gastro-Intestinal Unit, University of Edinburgh
Western General Hospital, Edinburgh EH4 2XU

Summary
Hospital admissions for diverticular disease were recorded from the Scottish Hospital In-patient Statistics from 1968-1977, the second five years of which fall within the 'bran era'. There was a progressive increase in admissions, greater for females, and particularly affecting secondary and tertiary diagnosis. Forty-five per cent of the men were under the age of 65, whereas 36% of the women were over 75. The relatively high proportion of younger men suggests that the disease, or factors causing it, is more severe in males than in females. Few had surgery, though 50% were emergency admissions. The male colectomy rate was significantly higher than the female one, mainly due to operations in males under 65 years. The female colectomy rate, however, rose between the two periods, the male rate remaining constant. This was largely due to an increasing number of operations in women over 75 years of age. Throughout the period examined there was thus no sign of a decrease in diverticular disease as it presented in Scottish hospitals. Admission rates varied between Health Boards, the highest rates being in the Highland, Grampian and Tayside areas.

Introduction
Diverticular disease of the colon is common in Western countries1 and especially so in Scotland2. Although questioned3,4, it is widely held that dietary cereal bran is beneficial in treatment5,6,7,8. Our impression has been that hospital admissions to the Gastro-Intestinal Unit in Edinburgh were falling. If so, this could have formed evidence favouring the bran hypothesis. Somewhat to our surprise initial examination of the Scottish Hospital In-Patient Statistics (SHIPS) did not confirm a downward trend in admissions and we therefore thought it worthwhile to examine the data in more detail. The period examined spans the years of change from the management of diverticular disease by a low residue diet to one advocating a high fibre intake9.

Hospital admission data of course need careful interpretation and conclusions only can be drawn from their analysis with caution. Amongst the many factors governing the

*Now Communicable Diseases (Scotland) Unit, Ruchill Hospital, Glasgow G20 9NB
†Now retired
11. Previous contact with West Lothian Department of Psychology (1=Yes, 2=No, 9=N/K)
12. Appointment kept (1=Yes, 2=Called off, 3=Did not appear, 9=N/K)
13. Site of appointment (1=Home, 2=Health Centre/Surgery, 3=Health Clinic, 4=Psychology Department, 5=Other, 9=N/K)
14. Professions involved (1=Psychologist alone, 2=Co-therapy, 3=Team, 4=Trainee, 5=Other, 9=N/K)
15. Patient seen alone or with another (1=Alone, 2=Patient plus relative, 3=Patient plus relative jointly, 4=Group, 9=N/K)
16. Formulation of presenting problem (Coded List of Problems)
17. Assessment procedures at first contact (Up to 3 procedures permitted; 1=None, 2=Basic History, 3=Detailed History or Behavioural Analysis, 4=Cognitive Testing, 5=Other Testing, 6=Other, 9=N/K)
18. Therapeutic procedures at first contact (Up to 3 procedures permitted; 1=None, 2=Counselling, 3=Behavioural Therapy, 4=Psychotherapy, 5=Other, 9=N/K)
19. Further management or disposal (1=No follow up, Opinion Made/Problem Resolved, 2=Further Appointment—Psychologist, 3=Further Appointment—Co joint, 4=Patient to Return if Wished, 5=Referred to Other Specialist, 6=Combinations of 5+2 or 3, 7=Returned to Referring Agent, Patient Declined Offer of Further Appointment, 9=N/K)
20. Duration of Appointment (Minutes)
interpretation of changes in the number of admissions over a period of time are changes in admission policy, changes in diagnostic practice and changes in the techniques of medical recording. The data do not necessarily reflect the incidence of disease in the population at large since they only record that proportion of disease admitted as in-patients (patient-specific data on out-patients is not at present available). For diverticular disease the hospital population certainly comprises only a small proportion of prevalent disease. In spite of this hospital admissions probably represent the more severe symptomatic cases and those with complications so that, should dietary cereal bran be proving an effective remedy in the community, we could expect this effect to be reflected in the number of patients admitted to hospital.

Methods and definitions
Requests were made to the Scottish Office Computer Service (SOCS) for analyses of Scottish Hospital In-patient Statistics (SHIPS) data, aggregated from the information recorded on the form SMR1 completed for each hospital discharge, transfer or death. For convenience these are referred to as ‘admissions’ even though the two terms are not synonymous e.g. the number of discharges in a year will differ from the number of admissions, depending on how many patients remain in hospital from the end of one year to the beginning of the next. The form SMR1 provides space for three, and since 1975, four diagnoses. The first diagnosis is generally considered the main condition and the reason for hospital admission. Where diverticular disease is ranked second or third, a more important condition or complication preceded it. The paper initially looks at all admissions for diverticular disease of the colon (International Classification of Diseases (ICD) (Eighth Edition), code 562.1) as a first, second or third diagnosis between 1968 and 1977.

To obtain an estimate of first admissions records were linked by computer for all admissions with a first, second or third position diagnosis of diverticular disease of the colon between 1968 and 1977. Records were compared by name, date of birth etc., and any patient with more than one admission had the second and any subsequent admission excluded from the first admission analysis. Since many patients had been in hospital before 1968 the number of ‘first admissions’ in the early years of the study was presumably over-estimated. In an attempt to minimise bias the three years 1968—70 were excluded from the analyses. First admissions were analysed by position of the diagnosis.

Results
Number of admissions
Tables I and II show for 1968–1977 and 1971–1977 respectively all the admissions to hospital with diverticular disease in Scotland and also the first admissions only; in both, the female admissions are not far short of double the male admissions. There has been an increase in the total hospital admissions for diverticular disease, more for females than males, and this is mainly due to an increase in secondary and tertiary diagnoses. To a lesser extent (see comparison of two 3-year periods 1971—73 and 1975—77) first admissions show the same picture, but those with a principal diagnosis of diverticular disease show little change between the two periods.

The large proportionate increases in secondary and tertiary diagnoses may reflect changing diagnostic practice to a greater extent than principal diagnoses. For this reason only admissions with a first position diagnosis are examined in the remainder of the paper, since the aim of the study is to determine as far as possible whether there has been a ‘real’ change in the number of admissions and admission rates.
**Table I:** All Diverticular Disease of the Colon (ICD 562.1); by Position of Diagnosis, Sex and Year, Scotland 1968–77

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st Diagnosis</td>
<td>2nd Diagnosis</td>
</tr>
<tr>
<td>1968</td>
<td>559</td>
<td>106</td>
</tr>
<tr>
<td>1969</td>
<td>537</td>
<td>127</td>
</tr>
<tr>
<td>1970</td>
<td>584</td>
<td>128</td>
</tr>
<tr>
<td>1971</td>
<td>598</td>
<td>126</td>
</tr>
<tr>
<td>1972</td>
<td>641</td>
<td>171</td>
</tr>
<tr>
<td>1973</td>
<td>631</td>
<td>162</td>
</tr>
<tr>
<td>1974</td>
<td>608</td>
<td>169</td>
</tr>
<tr>
<td>1975</td>
<td>624</td>
<td>168</td>
</tr>
<tr>
<td>1976</td>
<td>591</td>
<td>190</td>
</tr>
<tr>
<td>1977</td>
<td>626</td>
<td>185</td>
</tr>
<tr>
<td>1968–77</td>
<td>5,999</td>
<td>1,532</td>
</tr>
<tr>
<td>1968–72</td>
<td>2,919</td>
<td>658</td>
</tr>
<tr>
<td>1973–77</td>
<td>3,080</td>
<td>874</td>
</tr>
<tr>
<td>Percentage change between 1968–72 and 1973–77</td>
<td>+5.5</td>
<td>+32.8</td>
</tr>
<tr>
<td>Year</td>
<td>Males</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>1st</td>
<td>2nd</td>
</tr>
<tr>
<td></td>
<td>Diagnosis</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>1971</td>
<td>439</td>
<td>103</td>
</tr>
<tr>
<td>1972</td>
<td>497</td>
<td>128</td>
</tr>
<tr>
<td>1973</td>
<td>468</td>
<td>122</td>
</tr>
<tr>
<td>1974</td>
<td>456</td>
<td>131</td>
</tr>
<tr>
<td>1975</td>
<td>456</td>
<td>125</td>
</tr>
<tr>
<td>1976</td>
<td>429</td>
<td>142</td>
</tr>
<tr>
<td>1977</td>
<td>451</td>
<td>136</td>
</tr>
<tr>
<td>1971–77</td>
<td>3,196</td>
<td>887</td>
</tr>
<tr>
<td>1971–73</td>
<td>1,404</td>
<td>353</td>
</tr>
<tr>
<td>1975–77</td>
<td>1,336</td>
<td>403</td>
</tr>
<tr>
<td>Percentage change between 1971–73 and 1975–77</td>
<td>-4.8</td>
<td>+14.2</td>
</tr>
</tbody>
</table>
Admission rates
Table III shows clearly the much higher admission rate (diverticular disease per million of the population) for females compared with males, both for total and first admissions. Between the two periods 1971–73 and 1975–77 there has been a small, non-significant, fall in the male rate in both first and total admissions. By contrast, the female rates have risen, though only significantly for total admissions.

**Table III: Total and First Admission (Diverticular Disease of the Colon: ICD 562.1) Rate per Million Population; by Sex and Years, First Position Diagnosis, Scotland**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>First</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>1971–1973</td>
<td>249·0</td>
<td>395·1</td>
</tr>
<tr>
<td>1975–1977</td>
<td>245·0</td>
<td>426·8</td>
</tr>
<tr>
<td>Percentage change</td>
<td>-1·6%</td>
<td>+8·0%**</td>
</tr>
</tbody>
</table>

**Significant at 1% level.

Age of admission
An analysis of total admissions by age and sex showed that over 45% of men were aged less than 65 years, compared with only 30% of women. By the same token women over 75 comprised the largest of the age groups, 36%. This female age group, 75 and over, also had the highest admission rate, which increased by nearly 70% from 1,800 per million population in 1968 to 3,000 per million in 1977 (Figure 1). The admission rate for males over 75 also showed a rise of over 55% between 1968 and 1977.

**Figure 1. Hospital diverticular disease of the colon per million population in Scotland by sex, age and first position diagnosis from 1968–1977.**
Admission by specialty and type of admission

As Figure 2 shows, some three quarters of patients are admitted to general surgical departments, and most of the rest to general medicine. Women account for a considerable rise in surgical admissions, an increase of 45% between 1968 and 1977. Throughout the study period about 50% of total admissions were designated emergencies (Figure 3). These admissions increased in number over the period 1968–1977, again mainly due to female emergencies.
Surgery
The female, but not the male, colectomy* rate for all ages has risen between the first and second 5-year periods, largely accounted for by a rise in the operation rate in the over 75s.

For the whole period together, as Figure 4 shows, the male colectomy rate is higher than the female, the difference being statistically highly significant. This is due to higher operation rates in males at ages under 65 years. The 15% operation rate for the less than 44 year-old age group and the 11% rate for the 45–64 group differ highly significantly from the rate of 9% for males of all ages. The age trend in females, though similar, does not reach the level of statistical significance.

![DIVERTICULAR DISEASE OF COLON COLECTOMY RATE PERCENT ADMISSIONS](image)

Figure 4. Colectomy rate percent admissions, by age group and sex.

Area of residence
Admission rates vary considerably between health boards of residence. The patterns are similar for both sexes but the female rate is higher in all health boards. The highest rates are for the predominantly rural areas of the Highland, Grampian and Tayside Health Boards (Figure 5). High rates are evidently not explained by the age of the population, the hospital admission rates correlate poorly with the proportion of population aged 65 and over. Possible reasons for these differences are discussed below.

*Colectomy' includes 'colectomy and resection' (OPCS codes 453 from 1968–70, 460 from 1971–77) and 'complete colectomy' (OPCS codes 452 from 1968–70, 461 from 1971–77).
Certified mortality
Mortality from diverticular disease of the colon is relatively low; on average over the 10-year period 1968–1977 there were 42 male and 86 female certified deaths per year in Scotland (this includes hospital deaths). The male death rate, about half that of the female rate, showed some decline over the period, while the female rate increased slightly, attributable to a rise in the death rate in women over 75.

Discussion
Diverticular disease is widely distributed in the Western World as has been emphasised by the report\(^6\) that its prevalence may reach 50% in the age group over 65 years. The change towards a high residue diet with an enhanced content of fibre was found\(^9\) to relieve most of the symptoms of patients with diverticular disease. The rational basis of this was confirmed\(^6\) and it was shown that cereal bran reduced the high intraluminal colonic pressure in symptomatic diverticular disease and should thus be capable of protecting the colon wall from the factor which causes damage to it and also promotes the extrusion of the diverticulum. This was the first objective evidence to relate the possible use of fibre not only to counteract the symptoms of the condition but to prevent it. Against the background of the continuing popularity of high fibre high residue diets since 1974 for the management of diverticular disease, it had been our expectation that the numbers admitted to Scottish hospitals might have fallen but our findings suggest that, from the numbers admitted to hospital both for medical management and operations, this is not so.

There is often an increased interest in the detection and management of any medical condition following the introduction of a new form of therapy. The use of high fibre diets in the treatment of diverticular disease in the latter part of the study period may in part
explain the rise in hospital admissions seen for all positions of diagnosis. This increase is largely due to secondary and tertiary diagnoses, which probably results from better diagnosis of the condition while patients are in hospital for other conditions.

The most notable change seen with first position diagnoses is the large increase in the age-specific admission rates for females 75 and over and to a lesser extent for females 65–74. This is more than a reflection of the increasing number of elderly females in the population, since these are age-specific rates.

Males are admitted at a younger age than females; over 45% are under the age of 65 compared with only 30% of females. The relatively younger age of the male patient is also reflected in colectomy operations—63% of male colectomies are under 65 compared with 44% of female operations. This suggests that either or both physiological and environmental differences between the sexes may result in a different pathogenesis between males and females; males evidently enter hospital earlier and with a more severe condition.

It is interesting that hospital admissions for diverticular disease vary between health board areas in Scotland. This could conceivably be due to the greater severity of cases, the age-structure of the health board populations or the differing admissions policies between health boards. If the high rates in rural areas are due to greater severity of cases one possible factor might be that less fresh fruit and vegetables are eaten in more remote areas; this problem is probably reflected in the higher than average published food prices in the Highlands. Other factors that might have a bearing on the variations in admission rate from health board to health board are: differences in the access of patients to medical services and differences in the availability of hospital beds. None of these factors on their own, though correlating positively with health board admission rates, reaches the level of statistical significance. However, the higher admission rates in the more isolated areas of Scotland may be related to a combination of the various factors causing general practitioners to take the general precaution of referring more patients for in-patient investigations and treatment.

There is no real evidence that there has been an alteration in the pattern of hospital admissions for diverticular disease of the colon in Scotland. It may be that increased interest in the condition has helped to maintain the level of hospital admissions to that prior to the introduction of fibre diets as a treatment. It is also possible that a high fibre diet is not being adequately or properly prescribed or taken. There are differences in action between different fibre sources in their action on the colon, cereal bran that is cooked is for example less effective than raw bran. Yet cooked bran is overall more palatable, an acceptability which may be of importance to an older population.

Whatever the reason, the anticipated reduction in Hospital admissions for diverticular disease since bran was first introduced for the symptomatic relief of diverticular disease has not yet occurred.

Acknowledgements
We wish to thank Dr M A Heasman and the other members of the Royal College of Physicians of Edinburgh Council Committee on Information for Clinical Management for their guidance and constructive criticism. Special thanks are due to Lorna Robertson for clerical assistance. Dr Wilson and Miss Chalmers were supported under a grant from the Scottish Home and Health Department.
References

The Chief Scientist reports . . .

Prostaglandins, Thromboxanes and the Early Events of Myocardial Ischaemia

J R Parratt, MSc, PhD, DSc, FPS, FBiol
Professor
Department of Physiology and Pharmacology
University of Strathclyde, Glasgow

S J Coker, BSc, MSc, PhD, MPS
Research Fellow
Department of Physiology and Pharmacology
University of Strathclyde, Glasgow

I McA Ledingham, MD, FRCS, FRSE
Professor of Clinical Physiology
University Department of Surgery
Western Infirmary, Glasgow

Introduction
One of the most serious consequences of the interruption of blood flow to the muscle of the heart is the generation of ventricular arrhythmias. Ventricular ectopic activity commences within minutes of the onset of myocardial ischaemia in experimental animals and probably also in the clinical situation of an acute coronary attack. Certainly the clinical experience of the Belfast group\(^1\) is that the incidence of ventricular arrhythmias, and especially fibrillation, is highest within one hour of the onset of symptoms. Only a small proportion of such patients are seen by a medical person during this period and it follows that the contribution to the reduction of very early cardiac mortality by coronary care units (when the mean time of admission is usually four hours or more) or even of mobile coronary care units, cannot be expected to be great\(^2\). This problem, of coronary heart disease in general and of sudden cardiac (coronary) death in particular, is of course especially serious in West Central Scotland.

There are a number of factors that determine the incidence and severity of these early and life-threatening, ischaemia-induced ventricular arrhythmias. They include the site of the coronary occlusion, the duration of ischaemia, the extent of the existing coronary collateral circulation and whether reperfusion of the ischaemic region occurs. However, these are almost certainly not the only factors involved in whether or not ventricular fibrillation develops as a consequence of ischaemia and there has been considerable experimental research, much of it supported by the Scottish Hospitals Endowment Research Trust, on the relationship between the biochemical consequences of ischaemia and the generation of life-threatening arrhythmias. Particular attention has been placed on the possible early release of myocardial noradrenaline, the increase that occurs in the intramyocardial levels of cyclic adenosine monophosphate and the possible role of derivatives of arachidonic acid. It is this last aspect that is the subject of this article.

The formation of prostaglandins and their effects in ischaemia.
The term ‘prostaglandin’ was first used by von Euler to describe the vasodepressor and smooth muscle stimulating substance which he found in accessory genital glands and human semen.
Colonie Function in Rural and Urban Populations of Turkey

Hamdi Aktan, M.D., Ali Ozden, M.D., Erol Kesim, M.D., Adam N. Smith, F.R.C.S.

Two Turkish populations, one with an urban background and the other rural, were compared in regard to their colonie function. Rural subjects consume a diet with higher fiber than urban people in Turkey. The rural group had a greater daily fecal output, faster intestinal transit, and lower intraluminal pressure, with a greater output of calcium in the feces than those living in an urban area in Turkey. The effects are similar to those described when fiber is added to the diet. Urban dwellers in Turkey who lack these effects are said to have a rising incidence of fiber-related diseases of the colon, such as diverticular disease. [Key words: Colon; Fiber; Rural; Urban; Turkey]

Turkey provides a good opportunity for comparing the effect of lifestyle and diet on colonie function. Rapid cultural changes, urbanization, and economic development in the past 50 years have created subpopulations, with marked differences as to their way of life, existing close to each other. At one extreme, people in the large cities lead a western style of life, while at the other extreme, villagers continue to live in the traditional way, one of the main differences being the manner in which bread is prepared. In the cities throughout Turkey, bread is made of a low-extraction (79 to 81 per cent) flour milled in modern factories, while in the villages, homemade whole meal bread made of local flour is preferred. It seemed important to determine whether there were changes in colonie function in rural areas compared with urban areas that were possibly related to the background of a differing dietary fiber intake.

Methods

Two groups of volunteers were chosen for the study. Urban Group: Fourteen individuals, ages 23 to 53 years (mean 41.8) included one office worker, three housewives, one university student, three manual workers, and six government employees engaged in various types of office work. All the subjects habitually consumed bread of low-extraction flour.

Rural Group: Twelve healthy individuals, aged 17 to 62 years (mean 37.8) were engaged in farming and domestic work, except for one male school teacher who nevertheless conformed to the village way of life. The subjects in this group habitually consumed whole meal bread prepared with local flour.

Pertinent points about the diet in the rural and urban populations were obtained through the "National Nutrition Survey of Turkey—1974" (Table 1).

Using "Fibre Analysis Tables" prepared by Southgate, and taking only the bread into consideration, the dietary fiber intake of the rural population was calculated as 3.7 times that of the urban population. The groups, in general, conformed to the dietary differences outlined in Table 1: in the villages there was a higher intake of cereal fiber, offset to some degree by a reduced intake of fiber sources in fruits and vegetables. There was also a reduced meat consumption in the villages, with a very large intake of milk products, principally yogurt. Rye bread was not consumed by either the rural or urban population.

Fecal Weight: Stool samples were collected daily in plastic bags and the mean weight determined over five days. The average fresh stool weight excreted for each 24-hour period was calculated for the period of collection. A small sample of homogenized feces was dried in an 80°C oven for 48 hours, the samples were reweighed, and the percentage change and per diem weight of the dried feces noted.

Fecal Magnesium and Calcium: Fecal magnesium concentration of the weighed stool sample was measured spectrophotometrically in fresh samples according to Haury's method and the daily excretion calculated. Fecal calcium concentration was estimated according to Goff's method (1961), and titrated with sodium EDTA, with calcine-thymolphthalein as an indicator. Daily fecal calcium excretion was also calculated.

Intestinal Transit Time: Twenty radiopaque plastic pellets1 were given either with breakfast or the evening...
meal. The passage of pellets through the intestinal tract was followed by x-ray of fecal samples and daily abdominal radiographs. The time between ingestion and 80 per cent passage of pellets was taken as the transit time.

**Colonic Motility:** Two polyvinyl catheters, internal diameter 2 mm, with lateral openings of 1.2 mm, were passed sigmoidoscopically into the distal colon so that side openings were at 25 and 20 cm, respectively, from the anus. Distilled water was continuously infused, 1 ml/minute. The tubes were connected to a Hewlett-Packard multichannel recorder and intraluminal pressures transmitted through 273 AC transducers were recorded as wave forms simultaneously at a speed of 0.5 mm/second. Tests started before breakfast. Basal pressure was recorded for 30 minutes before the subjects had a standard meal. The recording continued for a further 30 minutes postprandially and 1 mg of neostigmine was given intramuscularly. The colonic pressure was then recorded for another 30 minutes postneostigmine. Tracings were analyzed according to Connell et al.\(^5\) The pressure activity was expressed as an “index of total activity” for the sigmoid colon at 25 cm; basal, postprandial, and postneostigmine periods of activity were assessed separately. Because of the range of results, these are expressed as a median and the Mann-Whitney test for unpaired differences has been used for statistical analysis.

**Results**

**Fecal Weight (Table 2):** The median daily fecal weights in city dwellers and in villagers were 126.4 and 167.1 gm, respectively. The dry weight, reflecting solids, was doubled in the rural group. The per cent increase of the wet weight, reflecting fecal water, was also much higher in the village group \((P < 0.01, < 0.05, \text{respectively})\).

**Fecal Magnesium and Calcium (Table 3):** The median total excretion of magnesium and median fecal concentrations did not differ significantly between the groups. The median calcium concentration (mg/24 hours) in the feces of the two groups was not significantly different (378 and 363). The median daily total excretion of calcium (737.7 mg/24 hours), however, in the village population was significantly greater (472.6 mg/24 hours) than those living in the city.

**Transit Time (Table 4):** The median values for the 80 per cent radiopaque marker transit time in the city and village populations were 45.5 and 36.5 hours, respectively \((P < 0.01)\).

**Colon Motility Studies (Table 5):** This was measured in 11 subjects of each group. The basal pressure and pressure responses to meals were higher in the urban group, but only the median postneostigmine response was sufficiently different to reach levels of significance \((< 0.05)\) because of the wide range involved.

---

### Table 1. Food Consumption According to Urban or Rural Domicile in Turkey (1974) (Gram/Person/Day)

<table>
<thead>
<tr>
<th>Food Items</th>
<th>National Average</th>
<th>Urban*</th>
<th>Rural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bread</td>
<td>402</td>
<td>373</td>
<td>445</td>
</tr>
<tr>
<td>Other wheat products</td>
<td>51</td>
<td>42</td>
<td>70</td>
</tr>
<tr>
<td>Corn and other cereals</td>
<td>16</td>
<td>6</td>
<td>47</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>472</td>
<td>421</td>
<td>568</td>
</tr>
<tr>
<td>Milk</td>
<td>25</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>Yogurt</td>
<td>54</td>
<td>30</td>
<td>108</td>
</tr>
<tr>
<td>Cheese and other milk products</td>
<td>24</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Meat</td>
<td>49</td>
<td>76</td>
<td>15</td>
</tr>
<tr>
<td>Chicken</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Fish</td>
<td>5</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>55</td>
<td>89</td>
<td>19</td>
</tr>
<tr>
<td>Dry pulses</td>
<td>10</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Potatoes</td>
<td>32</td>
<td>37</td>
<td>31</td>
</tr>
<tr>
<td>Fresh vegetables (all kinds)</td>
<td>289</td>
<td>320</td>
<td>394</td>
</tr>
<tr>
<td>Fresh fruits (all kinds)</td>
<td>221</td>
<td>215</td>
<td>175</td>
</tr>
<tr>
<td>Fats and vegetable oils</td>
<td>38</td>
<td>49</td>
<td>32</td>
</tr>
<tr>
<td>Sugar</td>
<td>36</td>
<td>43</td>
<td>30</td>
</tr>
</tbody>
</table>

*Ankara, Istanbul, Izmir.
†Areas populated less than 2000.
TABLE 3. Fecal Electrolytes

<table>
<thead>
<tr>
<th></th>
<th>Fecal Calcium Excretion</th>
<th>Fecal Magnesium Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily Total</td>
<td>Per Cent Wet Weight</td>
</tr>
<tr>
<td></td>
<td>(mg/24 hrs)</td>
<td>(mg/100 gm)</td>
</tr>
<tr>
<td></td>
<td>(mg/24 hrs)</td>
<td>(mg/100 gm)</td>
</tr>
<tr>
<td>Urban group</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Median</td>
<td>472.5</td>
<td>363</td>
</tr>
<tr>
<td>Range</td>
<td>60-1296</td>
<td>255-516</td>
</tr>
<tr>
<td>Number</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Median</td>
<td>723.7</td>
<td>378</td>
</tr>
<tr>
<td>Range</td>
<td>432-1443</td>
<td>315-561</td>
</tr>
<tr>
<td>Rural group</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Daily Total</td>
<td>516.8</td>
<td>490</td>
</tr>
<tr>
<td>Per Cent Wet Weight</td>
<td>108-872</td>
<td>270-774</td>
</tr>
</tbody>
</table>

Discussion

Most of the studies that demonstrate an action of fiber on colonic function deal with the effects of fiber added to the diet of normal subjects and those with diverticular disease or the irritable colon syndrome.6,7 Those studies often do not discriminate between what is truly normal in regard to a diet, what its effect on bowel function is, or whether the subjects are truly normal. In Edinburgh,8 patients with diverticular disease had ranges of stool weight and transit times similar to those of unaffected people. The pressures measured in the diverticular disease patients had such a wide range that they overlapped the normal for Edinburgh. Since the diverticular disease patients and the normal subjects were apparently so similar, it appeared that many of the normal citizens of Edinburgh were perhaps developing some of the characteristics of diverticular disease, and that controls, therefore, might have been chosen for studies from those who were partly affected by the abnormality being studied. Studies of two populations in Turkey show how different fiber intake allowed the detection of differences in colonic function due to natural variation in fiber intake without artificially changing the amounts consumed by altering exogenous sources. It also demonstrates that, within a country, radical changes may be taking place as a result of cultural and social changes.

The present study demonstrates that the daily stool weight in Turkish subjects living in villages is, on the average, 40 gm greater than in those living in a large city. The output of fecal solids was doubled, in spite of the excess fiber consumption as bread being reduced by the lower intake of fruit and vegetables. The intestinal transit time for the rural population was shorter than that of the urban population and the motor responses of the colon to a cholinergic stimulation were reduced, though the basal pressure and food responses were not significantly affected; partly, however, this may reflect the wide range of results obtained, as well as the dietary differences, which, while predominantly those of fiber intake, are also represented by a differing intake of meat protein and calcium in milk products. The differences in the fecal output of calcium fairly obviously reflect the latter, having a significantly higher intake in the rural group; yet the increased bulk of the feces as a result of the enhanced fiber intake could be the reason for the concentrations in both rural and urban groups being similar. A higher calcium excretion has been seen in diverticular disease after the addition of fiber to treatment regimens.9

Other influences, such as physical activity, may affect colonic motility. The city dwellers were largely sedentary office workers, whereas the villagers were active, mainly in farming. We believe, however, that the effects of a raised metabolism, a more rapid transit, and a reduced intraluminal colonic pressure in the rural dwellers are typical fiber effects on colonic function. These changes, moreover, have been shown to occur without resorting to changing the levels of fiber in the diet, either by addition or deletion. It is of interest that, in recent years, urban dwellers in Turkey, who have a lower fecal output, a longer transit time, and a generally lower pressure in the sigmoid colon, have been described as having an increasing incidence of diverticular disease,10 which is rarely seen in rural settings. The changes that are described in the urban dwellers in Turkey in this study are, furthermore, those that favor the development of diverticular disease.11

TABLE 4. Transit Time

<table>
<thead>
<tr>
<th></th>
<th>80 Per Cent Excretion (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>Urban group</td>
<td>14</td>
</tr>
<tr>
<td>Rural group</td>
<td>11</td>
</tr>
</tbody>
</table>

TABLE 5. Pressure and Motility in Sigmoid Colon

<table>
<thead>
<tr>
<th></th>
<th>Index of Total Activity*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td>Urban group</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>11</td>
</tr>
<tr>
<td>Median</td>
<td>65</td>
</tr>
<tr>
<td>Range</td>
<td>0-372</td>
</tr>
<tr>
<td>Rural group</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>11</td>
</tr>
<tr>
<td>Median</td>
<td>28</td>
</tr>
<tr>
<td>Range</td>
<td>2-73</td>
</tr>
</tbody>
</table>

*Duration X mean amplitude of all pressure waves.
References

MECHANICAL PROPERTIES OF THE RAT COLON: THE EFFECT OF AGE, SEX AND DIFFERENT CONDITIONS OF STORAGE


Wolfson Laboratories, Gastrointestinal Unit, Western General Hospital, Edinburgh EH4 2XU; University of Edinburgh; Ethicon Research Unit, Sighthill, Edinburgh; Medical Computing and Statistics Unit, University of Edinburgh

(RECEIVED FOR PUBLICATION 7 MAY 1984)

SUMMARY

The mechanical properties of the rat colon were studied in old and young Sprague-Dawley rats which were also grouped by sex. Different storage media were used. Rings of colonic tissue were submitted to pulls on an Instron 1026 tensiometer. Gender did not affect the properties of the young rat colon. The rat colon has a tensile strength of around 50 g/mm² (which places it between the dog and the cat). It increased in strength from proximal to distal, though the rectum was weaker than the colon. The pre-strain of the rat colon was 10% and it was capable of stretching to 200% of its original dimensions. The strength and ability to stretch fell with age, although it initially increased, in the first year of life. Physiological saline at 4 °C preserved the burst strength, percentage elongation, hysteresis and Young's modulus between 25 and 100 g stress for up to 1 week. Young's modulus between 125 and 200 g fell progressively with each day of storage. Stress relaxation rose in the first 24 h and thereafter remained constant. Salt appeared to be a good long-term storage medium. Irradiation of the colons before storage did not affect the mechanical properties.

INTRODUCTION

In the study of the mechanics of biological tissues the colon has been largely neglected to date. There was little motivation to study the mechanical properties of the large bowel until recent work suggested that there was a difference in the tensile strength of the bowel wall in diverticular disease (Parks, 1970; Smith, Shepherd & Eastwood, 1981). Diverticular disease of the colon increases from the middle years of life onwards (Eastwood, Eastwood & Ward, 1976), and Yamada (1970) has reported that the tensile strength of the human colon declines with age. A study was therefore made of the effects of age on the mechanical properties of the rat colon. The rat colon was chosen because human colonic tissue is not readily available for the purpose. Human colon that is free of disease can only be obtained at autopsy, and therefore the influence of time of removal after death and mode and duration of storage was examined in the rat to serve as a model for human studies (Watters, Smith, Eastwood, Anderson, Elton & Mugerwa, 1984).

METHODS

Sprague-Dawley rats as 7 week old male and female immature rats, mature 1 year old male rats and old (14-17 months) female rats were used to compare the effect of gender and age. They were killed by carbon dioxide intoxication. Their colons were excised immediately after death, emptied of faecal contents, irrigated with physiological saline and cut into 10 mm wide rings using a template. Five
Table 1. Latin square design of experiment storing colon in physiological saline at 4°C

<table>
<thead>
<tr>
<th>Storage time (d)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat 1</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
</tr>
<tr>
<td>Rat 2</td>
<td>B</td>
<td>A</td>
<td>D</td>
<td>E</td>
<td>C</td>
</tr>
<tr>
<td>Rat 3</td>
<td>C</td>
<td>D</td>
<td>E</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Rat 4</td>
<td>D</td>
<td>E</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Rat 5</td>
<td>E</td>
<td>C</td>
<td>A</td>
<td>B</td>
<td>D</td>
</tr>
</tbody>
</table>

A, B, C, D and E represent five contiguous segments of colon where A is the most proximal and E the most distal. Each square represents one colonic ring at the site specified by A to E.

Table 2. Latin square design of study of the effects of storage medium, storage duration and time after death of removal of colon

<table>
<thead>
<tr>
<th>Storage time (d)</th>
<th>7</th>
<th>11</th>
<th>21</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after death (h)</td>
<td>Salt (20 °C)</td>
<td>Salt (4 °C)</td>
<td>−20 °C</td>
<td>N₂</td>
</tr>
<tr>
<td>0</td>
<td>Salt (4 °C)</td>
<td>−20 °C</td>
<td>N₂</td>
<td>−20 °C</td>
</tr>
<tr>
<td>6</td>
<td>−20 °C</td>
<td>N₂</td>
<td>Salt (4 °C)</td>
<td>Salt (20 °C)</td>
</tr>
<tr>
<td>24</td>
<td>−20 °C</td>
<td>N₂</td>
<td>Salt (4 °C)</td>
<td>Salt (20 °C)</td>
</tr>
<tr>
<td>48</td>
<td>N₂</td>
<td>−20 °C</td>
<td>Salt (4 °C)</td>
<td>Salt (20 °C)</td>
</tr>
</tbody>
</table>

N₂ represents storage in liquid nitrogen (−185 °C). Each square represents four colonic and four rectal rings, two of each being irradiated.

The rings were cut from each colon and a mean value obtained for each colon in the age and sex experiments. Regional differences were studied using the Latin square design shown in Table 1. The rings were stored in physiological saline at 20 °C until tested, this being done within 2 h. Intact colonic rings were slipped onto steel hooks (2.25 mm diameter) passing through the lumen. The hooks were adapted to fit an Instron 1026 tensiometer. This distracts tissue from a fixed base by a moveable cross-head and records the stress registered. The viscoelastic property of stress relaxation was tested in physiological saline at 37 °C. Stress relaxation was recorded at 100% strain, and stress decay was converted to a straight line using a Hewlett Packard 85 Desk Top Computer (see below).

Storage

The effects of storage time, medium and time of removal after death were studied using a Latin square experimental design (Table 2), one rat colon and one rat rectum being tested for each square. The colons stored in salt were rehydrated in physiological saline and those stored at −20 °C and −185 °C (liquid nitrogen) were thawed before testing. Two 10 mm rings were cut from each colon and rectum, one proximally and one distally, and a mean calculated for both tissue samples. A Latin square design was also used to examine the effects of storage in physiological saline at 4 °C for 0, 1, 2, 4 and 7 d (Table 1).

Reference dimensions

The internal diameter of the colon was measured as the distance between the testing hooks at zero stress, and the thickness of the colon was measured between two microscope slides on a Mercer 54 gaugemeter. The purpose of the slides was to reduce the compressive stresses placed on the tissue by the plates of the gaugemeter, and thus to reduce inaccuracy. Burst strength, tensile strength,
Fig. 1. The stress/strain curve of rat colon from 0 (start) to E (burst). B.s., burst strength.

percentage elongation, width of the colon at burst and stress were calculated from the stress/strain curve to rupture in air at 20 °C. The viscoelastic testing was carried out at 37 °C in physiological saline. The specimen was first pre-conditioned for ten cycles at 100% strain. The stress registered at this degree of strain was between 10 and 30 g. The tenth cycle was used to calculate a hysteresis ratio (the area under the descending part of the curve divided by the area under the ascending part of the curve). Stress relaxation was then measured at 100% strain for 3 min. The stress decay against time was converted to a semilogarithmic scale, with the ratio of stress at time t to initial stress plotted against log time, as described by Fung (1981). A straight line was consistently obtained (r > 0.95) and the slope of this line is quoted as the value for stress relaxation.

Definitions

Stress is the load per unit area expressed as Newtons per square metre (N/m²). Strength is force or stress required to break the material. Strain is the amount of stretch or elongation which occurs when a load is applied. A material is elastic if the process of extension is reversible and can be repeated. Biological materials are not truly elastic. Many tissues are in a permanent state of tension in the body and when removed shorten by as much as 30%; this is known as pre-strain. They also show viscoelastic properties. The advantage of a viscoelastic design is to give a combination of expansibility, strength and maintenance of shape.

Burst strength. This is the maximum stress in grams registered as the tissue is extended till it bursts. The tensile strength is the burst strength divided by the thickness of the tissue under test.

Young's modulus. This is the stress/strain ratio measured between specified points on the stress/strain curve.

L values (L₁, L₂, L₃). These are measured on the stress/strain curve (Fig. 1) after drawing the best possible tangent to the steep part of the slope and extending it to the base line. They are an attempt to measure elasticity from the stress/strain curve (Daly & Odland, 1979).

Percentage elongation. This is calculated by expressing the amount of extension of the tissue until it ruptures, as a percentage of its internal diameter at stress 0.
Table 3. Values of results comparing five equally spaced colonic segment sites, A–E, progressing distally

<table>
<thead>
<tr>
<th>Parameter</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burst strength (g)</td>
<td>251–0±55–0</td>
<td>251–0±43–0</td>
<td>250–0±39–0</td>
<td>268–0±37–0</td>
<td>270–0±50–0</td>
</tr>
<tr>
<td>Percentage elongation</td>
<td>81–0±23–0</td>
<td>89–0±18–0</td>
<td>97–0±16–0</td>
<td>120–0±30–0</td>
<td>118–0±31–0</td>
</tr>
<tr>
<td>$L_0$ (mm)</td>
<td>40–2±12–2</td>
<td>37–2±6–6</td>
<td>33–0±2–9</td>
<td>37–2±7–9</td>
<td>32–2±1–6</td>
</tr>
<tr>
<td>$L_0$ (mm)</td>
<td>21–2±9–1</td>
<td>21–6±8–0</td>
<td>19–4±8–0</td>
<td>25–0±7–1</td>
<td>27–6±5–0</td>
</tr>
<tr>
<td>Stressed relaxation (mm)</td>
<td>11–6±5–3</td>
<td>10–8±3–7</td>
<td>16–6±6–5</td>
<td>18–0±7–8</td>
<td>16–9±4–3</td>
</tr>
<tr>
<td>Hysteresis</td>
<td>0–77±0–04</td>
<td>0–85±0–06</td>
<td>0–74±0–10</td>
<td>0–78±0–08</td>
<td>0–76±0–05</td>
</tr>
<tr>
<td>Energy under curve (kJ)</td>
<td>55–0±21–0</td>
<td>45–0±15–0</td>
<td>55–0±84–0</td>
<td>73–0±14–0</td>
<td>82–0±38–0</td>
</tr>
<tr>
<td>Young’s modulus (25–100 g)</td>
<td>327–0±109–0</td>
<td>374–0±239–0</td>
<td>303–0±116–0</td>
<td>206–0±63–0</td>
<td>325–0±135–0</td>
</tr>
<tr>
<td>Young’s modulus (25–100 g)</td>
<td>754–0±320–0</td>
<td>802–0±359–0</td>
<td>832–0±403–0</td>
<td>638–0±388–0</td>
<td>729–0±623–0</td>
</tr>
</tbody>
</table>

* $P < 0.05$ (analysis of variance).

**Stress relaxation.** The stress registered in a tissue declines exponentially with time when the tissue is held at a fixed strain. The resultant curve can be plotted on a semilogarithmic graph of the ratio of initial stress at any given time against log time. 100% strain was used as the fixed strain and stress decline was followed for 3 min.

**Hysteresis.** The tenth pre-conditioning cycle was used to calculate the hysteresis ratio because by the tenth cycle the tissue was pre-conditioned (Fung, 1981). The area under the descending part of the curve was expressed as a ratio to that under the ascending part. This viscoelastic property refers to the failure of a tissue to return rapidly to its original dimensions on removal of stress. In most biological materials, the stress/strain curve is steeper on removal of the stress, implying that energy has been lost in the deformation.

**Energy under the curve.** This is the area under the stress/strain curve to burst. It is a measure of the energy required to burst the tissue.

**Width at burst.** This is the diameter of the ring as it ruptures and shows how far it is able to ‘stretch’.

**Statistical methods**

Analysis of variance was used in those experiments designed by Latin square. Student’s $t$ tests were used to study the effect of age and sex.

**RESULTS**

**Pre-strain**

The pre-strain measurements on nine 7 week old male rats ranged from 8 to 13%, median 10%.

**Effect of segment site (Tables 3 and 4)**

Distally placed segments of colon were stronger and more extensible than proximal ones. The burst strength ($P < 0.05$), stress relaxation ($P < 0.05$) and the energy under the curve ($P < 0.05$) increased distally (Table 3). Increases in the percentage elongation and $L_0$ failed to reach significance. Other parameters were not affected. The burst strength of the rectum...
### Table 4. Colon and rectum compared

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Colon</th>
<th>Rectum</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burst strength (g)</td>
<td>191±0±44-0</td>
<td>161±0±35-0</td>
<td>**</td>
</tr>
<tr>
<td>Percentage elongation</td>
<td>130±0±24-0</td>
<td>128±0±26-0</td>
<td>N.s.</td>
</tr>
<tr>
<td>$L_1$ (mm)</td>
<td>18±6±4-0</td>
<td>14±5±5-3</td>
<td>***</td>
</tr>
<tr>
<td>$L_2$ (mm)</td>
<td>11±3±3-7</td>
<td>7±4±3-7</td>
<td>***</td>
</tr>
<tr>
<td>Energy under curve (kJ)</td>
<td>51±5±13-8</td>
<td>52±7±13-0</td>
<td>N.s.</td>
</tr>
<tr>
<td>Young's modulus (10-25 g) (g/mm$^2$)</td>
<td>14±8±4-3</td>
<td>16±3±3-7</td>
<td>N.s.</td>
</tr>
<tr>
<td>Young's modulus (30-60 g) (g/mm$^2$)</td>
<td>32±6±8-1</td>
<td>33±3±7-1</td>
<td>N.s.</td>
</tr>
</tbody>
</table>

** $P < 0.01$, *** $P < 0.001$ (analysis of variance); n.s., not significant.

Table 5. Young female 7 week old rats compared with 14–17 month females, already ageing

<table>
<thead>
<tr>
<th>Measurement</th>
<th>7 week females</th>
<th>14–17 month females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burst strength (g)</td>
<td>276±39</td>
<td>229±42*</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>0-54</td>
<td>0-65*</td>
</tr>
<tr>
<td>Tensile strength (g/mm$^2$)</td>
<td>51±1±7-2</td>
<td>35±2±6-5***</td>
</tr>
<tr>
<td>Percentage elongation</td>
<td>21±2±23</td>
<td>183±22*</td>
</tr>
<tr>
<td>Width at burst (mm)</td>
<td>10±6±1-0</td>
<td>11±7±1-3</td>
</tr>
<tr>
<td>Internal diameter (mm)</td>
<td>5±0</td>
<td>6-4</td>
</tr>
<tr>
<td>Stress relaxation</td>
<td>0.198±0.005</td>
<td>0.185±0.015*</td>
</tr>
</tbody>
</table>

* $P < 0.05$, *** $P < 0.001$ (t test).

Table 6. Young male 7 week old rats compared with mature 1 year old males

<table>
<thead>
<tr>
<th>Measurement</th>
<th>7 week males</th>
<th>1 year males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burst strength (g)</td>
<td>28±0±19</td>
<td>36±8±1***</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>0.5±0±0.07</td>
<td>0.6±0.09*</td>
</tr>
<tr>
<td>Tensile strength (g/mm$^2$)</td>
<td>52±8±3-6</td>
<td>60±3±13-2</td>
</tr>
<tr>
<td>Percentage elongation</td>
<td>223±7</td>
<td>251±15***</td>
</tr>
<tr>
<td>Width at burst (mm)</td>
<td>11±8±0.4</td>
<td>13±3±0.6***</td>
</tr>
<tr>
<td>Internal diameter (mm)</td>
<td>5±3</td>
<td>5-3</td>
</tr>
<tr>
<td>Stress relaxation</td>
<td>0.181±0.010</td>
<td>0.179±0.017</td>
</tr>
</tbody>
</table>

* $P < 0.1$, *** $P < 0.001$ (t test).

was, however, weaker than that of the colon ($P < 0.01$), though the percentage elongation was similar for both. $L$ values were significantly lower for rectum ($P < 0.001$) compared with distal colon (Table 4).

**Age and sex (Tables 5 and 6)**

Table 5 shows the difference between young, 7 week old and older (14–17 months) female rats. The burst strength was significantly reduced in the ageing rats, as was percentage elongation, and the stress relaxation slope was flatter. The colons from the older animals
Table 7. Mean values (±s.d.) of results obtained storing the colon in physiological saline at 4°C for up to 7 d

<table>
<thead>
<tr>
<th>Measurement</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>7</th>
<th>Significance of difference 1–7 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burst strength (g)</td>
<td>264·0±41·0</td>
<td>256·0±49·0</td>
<td>243·0±43·0</td>
<td>231·0±52·0</td>
<td>252·0±58·0</td>
<td>N.s.</td>
</tr>
<tr>
<td>Percentage elongation</td>
<td>195·0±11·0</td>
<td>187·0±18·0</td>
<td>212·0±27·0</td>
<td>200·0±43·0</td>
<td>223·0±31·0</td>
<td>N.s.</td>
</tr>
<tr>
<td>$L_1$ (mm)</td>
<td>22·0±3·3</td>
<td>25·4±6·5</td>
<td>27·4±4·8</td>
<td>21·0±11·2</td>
<td>19·0±8·6</td>
<td>N.s.</td>
</tr>
<tr>
<td>Stress relaxation</td>
<td>0·1769±0·0221</td>
<td>0·2157±0·0711</td>
<td>0·2041±0·0244</td>
<td>0·1967±0·0190</td>
<td>0·2114±0·0470</td>
<td>*</td>
</tr>
<tr>
<td>Hysteresis</td>
<td>0·79±0·05</td>
<td>0·69±0·06</td>
<td>0·70±0·08</td>
<td>0·78±0·05</td>
<td>0·86±0·06</td>
<td>N.s.</td>
</tr>
<tr>
<td>Energy under curve (kJ)</td>
<td>68·0±28·0</td>
<td>59·0±15·0</td>
<td>59·0±22·0</td>
<td>61·0±13·0</td>
<td>55·0±36·0</td>
<td>N.s.</td>
</tr>
<tr>
<td>Young's modulus</td>
<td>282·0±76·0</td>
<td>429·0±87·0</td>
<td>302·0±109·0</td>
<td>238·0±90·0</td>
<td>267·0±249·0</td>
<td>N.s.</td>
</tr>
<tr>
<td>(25–100 g) (g/mm²)</td>
<td>1013·0±437·0</td>
<td>972·0±274·0</td>
<td>894·0±202·0</td>
<td>461·0±163·0</td>
<td>350·0±118·0</td>
<td>***</td>
</tr>
<tr>
<td>Young's modulus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(125–200 g) (g/mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* $P<0·05$, *** $P<0·001$ (analysis of variance).
Table 8. Effects of varying storage medium on mechanical properties (mean ± S.D.)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Salt (20 °C)</th>
<th>Salt (4 °C)</th>
<th>−20 °C</th>
<th>Liquid N₂</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burst strength (g)</td>
<td>Colon</td>
<td>208.0 ± 37.0</td>
<td>220.0 ± 45.0</td>
<td>164.0 ± 41.0</td>
<td>176.0 ± 29.0</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>176.0 ± 49.0</td>
<td>149.0 ± 25.0</td>
<td>161.0 ± 32.0</td>
<td>157.0 ± 32.0</td>
</tr>
<tr>
<td>Percentage elongation</td>
<td>Colon</td>
<td>244.0 ± 20.0</td>
<td>229.0 ± 26.0</td>
<td>217.0 ± 30.0</td>
<td>225.0 ± 20.0</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>248.0 ± 29.0</td>
<td>235.0 ± 15.0</td>
<td>218.0 ± 24.0</td>
<td>211.0 ± 21.0</td>
</tr>
<tr>
<td>Young's modulus (10-25 g) (g/mm²)</td>
<td>Colon</td>
<td>13.8 ± 3.3</td>
<td>14.3 ± 5.4</td>
<td>15.2 ± 4.9</td>
<td>15.3 ± 4.4</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>14.4 ± 2.7</td>
<td>17.8 ± 3.7</td>
<td>16.3 ± 4.1</td>
<td>16.8 ± 4.6</td>
</tr>
<tr>
<td>Young's modulus (30-60 g) (g/mm²)</td>
<td>Colon</td>
<td>35.5 ± 8.6</td>
<td>29.5 ± 4.2</td>
<td>32.8 ± 9.2</td>
<td>31.4 ± 10.1</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>29.8 ± 7.8</td>
<td>34.4 ± 7.0</td>
<td>33.3 ± 5.1</td>
<td>36.0 ± 8.4</td>
</tr>
<tr>
<td>Energy under curve (kJ)</td>
<td>Colon</td>
<td>63.0 ± 15.0</td>
<td>58.0 ± 14.0</td>
<td>42.0 ± 15.0</td>
<td>44.0 ± 8.0</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>66.0 ± 16.0</td>
<td>55.0 ± 16.0</td>
<td>45.0 ± 10.0</td>
<td>46.0 ± 9.0</td>
</tr>
</tbody>
</table>

* P < 0.05, ** P < 0.001 (analysis of variance).
† Lower set points were chosen to measure Young’s modulus in the experiments in Tables 4-8 than those in Tables 3 and 7. The range of strains in Tables 4-8 was more in the physiological range, and the tissues were significantly weakened by, for example, liquid nitrogen storage and by deep freezing, etc.

were thicker, with a greater internal diameter and this contributes to the tensile strength being low. Table 6, however, shows values obtained for male rats aged 7 weeks and 1 year. The burst strength was greater in the mature (1 year) age group, but there was no corresponding increase in tensile strength since the thickness of the colon also increases with age.

The tensile strength of the young colon is highly developed (> 50 × 10⁶ N/m²) and increases in the first year of life, but then decreases as the rat ages. The young rat colon is 0.54 mm thick at 7 weeks but thickens with age, becoming 0.65 mm for rats 14–17 months old.

The internal diameter of the rat colon is fairly constant at 5.0–5.3 mm in the young rat. When the tissues age this diameter rises, becoming 6.4 mm in the oldest group. The young rat colon is capable of extending to a width of approximately 12 mm or 200–225% of its initial diameter. This increased to maturity (P < 0.001) and then became less in the oldest rats (P < 0.1).

The width at burst increased (P < 0.001) markedly in the mature rats, but in older animals this difference was lost. The strength of the colon and its stretch capacity (width at burst) seem to increase together in the first year. There was no significant difference between 7 week old male and female rats in any of the measurements made in Tables 5 and 6. The older rats were not comparable age groups.

**Effects of storage (Table 7)**

Burst strength, percentage elongation at burst, L value, energy under the curve, Young’s modulus between 25 and 100 g, and hysteresis ratio did not alter significantly over 7 d storage in physiological saline (Table 7). Stress relaxation rose in the first 24 h of saline storage and remained constant for the next 6 d (Table 7). The Young’s modulus between 25 and 100 g rose on day 1 but returned to initial values thereafter, whereas Young’s modulus between 125 and 200 g fell progressively with each day of storage.

Because there appeared to be little change in the mechanical properties of the rat colon
Table 9. Effects of length of storage in salt on mechanical properties (mean ± S.D.)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Time of storage (d)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Burst strength (g)</td>
<td>Colon</td>
<td>196.0 ± 63.0</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>145.0 ± 35.0</td>
</tr>
<tr>
<td>Percentage elongation</td>
<td>Colon</td>
<td>200.0 ± 25.0</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>202.0 ± 23.0</td>
</tr>
<tr>
<td>Young's modulus</td>
<td>Colon</td>
<td>—</td>
</tr>
<tr>
<td>(10–25 g) (g/mm²)</td>
<td>Rectum</td>
<td>—</td>
</tr>
<tr>
<td>Young's modulus</td>
<td>Colon</td>
<td>—</td>
</tr>
<tr>
<td>(30–60 g) (g/mm²)</td>
<td>Rectum</td>
<td>—</td>
</tr>
<tr>
<td>L₁ (mm)</td>
<td>Colon</td>
<td>20.7 ± 4.7</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>16.6 ± 6.3</td>
</tr>
<tr>
<td>Energy under curve (kJ)</td>
<td>Colon</td>
<td>52.0 ± 24.0</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>45.0 ± 13.0</td>
</tr>
</tbody>
</table>

* P < 0.05, ** P < 0.01 (analysis of variance).

Table 10. Effects of time after death of removal on mechanical properties of rat colon stored in salt (mean ± S.D.)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Time after death (h)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Burst strength (g)</td>
<td>Colon</td>
<td>202.2 ± 34.0</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>180.0 ± 20.9</td>
</tr>
<tr>
<td>Percentage elongation</td>
<td>Colon</td>
<td>228.0 ± 10.0</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>234.0 ± 11.0</td>
</tr>
<tr>
<td>Young's modulus</td>
<td>Colon</td>
<td>12.5 ± 4.8</td>
</tr>
<tr>
<td>(10–25 g) (g/mm²)</td>
<td>Rectum</td>
<td>13.8 ± 2.6</td>
</tr>
<tr>
<td>Young's modulus</td>
<td>Colon</td>
<td>25.0 ± 4.1</td>
</tr>
<tr>
<td>(30–60 g) (g/mm²)</td>
<td>Rectum</td>
<td>31.4 ± 4.2</td>
</tr>
<tr>
<td>L₁ (mm)</td>
<td>Colon</td>
<td>21.8 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>18.5 ± 4.1</td>
</tr>
<tr>
<td>Energy under curve (kJ)</td>
<td>Colon</td>
<td>57.0 ± 18.0</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>59.0 ± 10.0</td>
</tr>
</tbody>
</table>

* P < 0.05, ** P < 0.01 (analysis of variance).

at day 7, specimens being viscoelastically tested were stored under the same conditions until day 17. The stress relaxation then rose to 0.2350 and the hysteresis ratio to 0.98. However, of the five specimens only three could be tested because the other two could not be extended to 100% strain before rupture.

Effect of storage medium (Table 8). Burst strength was significantly greater in the colons which were stored in salt, although there was not a similar trend for the rectum. The percentage elongation was significantly greater in the case of salt storage for the rectum. Neither burst strength nor percentage elongation appeared to be influenced by the temperature of salt storage. The energy under the curve was significantly greater for both colons and rectums stored in salt compared with those stored in liquid nitrogen or at —20°C. The other measurements were unaffected by the choice of storage medium.
Table 11. Effects of irradiation on mechanical properties (mean ± S.D.)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Irradiation</th>
<th>No irradiation</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burst strength (g)</td>
<td>Colon</td>
<td>196.0 ± 36.0</td>
<td>188.0 ± 51.0</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>155.0 ± 31.0</td>
<td>167.0 ± 39.0</td>
</tr>
<tr>
<td>Percentage elongation</td>
<td>Colon</td>
<td>230.0 ± 26.0</td>
<td>227.0 ± 25.0</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>224.0 ± 21.0</td>
<td>231.0 ± 31.0</td>
</tr>
<tr>
<td>Young's modulus</td>
<td>Colon</td>
<td>12.9 ± 2.7</td>
<td>16.4 ± 4.9</td>
</tr>
<tr>
<td>(10-25 g) (g/mm²)</td>
<td>Rectum</td>
<td>15.5 ± 3.5</td>
<td>17.0 ± 4.0</td>
</tr>
<tr>
<td>Young's modulus</td>
<td>Colon</td>
<td>29.5 ± 6.2</td>
<td>35.0 ± 8.9</td>
</tr>
<tr>
<td>(30-60 g) (g/mm²)</td>
<td>Rectum</td>
<td>30.1 ± 7.6</td>
<td>35.9 ± 5.7</td>
</tr>
<tr>
<td>L₁ (mm)</td>
<td>Colon</td>
<td>19.0 ± 2.8</td>
<td>18.4 ± 4.9</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>13.0 ± 4.1</td>
<td>16.0 ± 5.9</td>
</tr>
<tr>
<td>Energy under curve (kJ)</td>
<td>Colon</td>
<td>56.0 ± 14.0</td>
<td>48.0 ± 16.0</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>51.0 ± 13.0</td>
<td>54.0 ± 17.0</td>
</tr>
</tbody>
</table>

* P < 0.05 (analysis of variance).

Effect of length of storage (Table 9). The percentage elongation rose with increasing length of storage. The energy under the stress/strain curve showed a similar trend in the rectum only. The other measurements were unaffected by length of storage between 7 and 28 d.

Effect of time after death of removal of colon (Table 10)

L₁ values fell and Young's modulus values rose with increasing time after death (Table 10). The burst strength fell if the colon was not removed within 24 h of death, although this change was only significant in the rectum. Other measurements were unchanged with time after death between and 0 and 48 h.

Effect of irradiation (Table 11)

Only one out of six tissue measurements was affected by irradiation (Table 11). This was the Young's modulus between 10 and 25 g in the colon only, the tissue becoming less stiff with irradiation (P < 0.05).

Discussion

The rat is a readily available, reasonably cheap laboratory animal and is therefore convenient for developing a model for biomechanical testing of the colon. Although the properties of the rat colon may not be directly extrapolated to the human colon, a study is nonetheless worthwhile to establish certain basic principles, since normal living human colonic tissue is not readily obtainable. Although autopsy colonic tissue may be obtained (Watters et al. 1984), the effects of time after death of removal and storage are not well defined. The use of an intact ring of colon has certain advantages. Circumferential measurements and width are preserved by slipping the ring onto steel testing hooks. Damage to the tissue by the application of clamps is avoided. One disadvantage is that the bowel is tested in one direction only (transversely in the longitudinal axis). There have now been various reports of subtle differences in values obtained in tensile testing, depending on the axis of pull (Yamada, 1970; Lee & Boughner, 1981). The axis of pull was, however, constant throughout this study.

The longitudinal pre-strain of the colon was 10%, which compares with a value of 30%...
for arteries (Caro, Pedley, Schroter & Seed, 1978). The colon experiences much lower pressures in its wall than an artery, so the need for pre-strain is less, given that pre-strain is a means of preserving shape at a wide range of pressures (Gordon, 1978).

The tensile strength of the rat colon is of the order of 50%, which places it between that of the dog and the rabbit, at about the same strength as that of the cat and the domestic fowl (Yamada, 1970). The increase in tensile strength from proximal to distal in the rat colon may be related to the need to propel more-solid faeces, and thus represents adaptation to higher stresses. The development of strength in the colon wall may be related to diet, since lack of fibre in the human is known to be associated with high intraluminal pressure. The colon is an extremely expansile structure, being able to extend to over 100% of its original dimensions. This property, measured by the percentage elongation, is vital to its function as a storage organ and in propelling faeces and gas distally.

The percentage elongation was lower in the old female rats, although the width at burst was not significantly higher, and so the significant reduction in percentage elongation ($P < 0.05$) is only a reflection of a greater initial internal diameter in the old female rat.

The viscoelastic property of stress relaxation describes the capacity of tissue to reduce the circumferential stress with time in response to a distending pressure. This may reduce ‘wear and tear’ in the colon wall. The old female rats showed less ability to reduce the stress experienced in the wall of the colon, which confirms the finding of Daly & Odlam (1979), that recovery after compression of the pre-tibial skin was reduced in old age. Males, 1 year old, had a significantly higher burst strength than their 7 week old counterparts. This was, in fact, related to an increase in thickness of the colon rather than its tensile strength. The 1 year old males had a greater capacity for expansion and thus distension. Yamada (1970) demonstrated a rise in burst strength, tensile strength and percentage elongation in early adult life. The fact that the rat continues to grow throughout its life is consistent with the increased values in 1 year old males. Thus, the strength and elasticity of the colon may first rise as the rat continues to grow, and then decline as the post-mature animal ages.

The thickness of the colon rose with age, which confirms the post-mortem study of Pace (1966) in the human. The lower strength in, for example, old female rats was not merely the result of increasing thickness since the burst strength was also lessened. The general picture is one of the colon becoming mechanically less efficient with ageing. The elastic properties share the same trend. Internal diameter rose with age, possibly reflecting loss of pre-strain or elasticity. Physiological saline at 4 °C preserves the mechanical properties for up to 1 week. Two properties which were exceptions were stress relaxation which increased in the first 24 h, thereafter remaining constant for 6 d, and the Young’s modulus between 125 and 200 g which progressively declined with storage. This rise in stress relaxation may well reflect altered tissue hydration with storage in saline. Alternatively, sodium/potassium or calcium homoeostasis may be disturbed by storage in unbuffered saline. The progressive fall in Young’s modulus implies an increasing flexibility in the steep part of the stress/strain curve since this part of the stress/strain curve tests the tissue when the collagen fibres are all taut (Daly & Odlam, 1979); it is probably the collagen which becomes more flexible. The trend is significant by day 4, so that taking all measurements into account it is probably safe to assume that there is a mechanically stabilized state in physiological saline at 4 °C for at least 2 d. This confirms the report of Yamada (1970).

Since a longer time of storage may be desirable, the effects of salt storage at 4 and 20 °C, deep freezing ($-20$ °C) and liquid nitrogen ($-185$ °C) were examined. The strength of the rat colon was better preserved in salt although this was not so for the rat rectum. Percentage elongation was higher in rectums stored in salt with a similar, but non-significant trend in
the colon. This finding suggests increasing flexibility of the bowel in this storage medium. The Young's modulus at low ranges of stress was unaffected by the method of storage. The increase in percentage elongation in the salt groups were small and only significant in the rectum. The tissue was well hydrated before testing and a constant gauge length was used, so the increased percentage elongation is not due to tissue dehydration. The energy under the stress/strain curve was greatest in the salt-stored groups, which is to be expected in view of the tendency for burst strength and percentage elongation to be greatest since the energy under the curve is essentially the product of these two measurements.

The duration of storage over 7–28 d did not affect the mechanical properties, with the exception of percentage elongation which rose with length of storage. This change is compatible with tissue decay, although the consistency of the other measurements suggests that the tissue decay is small.

The time after death that the bowel was removed was also studied. Burst strength was significantly lower if the colon was left for 24 h or more before removal, which suggests tissue autolysis. The fall in the $L$ values suggests increasing stiffness in the early part of the stress/strain curve. This might be due to biochemical changes within smooth muscle cells, such as calcium leakage due to intracellular acidity. The Young's modulus between 30 and 60 g rose after death but the time course was not consistent.

The similarity between irradiated and non-irradiated colons and rectums suggests that irradiation exerts little destructive effect. All tissue in this experiment was irradiated in physiological saline before storage. Had the tissue been irradiated whilst in salt these minimal effects would have been even less marked since salt dehydrates tissue and dehydration protects against irradiation.

These results suggest that the large bowel of the rat may be stored for the purposes of mechanical testing for 2 and possibly up to 7 d in physiological saline at 4 °C without gross changes in its properties. If longer periods of storage are necessary, salt is a simple, cheap and efficient mode of storage for up to 25 d. The length of time after death that the bowel is excised affects the mechanical properties derived from the early part of the stress/strain curve and possibly the strength. The bowel should be excised as quickly as possible after death and the time after death should be recorded. Further studies of biochemical changes at a cellular level relating these changes to biomechanical properties would be of interest using this model with different conditions of storage. These results were obtained using rings of colonic and rectal tissue. Microdissection techniques would define the contribution from the various layers in the colonic wall. The model used here could also be used to study the interaction between diet, disease and the mechanics of the large bowel.

We gratefully acknowledge the help given by Mr Ian Capperauld, Executive Research Director, Ethicon; Dr Peter Lawrie, Chief Biologist, Ethicon; and Dr Evans and Dr Barbenel of the Department of Bioengineering, Strathclyde University.

REFERENCES


Mechanical properties of the colon: comparison of the features of the African and European colon in vitro

D A K WATTERS, A N SMITH, M A EASTWOOD, K C ANDERSON, R A ELTON, AND J W MUGERWA

From the Wolfson Laboratories, Gastrointestinal Unit, Western General Hospital and University of Edinburgh; Ethicon Research Unit, Sighthill, Edinburgh; Medical Computing and Statistics Unit, University of Edinburgh and Department of Pathology, Makerere University, Kampala, Uganda

Summary
The tensile properties of the colon have been examined using methods which gave repeatable results. They showed little change after storage in salt for up to five weeks. The burst strength remained unchanged along the length of the colon. The tensile strength fell distally, as the thickness of the colonic wall increased. The width at burst decreased distally as did the internal diameter. The visco-elastic property of stress relaxation was constant in all regions. The tensile property of the colon was well developed at birth, but fell with age as did the width at burst and the internal diameter. Stress relaxation was unaffected. Because there may be a mechanical abnormality of the colonic wall in diverticular disease and as Europeans are prone to this condition while Africans are not commonly affected, European and African colons were compared. The tensile strength in a Kampala group was greater than in an Edinburgh one, but fell significantly in both groups with age. The width at burst was greater in the Kampala group, but also declined with age. Stress-relaxation was similar in both groups. In view of the similar properties in childhood of colons from Edinburgh and Kampala, the strength of the adult African compared with European colons may derive later from environmental factors such as diet. There were, however, no differences between the colons with and without diverticular disease in European subjects over the age of 50 years.

Diverticular disease is prevalent in Western countries, affecting a substantial proportion (over 30%) of those over 60 years of age. Its prevalence rises with age and is most common in the sigmoid colon. It has been suggested that there may be a change in the physical property of the bowel wall in patients with diverticular disease as balloon distension of the distal colon in diverticular disease does not produce the volume/pressure change that occurs in normal subjects. Iwasaki found that the tensile strength of the Japanese necropsy colon declined with age. Burkitt and colleagues have suggested that the mechanical properties of the colon might be different in African and European subjects, as one group, the Africans, are exposed throughout life to a diet containing much more fibre resulting in bulky faeces with a fast intestinal transit and belong to a part of the world where diverticular disease is reputedly rare. We have examined in vitro the mechanical properties of the colon of European and African subjects to determine whether they are uniformly exhibited throughout the length of the colon, whether they change with age, and whether any possible changes predispose to the development of diverticula.

Methods

Specimens
The mechanical properties of portions of the colon, 6–8 cm long, were examined at necropsy in the Edinburgh and Kampala at four sites: 6 cm from the iloocaecal junction, the transverse colon adjacent to the middle colic artery; the descending colon 10 cm below the splenic flexure and the middle of the sigmoid loop. The colon segments were washed and then preserved in salt (coarse sea salt or Analarsalt) in polyethylene bags unless tested within 24 hours when they were kept in physiological saline. The
European colons were taken from sudden deaths at a city mortuary or in the Pathology Department, Western General Hospital, Edinburgh. The age of the 32 subjects ranged from 28 weeks gestation to over 70 years; in all 10 infant colons and 22 adult ones were examined; five of the latter the colon was affected by diverticular disease. The bodies had been preserved at 4°C before necropsy.

Postmortem colons were also obtained from 17 adult and three infant African subjects in Kampala. All colons were obtained at necropsy and stored in salt for 28 days before testing. The colonic tissue was irradiated before testing to satisfy the health and safety protocols of Ethicon Laboratories, Sighthill Industrial Estate, where the testing procedure was undertaken, 2-5 megarads being delivered over nine hours in a radiocobalt plant. This amount of irradiation has been shown to change insignificantly the tensile properties of tissues.2

PREPARATION OF TISSUE FOR TESTING
The colons which had been stored in salt were rehydrated in physiological saline at 20°C for two to six hours. Two rings of tissue 10 mm wide were cut for testing in duplicate and used to measure reference dimensions.

MEASUREMENT OF REFERENCE DIMENSIONS
Three measurements were required: (1) The width: a constant 10 mm ring was cut out by means of a template. (2) The thickness of a piece of bowel wall was measured with a Mercer No 54 gaugemeter between two glass microscope slides. The cross-sectional area of the ring was calculated on the basis of thickness and width. (3) The internal diameter of the bowel was estimated the distraction apparent as soon as stress was registered on the Instron tensiometer and is an approximation from the semi-circumference measured (allowing for a constant error due to π).

MECHANICAL TESTING
An Instron 1026 tensiometer was used to test the mechanical properties of the colonic tissue. It maintained a constant strain, cycling to constant strain. The load range was from 0–50 kg and the minimum full scale chart deflection was from 0–50 grams. Stainless steel hooks, 4-76 mm in diameter, were adapted to fit the clamp holding sockets of the tensiometer. Testing was carried out by upward movement of the hook attached to the cross-head away from the fixed lower hook.

The burst properties were tested in air at room temperature as these tests took only a few seconds so that dehydration was not a significant factor affecting the stress/strain characteristics. Viscoelastic properties were tested in physiological saline at 35–37°C. A large plastic basin with a window insert was adapted to fit over the lower clamp socket of the Instron during these tests. The basin was filled with physiological saline from a water bath maintained and circulated at 37°C. The circulation of saline was stopped during the actual test.

One of the two rings of colon was first preconditioned for 10 cycles at 30% strain, and then stress relaxation was measured for three minutes. No recovery period was allowed between preconditioning and testing. In every case the strain rate was 50 mm per minute.

Once the visco-elastic tests had been done the ring of colon was returned to physiological saline at 20°C. Approximately an hour elapsed before recording the stress/strain curve to rupture.

ANALYSIS OF RESULTS
The stress relaxation curve was converted to a straight line by plotting the ratio of stress over initial peak stress against log time (r<0.95). The numeral value for stress relaxation taken for statistical comparison was the slope of this line. From the stress/strain curve to rupture, the burst strength, tensile strength and percentage elongation at burst were calculated.

STATISTICAL METHODS
Because many of the measurements were skewed, non-parametric tests were used for comparisons of groups: Wilcoxon's signed-rank test for salt versus saline storage, site differences and the effect of preconditioning: Wilcoxon's rank sum test was used for comparison of subjects aged 50 or over with and without diverticular disease. Regression analysis against age was carried out on the logarithms of the measurement values, which appeared to be approximately symmetrically distributed and regression lines for the two groups were compared by analysis of covariance. Coefficients of variation were calculated using the preconditioned and non-preconditioned values as replicates.

The following parameters were measured: Burst strength (BS), tensile strength (TS), thickness (T), internal diameter (ID), width at burst (WB), percentage elongation (E) and stress relaxation (SR). Burst strength in grams is the force necessary to disrupt the tissue ring. It is a measure of the strength of the tissue components in the colon wall, mainly collagen. The cross-sectional area was derived as already described in mm². The tensile strength is derived from the burst strength and the thickness of the colonic wall being a measure of...
stress per unit area and is expressed in units g/mm². The internal diameter was derived from half the circumference at stress 0 in mm as already described. The width at burst is the internal diameter or width of the colon in mm at burst. The percentage elongation was derived at burst as a % fraction of the initial tissue width (internal diameter) and gives a measure of the stretch capacity of the tissue. The stress relaxation represents the visco-elastic property of the tissue. It is a regression slope based on a ratio and therefore has no units.

Results

THE EFFECT OF SALT STORAGE

Six colons were tested, in duplicate, once at 24 hours after overnight irradiation while in physiological saline and once at 28–35 days after salt storage followed by irradiation. Each colon was tested at the standard four sites. The means for the values of these parameters for sigmoid colon together with standard deviations are given in Table 1. These figures suggest that salt storage for 28–35 days had little effect on the mechanical properties tested.

REPRODUCIBILITY BETWEEN ADJACENT SEGMENTS

Burst strength, per cent elongation and width at burst were measured from two adjacent segments. One segment was tested for its visco-elastic properties and therefore preconditioned first, while the other was tested without preconditioning. Table 2 illustrates the reproducibility of the results. All subsequent analyses were carried out on the means of the two replicates.

VARIATION WITH SITE IN EUROPEAN AND AFRICAN COLONS

The properties of the wall of the large intestine taken from European and African subjects were examined for each segment (Table 3). The burst strength did not vary significantly throughout the colon. The cross-sectional area was not significantly different from the ascending to transverse to the descending colon but these three segments showed a difference from the sigmoid colon (Table 4) (p<0.001), which was thicker than the others. The tensile strength, which is dependent on cross-sectional area and varies inversely with it, was less in the sigmoid area than in the other zones.

The width at burst showed significant changes between ascending and transverse versus descending and sigmoid (p<0.001 in Table 4). Both sigmoid and descending colon had a reduced width at burst than the more proximal zones. The fall in the internal diameter from the proximal zones to the sigmoid colon was also highly significant (p<0.001 in Table 4). The percentage elongation was higher in the sigmoid but in this only differed consistently from the ascending colon. The stress relaxation was unchanged in all four segments tested.

COMPARISON OF EDINBURGH AND KAMPALA COLONS BY AGE IN ADULTS

For each of the four regions of the colon, regression lines of each measurement (on a log scale) against age for the two racial groups were fitted to the data for subjects aged over 10 years. In no case did the slopes of the two lines differ significantly, and therefore parallel lines were fitted. Table 5 shows the parameter estimates of these lines together with the significance of slope and difference in intercept, while Figs. 1–7 show the data and fitted lines for the

---

### Table 1: Effect of testing after salt storage or immediately in saline, for sigmoid colon only

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Salt</th>
<th>Saline</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>BS</td>
<td>1273±67</td>
<td>1010±474</td>
<td>NS</td>
</tr>
<tr>
<td>CSA</td>
<td>24-5±6-6</td>
<td>23-5±5-6</td>
<td>NS</td>
</tr>
<tr>
<td>TS</td>
<td>54±27</td>
<td>45±21</td>
<td>NS</td>
</tr>
<tr>
<td>ID</td>
<td>26±10</td>
<td>30±10</td>
<td>NS</td>
</tr>
<tr>
<td>WB</td>
<td>86±16</td>
<td>83±18</td>
<td>NS</td>
</tr>
<tr>
<td>E</td>
<td>262±99</td>
<td>195±82</td>
<td>NS</td>
</tr>
<tr>
<td>SR</td>
<td>0-188±0-019</td>
<td>0-173±0-020</td>
<td>NS</td>
</tr>
</tbody>
</table>

Figures given are mean±SD, n=24 for each group.
Comparison of the mechanical properties of the colon

Table 3  Overall means and standard deviations for colonic sites by group (Edinburgh or Kampala)

<table>
<thead>
<tr>
<th></th>
<th>Ascending colon</th>
<th>Transverse colon</th>
<th>Descending colon</th>
<th>Sigmoid colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burst strength (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edinburgh</td>
<td>1378±822</td>
<td>1223±701</td>
<td>1242±657</td>
<td>1266±646</td>
</tr>
<tr>
<td>Kampala</td>
<td>1799±648</td>
<td>1687±585</td>
<td>1638±499</td>
<td>1618±663</td>
</tr>
<tr>
<td>Cross-sectional area (mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edinburgh</td>
<td>14.7±6.5</td>
<td>14.1±6.2</td>
<td>14.7±7.4</td>
<td>19.0±9.3</td>
</tr>
<tr>
<td>Kampala</td>
<td>14.3±4.2</td>
<td>13.1±4.2</td>
<td>14.8±5.7</td>
<td>16.6±5.9</td>
</tr>
<tr>
<td>Tensile strength (g/mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edinburgh</td>
<td>104±65</td>
<td>98±57</td>
<td>104±61</td>
<td>81±49</td>
</tr>
<tr>
<td>Kampala</td>
<td>134±56</td>
<td>129±57</td>
<td>127±65</td>
<td>311±51</td>
</tr>
<tr>
<td>Internal diameter (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edinburgh</td>
<td>36±20</td>
<td>30±15</td>
<td>33±12</td>
<td>31±13</td>
</tr>
<tr>
<td>Kampala</td>
<td>49±22</td>
<td>43±22</td>
<td>35±15</td>
<td>36±16</td>
</tr>
<tr>
<td>Width at burst (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edinburgh</td>
<td>99±48</td>
<td>90±39</td>
<td>70±31</td>
<td>71±30</td>
</tr>
<tr>
<td>Kampala</td>
<td>129±46</td>
<td>108±41</td>
<td>111±36</td>
<td>104±33</td>
</tr>
<tr>
<td>Elongation (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edinburgh</td>
<td>206±179</td>
<td>221±187</td>
<td>222±125</td>
<td>253±185</td>
</tr>
<tr>
<td>Kampala</td>
<td>182±99</td>
<td>171±122</td>
<td>192±143</td>
<td>235±148</td>
</tr>
<tr>
<td>Stress relaxation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edinburgh</td>
<td>0.179±0.028</td>
<td>0.189±0.029</td>
<td>0.185±0.020</td>
<td>0.188±0.024</td>
</tr>
<tr>
<td>Kampala</td>
<td>0.162±0.025</td>
<td>0.171±0.020</td>
<td>0.181±0.017</td>
<td>0.178±0.019</td>
</tr>
</tbody>
</table>

sigmoid colon. As these figures show, the relationships were approximately linear for each measurement over the adult age range in both racial groups, and the analysis was therefore done on all adult subjects in both groups in spite of the predominance of Edinburgh subjects in the older age range.

Strength (Figs 1, 2)
The burst strength fell with age in all regions except the ascending colon (Fig. 1), the Kampala colons having a greater burst strength (Table 5) in each site tested, but these differences were not quite significant. The tensile strength fell with age in all regions of the colon (Fig. 2). The Kampala group had stronger colons as shown by a regression of tensile strength against age (Table 5).

Reference dimensions (Figs 3, 4)
The tendency for the cross-sectional area – that is, thickness – of the colon to rise with age (Fig. 3) was not significant. The thickness of the colon was less in the Kampala group but this was only significant (p<0.05) in the sigmoid region (Table 5).
The internal diameter of the colon fell with age (Fig. 3). In adult life the distal Kampala colon was wider than in Edinburgh (descending colon p<0.05) (Table 5 and Fig. 4).

Stretch (Figs. 5, 6)
The ability of the colon to stretch as measured by the width at burst remained constant with age in the proximal colon without any racial difference. The distal colon (Fig. 5) however showed a marked tendency to have a diminished width at burst with

Table 4  Comparison of tissue taken from Edinburgh and Kampala subjects. Wilcoxon's signed rank test for site differences between measurements

<table>
<thead>
<tr>
<th>Burst strength</th>
<th>Cross-sectional area</th>
<th>Tensile strength</th>
<th>Internal diameter</th>
<th>Width at burst</th>
<th>Elongation %</th>
<th>Stress relaxation</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>K</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AvT</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>p&lt;0.05</td>
<td>p&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>AvD</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>AvS</td>
<td>NS</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>TV</td>
<td>NS</td>
<td>NS</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>TV</td>
<td>NS</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>TV</td>
<td>NS</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
| NS = not significant
A = ascending colon
T = transverse
D = descending
S = sigmoid
Table 5  Fitted parallel regression lines of Log₁₀ (measurement) on age (age >10)

<table>
<thead>
<tr>
<th></th>
<th>Intercept for</th>
<th>Common slope</th>
<th>Significance of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Edinburgh</td>
<td>Kampala</td>
<td>Slope</td>
</tr>
<tr>
<td>Burst strength</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascending</td>
<td>3.10</td>
<td>3.25</td>
<td>-0.0004</td>
</tr>
<tr>
<td>Transverse</td>
<td>3.24</td>
<td>3.34</td>
<td>-0.0038</td>
</tr>
<tr>
<td>Descending</td>
<td>3.26</td>
<td>3.34</td>
<td>-0.0037</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>3.24</td>
<td>3.32</td>
<td>-0.0033</td>
</tr>
<tr>
<td>Cross sectional area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascending</td>
<td>1.18</td>
<td>1.13</td>
<td>0.0008</td>
</tr>
<tr>
<td>Transverse</td>
<td>1.16</td>
<td>1.09</td>
<td>0.0010</td>
</tr>
<tr>
<td>Descending</td>
<td>1.28</td>
<td>1.21</td>
<td>0.0006</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>1.30</td>
<td>1.20</td>
<td>0.0009</td>
</tr>
<tr>
<td>Tensile strength</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascending</td>
<td>1.94</td>
<td>2.12</td>
<td>-0.0013</td>
</tr>
<tr>
<td>Transverse</td>
<td>2.08</td>
<td>2.25</td>
<td>-0.0049</td>
</tr>
<tr>
<td>Descending</td>
<td>1.98</td>
<td>2.14</td>
<td>-0.0030</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>1.94</td>
<td>2.12</td>
<td>-0.0042</td>
</tr>
<tr>
<td>Width at burst</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascending</td>
<td>2.16</td>
<td>2.18</td>
<td>-0.0011</td>
</tr>
<tr>
<td>Transverse</td>
<td>2.10</td>
<td>2.11</td>
<td>-0.0010</td>
</tr>
<tr>
<td>Descending</td>
<td>1.96</td>
<td>2.03</td>
<td>-0.0004</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>2.06</td>
<td>2.15</td>
<td>-0.0024</td>
</tr>
<tr>
<td>Internal diameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascending</td>
<td>1.84</td>
<td>1.86</td>
<td>-0.0043</td>
</tr>
<tr>
<td>Transverse</td>
<td>1.72</td>
<td>1.82</td>
<td>-0.0039</td>
</tr>
<tr>
<td>Descending</td>
<td>1.56</td>
<td>1.70</td>
<td>-0.0035</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>1.62</td>
<td>1.73</td>
<td>-0.0048</td>
</tr>
<tr>
<td>Percentage elongation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascending</td>
<td>2.05</td>
<td>2.04</td>
<td>0.0046</td>
</tr>
<tr>
<td>Transverse</td>
<td>2.14</td>
<td>2.03</td>
<td>0.0041</td>
</tr>
<tr>
<td>Descending</td>
<td>2.17</td>
<td>2.08</td>
<td>0.0040</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>2.23</td>
<td>2.21</td>
<td>0.0034</td>
</tr>
<tr>
<td>Stress relaxation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascending</td>
<td>-0.83</td>
<td>-0.85</td>
<td>0.0013</td>
</tr>
<tr>
<td>Transverse</td>
<td>-0.79</td>
<td>-0.81</td>
<td>0.0009</td>
</tr>
<tr>
<td>Descending</td>
<td>-0.73</td>
<td>-0.75</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>-0.74</td>
<td>-0.77</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Age (sigmoid p<0.001 in Table 5) but the Kampala subjects had a significantly greater stretch capacity in the distal colon (descending p<0.01, sigmoid p<0.001), when compared with the Edinburgh patients (Table 5). Percentage elongation showed a tendency to rise with age (Fig. 6) particularly in the Edinburgh group, but there was no significant racial difference (Table 5). The tendency to rise with age occurred because the internal diameter fell with age.

Viscoelastic properties (Fig. 7)

These were similar for both racial groups and showed no tendency to change with age (Table 5). The distal colon in both racial groups had a steeper stress relaxation slope than the proximal colon (Table 4).

Changes in the colonic wall during growth

As Figs. 1–7 show, the measurement values for children do not in all cases show the same linear trend with age as those for adults. The burst strength of the colons from very young Europeans and Africans is low but rises to adult values. The cross-sectional area also initially low, increases and continues to do so with age. The tensile strength is high in childhood but drops thereafter. The internal diameter is low in childhood as is the width at burst, both results being attributable directly to the mere physical size being less in the early years of life. The internal diameter is fully established, however, in adolescence and thereafter decreases as does the width at burst. The percentage elongation, low at birth, increases continuously from then onwards.
Comparison of the mechanical properties of the colon

Fig. 1  $\log_{10}$ burst strength against age for Edinburgh (lower line – open circles) and Kampala (upper line – closed circles). Regression slopes have been drawn parallel as there was no significant difference between them. There is a significant regression with age when both racial groups are considered together. There is no significant difference between the races though the Kampala group generally had a higher burst strength than the Edinburgh group.

Divertercular disease (in Figs. 1–7): Edinburgh subjects – superimposed crosses on open circles.

throughout life. The stress relaxation is established at birth and does not vary from then onwards and appears to be a property which is independent of growth change. Comparison of the colonic properties in young Edinburgh and Kampala subjects by Wilcoxon’s rank sums showed no significant difference between the racial groups in the limited specimens of African tissue obtained with the African values lying consistently within the

Fig. 2  $\log_{10}$ tensile strength (g/mm²) against age for Edinburgh (lower line – open circles) and Kampala (upper line – closed circles) sigmoid colons. The slope of the regression is identical for both race groups and the regressions with age have been drawn parallel. The Kampala group has a significantly higher intercept with the vertical axis, representing greater tensile strength ($p<0.05$).

Fig. 3  $\log_{10}$ cross-sectional area (mm²) against age for the sigmoid colon. The open circles represent the Edinburgh group (upper regression line) while closed circles represent Kampala (lower regression line). In this study the width was constant (10 mm) so that cross-sectional area represents thickness. The trend with each group to thicken with age was not significant either when the racial groups were analysed together or separately. The Edinburgh sigmoid colon was, however, significantly thicker than the Kampala ($p<0.05$).

Fig. 4  $\log_{10}$ internal diameter (mm) against age for sigmoid colon from Edinburgh (open circles – lower line) and Kampala (closed circles – upper line). There was a significant regression with age in the Edinburgh group ($p<0.01$) but not the Kampala group. Multiple regression analysis including both groups of colons (fitted parallel lines as in Figure) showed a significant regression with age ($p<0.05$), the Kampala colons just failed to be statistically wider than the Edinburgh.
Watters, Smith, Eastwood, Anderson, Elton, and Mugerwa

**Fig. 5** $\log_{10}$ width at burst (mm) for sigmoid colon from Edinburgh (open circles - lower line) and Kampala (closed circles - upper line). The difference between racial groups was highly significant ($p<0.001$) as was the regression with age ($p<0.001$). The two racial groups had similar slopes, although when analysed separately, only the Edinburgh regression was statistically significant. The Kampala width at burst was the greater.

**Fig. 6** $\log_{10}$ percentage elongation against age for the sigmoid colon from Edinburgh (open circles - upper line) and Kampala (closed circles - lower line). There is a wide scatter of values. The increase in percentage elongation with age just fails to reach statistical significance when the colons are analysed together. When analysed separately there is a statistically significant increase for the Edinburgh colons ($p<0.05$) but not for the Kampala ones. There was no significant differences between the races on multiple regression analysis.

**Fig. 7** $\log_{10}$ stress relaxation of the sigmoid colon for Edinburgh (open circles - lower regression line) and Kampala (closed circles - upper regression line). There was no significant regression with age when analysing both races together, nor when treating them separately.

Discussion

The study of the mechanical properties of the bowel wall first required the development of a satisfactory method. Iwasaki\(^5\) used rectangular strips of colonic tissue but as the colon functions as a tubular structure we tested 10 mm rings of tissue in an attempt to be more physiological. The living colon is inaccessible for mechanical testing except by intraluminal pressure recorders, so that the only practical source of non-diseased large bowel for performing mechanical tests on the colonic wall was necropsy material. A method of storage using salt was developed to enable preservation of mechanical properties of the tissue while awaiting testing and allowing for collection and transporting of tissue from Kampala to Edinburgh for testing. The results suggest that the method is reproducible as the mechanical properties were not altered by salt storage.

The results show that the tensile strength of the colon declines with age and becomes least in the distal colon. This confirms the findings of Iwasaki,\(^5\) the only other worker who has reported on mechanical properties of the human colon. His values for tensile strength were similar to ours for each age and site studied. Tensile strength was
calculated from the burst strength and the cross-sectional area of the colon. The significantly greater tensile strength in the Kampala group was related to an increased burst strength and reduced thickness, though neither of these measurements was changed to a statistically significant extent in their own right. The standard deviations were large in many cases, suggesting great variability between individual colons. The variation between adjacent segments from the same colon was much smaller (16-24%).

Tensile strength in the Kampala group was related to a statistically significant extent in their own right. An increased burst strength and reduced thickness, which gave variable results but the large individual variation.

Despite these difficulties, there was a trend for the Kampala group to be stronger, wider and thinner, thus more mechanically efficient. The possible increased thickness of the Edinburgh samples may be a means of providing for decreased strength, a greater amount of tissue being needed to compensate for the colonic work load. This difference in strength between Edinburgh and Kampala colons must be because of either genetic or environmental factors. Burst strength is a measure of the strongest material in the colonic wall and thus a measure of its collagen content. Cross-sectional area in this instance is a reflection of the thickness since the width was a constant 10 mm. The thickness remained fairly constant with age, showing only a non-significant rise, and it appears that the fall in tensile strength with age is not therefore a measure of increasing thickness, but rather due to a decrease in the integrity of connective tissue. Ultrastructural techniques have demonstrated changes in collagen and other connective tissue fibres with age.

There was a significant fall in width at burst of the distal but not proximal colon with age. There was an increase in the width of the colon at burst in both groups over the first few years of life, possibly related to growth. The width at burst remained fairly constant thereafter in the proximal colon in both groups, but the distal colon (both descending and sigmoid) had significantly lower width at burst in the Edinburgh group, though both African and European groups showed a significant fall in width at burst with age. Iwasaki also reported a declining expansibility with age because of the reduced internal diameter.

The viscoelastic property of stress relaxation was constant throughout all four regions of the colon. There was a significant rise in stress relaxation with age in the ascending colon and a significant fall in the descending colon. The changes, however, were small and it seems more likely that stress relaxation as tested by this method is unaltered by age or site. There was no consistent difference between the two groups of colons which may represent a methodological problem related to testing viscoelastic properties in dead and devascularised tissue. On the other hand the viscoelastic properties at the level of strain tested (30%) may be similar for colons of all races and diets.

Diverticular disease is most prevalent in old age and in the distal colon. The findings here are consistent with this distribution. The distal colon was found to be weaker and less expansile in old age and also narrower, weaker and less expansile than the proximal one. Caro in analysing the static mechanics of a tubular structure and applying them to blood vessels showed that the circumferential stress is greater when the internal diameter is narrower and the wall is thicker. It seems therefore that the aged sigmoid colon is predisposed to develop diverticular disease both because of its ageing features and static mechanical changes. Add to this greater intraluminal pressure, and there are ample reasons for a link between the mechanical integrity of the colonic wall and the development of diverticular disease.

The overall picture that emerged was one of a wider and possibly more distensible distal colon in the African. It is the distal colon which is the most prone to develop diverticular disease in Western countries so that the impaired stretch capacity in the Edinburgh group may reflect pre-diverticular change. Alternatively, diverticular disease may develop secondary to an impaired stretch capacity.

Some evidence which would support either of these views comes from in vivo studies of balloon distension in the human colon. Parks found that the sigmoid colon with diverticular disease is less able to withstand a stretching force than is the normal bowel. Parks later confirmed that the descending colon in those who had had their sigmoid colon resected for diverticular disease also had an impaired stretch capacity. This descending colon was probably 'pre-diverticular' in that it was noted to be free of diverticula at surgical resection of the diseased sigmoid. This was later confirmed by Smith et al who also showed that subsequent treatment with bran did not lead to recovery of the faulty stretch properties of the colon.

Five of our specimens from patients over 50 years had diverticular disease and there were no significant differences between these five and eight colons from patients over 50 without diverticular disease. The similarity between the two groups suggests that the changes that occurred in the distal colon with age renders it more susceptible to diverticular disease rather than mechanical changes occurring as a result of diverticular disease. This supports the findings of Parks, who found that the inability of balloon distension of the distal colon in
diverticular disease to produce a normal pressure change in response to increasing volumes was not impaired by surgical resection of the diverticular diseased area. Thus diverticular disease occurs in an area of the colon mechanically predisposed to its development. For the differences between the African and European colons, possibly the most important environmental factor is the diet, which is likely to have less fibre and more fat and sugar in the European group. Rats and rabbits fed long term on a low fibre, high fat diet developed colonic diverticula attributable to a weakening of the wall in relation to the pressures generated to propel faeces.

There was no apparent difference in any of the mechanical properties examined in the Edinburgh and Kampala children's colons, which implies an environmental cause for the differences in strength which develop later in life; much larger numbers would be needed, however, to prove conclusively whether environmental factors or genetic ones are responsible for the differences in strength detected in the two racial groups.

We gratefully acknowledge the help given by Mr Ian Capperauld, Executive Research Director, Ethicon and Dr Peter Lawrie, Chief Biologist. Our thanks are also due to Drs A D Bain, A Busuttil and R A A Macaulay of the Pathology Departments, Royal Hospital for Sick Children, and Western General Hospital, and Department of Forensic Medicine, University of Edinburgh respectively.

References

14 Wierda JL. Diverticular of the colon in rats fed high fat diet Arch Pathol 1943; 36: 621–4.
Colonie Muscle in Diverticular Disease

A. N. SMITH

Although diverticular disease was initially recognized as an inflammatory disease (diverticulitis), it soon became obvious that there was an earlier non-inflammatory phase (diverticulosis) related to a structural weakness in the bowel wall. This weakness is determined by the point of penetration of blood vessels—the vasa recta—through the colon wall. Exaggeration of the perivascular space by the deposition of adipose tissue around the blood vessels was considered to weaken the wall of the bowel still further, as was a degenerative state of its muscle (for historical review see Painter, 1975). Morson (1963) changed the emphasis by noting that the predominant picture was a thickening of the muscle layers. A possible muscle dysfunction was already receiving attention because studies had shown that there was a raised colonic intraluminal pressure in diverticular disease (Arfwidsson, 1964; Painter, 1964) which led to the suggestion that the diverticula developed as an extrusion of the mucosa through the muscle coat. There thus began attempts to correlate facets of the disease with muscle hyperactivity and to interpret its various pathologic features as a consequence.

Another landmark was the recognition that the disease is uncommon in the Third World. Claims have been made that it largely followed a dramatic fall in the consumption of dietary fiber during the 20th century (Painter and Burkitt, 1975). Modern research has thus sought a role for fiber deficiency as an etiologic factor and for fiber itself as a means of modifying the physiopathologic disturbances.

THE BOWEL WALL

Muscle

The muscle of the colon consists of circular and longitudinal layers. The circular muscle is arranged in a tight spiral so that the individual fasciculi are almost circular, while the longitudinal taeniae are concentrated into three bands whose individual fasciculi cross from one side of the taeniae to the other, a distance of 200 mm or so (Pace, 1966). The longitudinal muscle thus forms a loose spiral around the outside of the circular muscle and, except
where concentrated into taeniae, is thin. The two muscle layers are connected at the edges of the taeniae and there is a layer of connective tissue between them.

Three essential components of the colon wall are its taeniae, the haustra, and the semilunar folds. Such structures are typical of the large intestine of herbivorous or omnivorous hindgut fermenters where transit is slow (Langer, 1984). In all such species the large intestine has its muscularis externa reduced to longitudinal bands to allow the wall between the taeniae to expand easily (Figure 1). Bubble-like dilatations of the lumen easily form, based on the haustra. The large intestine can equally constrict its lumen by means of functionally mobile mucosal indentations known as the semilunar folds, each of which is anchored to two taeniae. In the folds the circular muscle is contracted, whereas in the haustra it is relaxed. Such an arrangement thus requires very little muscular effort to produce the variations in cross-sectional diameter of the lumen that propel the fecal bolus (Figure 2). The colon can thus operate locally as a ‘low-power’ system until the fecal bolus reaches the rectum, where there is no such mechanical advantage provided by the anatomical arrangement. At this site mass peristaltic movements lead to rectal filling; the left colon being emptied by powerful, intermittent contractions occurring a few times per day.

Smooth muscle has an ATP-dependent contractile system based on actin and myosin molecules. Changes in the cell membrane cause a flux of Na\(^{+}\) and K\(^{+}\) ions and create an action potential; the excitation–contraction coupling is mediated by a flux of Ca\(^{2+}\) ions. Between the muscle cells, which are interwoven with one another, is the extracellular space, constituting 9–12% of
Figure 2. Changes in circumference of an intestinal tube plotted against changes in cross-sectional area. A circular cross-section is considered as the starting point and the changes are represented as percentages of the circular cross-section data. The upper dashed curve (○) represents circular cross-sections with a changing diameter. The lower dashed curve (▲) represents corresponding triangles for different sizes. The bold curve shows the relation between changes in cross-sectional area and changes in circumference in an intestinal tube with three taeniae and with haustra and semilunar folds. The bold symbols represent the conditions indicated in Figure 1. A change from semilunar fold contraction (▲) to haustral dilatation (■) achieves a considerable change in cross-sectional area of the lumen and favors easy onward propagation of contents. From Langer (1984), with permission.

The total volume and containing a variety of materials, including collagen, blood vessels, nerves, fibroblasts, mucopolysaccharides, and elastin. Intestinal smooth muscle exhibits spontaneous contraction (Price et al., 1979), and intracellular recordings in man demonstrate regular action potentials. Human colonic contractions occur at two different frequencies: 3 cpm and 6–9 cpm (Duthie, 1979); they possibly originate from a pacemaker region to the right of the transverse colon. Patients with symptomatic diverticular disease have a predominant frequency of 12–18 cpm, and the pattern is said to change to normal when fiber is given (Taylor and Duthie, 1976).
Collagen

Collagen is a stiff material and has to be arranged in a criss-cross pattern to be expansile. It is interspersed in the muscle layer giving a conforming quality to the bowel—rather like a string bag might if wrapped around it. A factor limiting the distensibility is the angle between individual collagen fibers. A light-microscope study by Cavarlho (1973) provides evidence that the angle between the collagen fibers becomes more acute from the serosa inwards. Acute angles in the fiber mesh enhance the tensile qualities of the collagen. This might suggest that the bowel would, on distension, rupture from the mucosa to the serosa, but this is not so. The mucosa is the last to perforate when distended, possibly because it is more elastic. There is also additional support in the submucosal layer, which has smaller but numerous fibrils more tightly packed together (Thomson et al. 1986). Apart from muscle forces extruding the mucosa, diverticula could result from a prior change in the collagen in the stiffer external layers, allowing the more elastic mucosa, supported by its submucosa, to herniate through.

THE DEVELOPMENT OF DIVERTICULAR DISEASE

There is some evidence to suggest that a local abnormality of the muscle of the bowel wall underlies development of the disease. The disease is most prevalent and clinically most severe in the sigmoid area. It is virtually unknown in the rectum, which is, in part, wider and where segmentation is not a main action. Painter (1975) advanced the hypothesis that the segmentation process is slowly transformed from an intermittent event into a lasting structural change. Based on normal segmentation patterns, compartments form, each demarcated by thickened arcs of circular muscle. This conversion takes place initially in the rectosigmoid, where sphincter-like activity temporarily halts the onward transmission of fecal contents to the rectum. The lumen is encroached by thickened bars of circular muscle which divide it into a series of tortuous, inter-communicating chambers; mucosal folds complete the obstructive process. Diverticula form temporarily at first but become permanently extruded by an increase in intraluminal pressure. Sometimes the muscle thickening is so great that the diverticula remain intramural and ‘diverticular disease without diverticula’ exists, with every feature of the disease but without externally obvious diverticula.

There is, however, another form of diverticular disease well known to surgeons as an incidental finding at laparotomy. This type appears to result from a failure in the support afforded by the muscle coats or by the collagen intermingled between them. It principally affects elderly patients and has a diffuse, pan-colonic distribution as sacculations along the entire length of the large intestine. A ‘non-muscle’ form may also be present in diverticular disease as part of Marfan’s syndrome.

The intraluminal pressure is usually raised in the sigmoid diverticular segment. Arfwidsson (1964) and Painter (1964) demonstrated that it was highest when food or drugs stimulated the bowel muscle. The diverticula were
pushed out from the wall of the bowel and could be seen actively filling with barium on radiologic screening. However, since the basal pressure was not increased, Painter conceived of a thick muscle not in "spasm" but over-active when stimulated. It caused pressure increases higher than in normal subjects and these were sufficient to cause local pain. Reilly (1966) felt that the muscle disorder was essentially obstructive and he introduced the operation of longitudinal myotomy to overcome this. The thick bands of circular muscle in the wall of the bowel were divided through a longitudinal incision and this relieved the symptoms. Atnisha and Smith (1969) found that operation lowered the intraluminal pressure in the sigmoid colon but its effects were relatively short-lived; nor was it free from the risk of perforation. Since high-fiber diets achieved the same effects, the operation was abandoned. Nevertheless, the complete relief of symptoms it afforded stresses the importance of the muscle of the bowel wall in producing symptoms.

Another important aspect of diverticular disease is its worldwide distribution, especially its relative infrequency in Africa and India. Burkitt et al (1972) described how Africans on a native diet have a rapid intestinal transit with bulkier, moister stools than their European counterparts. Painter et al (1972) alleviated symptoms by giving fiber to diverticular patients. Findlay et al (1974b) found that bran markedly lowered the sigmoid intraluminal pressure. This observation was confirmed by Brodribb and Humphreys (1976), who also noted that the number of motor waves in the sigmoid colon was greatly reduced by fiber.

Whiteway and Morson (1985) have described end-stage diverticular disease (Figure 3). Both muscle layers are increased, with the taeniae showing a uniform thickness, marked shortening, and a concertinaing of the circular muscle, mesenteric fat, and mucosa. Crescentic arcs are formed out of the thickened circular muscle and these come to lie close together or override each other so that the mucosa is approximated to the serosa between each and diverticula become almost inevitable. While hypertrophy of the muscle may occur above the lesion. Whiteway and Morson agree with Slack (1966) that neither hypertrophy nor hyperplasia is present locally. Elastin was found in excessive amounts in the taeniae but not in the circular muscle coat. Elastosis of the taeniae may produce the final gross 'contracture' type of deformity commonly found in operative specimens (Williams, 1963).

FIBER AS A RESEARCH TOOL IN DIVERTICULAR DISEASE AND ITS MUSCLE DISORDER

Fiber has a general action on the motility of the gastrointestinal tract. In dogs it stimulates upper-gastrointestinal motility and reduces transit and flow through the jejunum (Bueno et al, 1981). Yet fiber produced little change in spike discharge of the colon and only minimal change in the contractions in primates. Colon intraluminal pressure was, however, increased by a low-fiber regimen (Brodribb et al, 1979). The precise means whereby the fiber-enriched fecal bolus acts to reduce the intraluminal pressure in diverticular disease is unknown. One distinctive result of high fiber intake is the production of
bulkier stools, which might increase the diameter of the bowel. A wider lumen would reduce pressure and so reduce tension on the wall of the bowel.

Fiber and analogues obtained from plant sources are classed together as fecal bulking agents. Bran is the external lignin-rich part of the wheat germ after removal of its polysaccharide and cellulose components. It is the most active agent for increasing the daily fecal output (Eastwood et al., 1978a). Most forms of dietary fiber derive from the cell wall of plants. Although insoluble, they act by binding salt and water (Eastwood and Mitchell, 1976), making a moister, unabsorbed residue which swells in the bowel lumen and stimulates peristalsis. However, some fiber sources, mainly pentosans, such as gums and pectin, are water-soluble and are more readily attacked by bacteria. Unlike bran, their fecal bulking action may be less. They act mainly by increasing the bacterial population of the stools (Stephen and Cummings, 1979). This action predominates when the fiber is from fruit or vegetables. The bacteria of the stool may add their own cell water directly to its water content. The postulated fiber deficiency in diverticular disease probably operates for 20 or 30 years before a clinical syndrome is produced. It is the old, rarely the young, who develop diverticular disease in areas where the incidence is high.
and where both groups might be expected to have experienced the same day-to-day fiber differences.

A reduced intake of fiber was found by Brodribb and Humphreys (1976) when they performed a survey of the incidence of diverticular disease related to fiber intake. Forty per cent of those with a fiber intake of less than 20 g per day had diverticular disease of the colon, against under 10% when the fiber intake was over 30 g per day. Manousos et al (1985), in a case control study, found evidence of a low intake of vegetables and brown bread and a high consumption of meat and milk products in subjects with diverticular disease in Greece. Aktan et al (1984) compared the position of one group who lived in a Turkish rural community and kept to a traditional high-fiber diet with another group who lived in Ankara, where fiber intake has diminished greatly with the advent of modern convenience foods. The subjects in the rural community had a significantly faster transit and a greater daily fecal output than those in the city. The intraluminal pressures were lower but not significantly so. This finding is of interest because diverticular disease, formerly unknown in Turkey, is now becoming established after two or three decades of change to Western dietary habits.

All the indications are that the motility of the colon as a whole is probably affected in diverticular disease. For example, transit is slow in all areas and fiber speeds it up throughout (Smith, 1978). Moreover, when the pelvic colon is excised, a high pressure may remain in the left colon above the anastomosis (Parks and Connell, 1969). Smith et al (1974) found that resection and myotomy cases varied postoperatively: the pressure remained high following resection, whereas post-myotomy there was a period of relatively low pressure before pressure rose in this group too. The postoperative administration of a high-fiber diet kept the intraluminal pressures low after both procedures and should be considered a requirement in the follow-up management (Smith, 1977). Bran or other bulking agents reduce the intraluminal pressure so effectively that elective operations for uncomplicated diverticular disease have largely been abandoned. Since the physiologic disturbance may have developed over some decades, it seems unlikely that the incidence of established diverticular disease, and thus the need for operation for its complications, will be quickly altered by fiber supplements. This requires that health education measures are implemented by succeeding generations. Evidence from figures available in Scotland (Chalmers et al, 1983) suggests that the incidence of diverticular disease discharges and operations has not fallen in the 'post-bran' era, but this has to be set alongside the greater proportion of elderly persons in the population, reflecting increased longevity in the community as a whole.

PROPERTIES OF THE COMMON BULKING AGENTS

Bran, ispaghula (Fybogel), sterculia (Normacol), and lactulose (Duphalac) do not have the same effects (Srivastava et al, 1976; Eastwood et al, 1978a). Although the first three act principally as a result of their fiber content, lactulose acts as an osmotically active sugar, undergoing fermentation in the
cecum; pH change and formation of free gases stimulate the motor action of the colon. All four agents speed intestinal transit but bran is the most active in reducing the intraluminal pressure. Ispaghula, paradoxically, increases the intraluminal pressure, beneficial in constipation but perhaps causing mucosal damage in the long term. The rise in pressure has been attributed to a colouring azo dye which contains radicals, possibly irritant to smooth muscle.

Though bran is generally the most effective agent in lowering the intraluminal pressure, this is not true of all forms of bran. Kirwan et al. (1974) compared coarse and fine bran and found that only the coarse form lowered the colonic pressure. Water and salt absorption were greater and the lignin content was higher in the coarse form; this was lost when it was milled to a finer form. The coarse form had more inter- and intra-particle spaces for holding water. Brodribb and Groves (1978) also found that the two forms had differing effects on intraluminal pressure and suggested that the deficiency of the finer form could be compensated for by increasing the dosage. Many of the effects of bran on bowel function are also lost after cooking (Wyman et al., 1976). The action of bran fiber also depends on the type of wheat. The effect on intestinal transit and intraluminal pressure was greater after administering fiber from Canadian coarse wheat than following fiber from a softer French variety (Smith et al., 1981a). It is now accepted that physical and chemical changes in fiber may determine many of its physiologic effects.

Bulk additives have been combined with antispasmodic agents to enhance the pressure reduction. One theory attributes the raised intraluminal pressure in diverticular disease to the presence of a spasmogen. The facilitation of the action of an otherwise inert bulk additive such as sterculia by an antispasmodic agent suggests that the presence of a spasmogen may be a reasonable supposition (Srivastava et al., 1976). Bran increases the solids in the intestinal tract and the fecal water in the stool (Findlay et al., 1974b) and could modify the action of an irritant agent by dilution. Fecal bile acids are possible candidates for the role of spasmogen since they stimulate the motility of the colon in man (Kirwan et al., 1975) and animals (Falconer et al., 1981). It is possible that bile acids in smaller concentrations could stimulate the circular smooth muscle of the colon irregularly to promote chronic, abnormal growth.

The transit of solids and liquids is normally adjusted so that they move through the colon proportionately and become equally represented in the feces (Findlay et al., 1974a). This has been shown by the use of solid and liquid markers which reveal that in diarrhea the fluid component streams more than the solid phase; in constipation, the reverse is true. In diverticular disease the ratio of fecal solid to liquid markers is markedly increased, mainly because water is less available because of absorption as a consequence of the slow rate of transit. Bran reverses this trend, not only increasing the amount of water moving along the colon.

**DIVERTICULAR DISEASE—A MOTILITY DISORDER?**

There is some evidence that is inconsistent with the view that diverticular disease is a motility disorder. Not all patients with diverticular disease have...
Elevation of the motility index correlated chiefly with symptoms of abdominal pain and distension whether diverticula were present or not. Patients with asymptomatic diverticular disease and patients with asymptomatic irritable bowel had normal motility findings. Eastwood et al (1978b) also found diverticular disease patients without a raised intraluminal pressure. They suggested that the patients with a raised motility index were mainly surgical patients with partial obstruction who had other features, such as a delayed transit and a low fecal output. But this study followed the time when high-fiber diets and bulk additives had been widely adopted in the UK, so another possibility was that many patients had induced changes by self-treatment before referral to hospital.

Diverticular disease may overlap with the irritable bowel syndrome (IBS). Painter (1972) holds that the two pathologies can affect the same patient and that both are evidence of fiber deficiency. Follow-up studies point to two conditions without progression of one to the other. The irritable bowel is most frequent in the third or fourth decade of life and patients have a long history of abdominal problems, whereas diverticular disease affects the sixth and seventh decades and later and has a shorter clinical course. Evidence from the electrical recordings of wave frequency patterns associated with motility responses is that there is an additional fast frequency in the irritable bowel syndrome (Snape et al, 1976; Taylor et al, 1978).

A further source of uncertainty is that patients with IBS and diverticular disease show marked placebo responses. Brodribb (1977) performed a double-blind crossover study of fiber and placebo in diverticular disease. The greatest relief of symptoms was with a high-fiber diet, but a significant effect was also achieved with the placebo low-fiber regimen, and this took one month to disappear. Weinreich and Andersen (1976) found that placebo management also induces a fall in the sigmoid intraluminal pressure in diverticular disease. It seems that great care is necessary in evaluating agents for use in management and Almy and Howell (1980) appeal for the use of objective criteria when making comparisons. Different degrees of severity of the disease may be admitted to hospital according to differing admission patterns; evidence for this is the quite markedly different features of diverticular disease in different published series. Parks (1975) found that a short history of less than one month was common in his patients, whereas Colcock (1968) had patients with problems for over a year.

Compliance changes

Parks and Connell (1969) found that the bowel wall had an increased compliance in diverticular disease. This is an apparent paradox because a thickened bowel might be expected to yield less readily than normal tissue. An enhanced capacity to yield must, however, normally follow from the presence of haustra and when excessively developed might relate to the presence of the diverticula themselves. Parks (1970) found that the colon exhibited the same
properties after resection and therefore must have been affected above the excised zone; hence the defect must be a fairly generalized one in the distal colon. Smith et al. (1981b) found that the compliance change was present in the sigmoid colon both in vivo and in vitro (Figure 4). This implied that there was a mechanical change in the structural support mechanisms of the wall of the bowel. The same compliance change was found whether the patient was symptomatic or not, nor did treatment with bran reverse it. Parks' finding that the change remained after resection in the residual left colon was confirmed, though initially an improvement in compliance was detected. It is not known whether the primary weakness is in the muscle coat or the supportive collagen, nor whether it is an expression of continued intraluminal high pressure exerted upon it. The initial improvement in compliance followed by a late deterioration does, however, point to this possibility. Once established, the altered compliance seems to remain at a very similar level since diverticula tend to remain more or less at the same size after formation.
Aging in the human colon

There is a close link between diverticular disease, the aging process, and the diminished strength of the colonic wall. Increase in thickness of the colonic wall could result from contracture, hypertrophy, hyperplasia, or inflammation, and all of these would reduce the tensile strength. In the sigmoid descending and transverse colon there is a significant reduction in tensile strength with age (Figure 5) (Watters et al, 1985). The tensile strength is highest in the first year of life and Iwasaki (quoted by Yamada, 1970) found that it falls progressively thereafter. The colon and rectum both lose their tensile qualities with age. It is suggested that the collagen content falls progressively or becomes altered either by rearrangement of its matrix or by weakness of the individual fibers. How much of this is provoked by dynamic changes in the muscle as it produces increments of pressure or whether it can be compensated for by other tissues, for example, the ‘elastosis’ noted by Whiteway and Morson (1985), is uncertain. Watters et al (1985) found that in Europeans as aging progressed, the left colon was reduced in both its diameter and its capacity to stretch but a noticeably lesser reduction in both functions occurred in Africans of all ages (Table 1). Viscoelastic properties of the colon wall were also studied by Watters (1983) with disappointingly negative results. It was hoped to show that there is an age-related change comparable to that
Table 1. Changes in colonic tensile strength, internal diameter, and width at burst compared for age and race in Africans (Kampala) and Europeans (Edinburgh) (Watters, 1983).

<table>
<thead>
<tr>
<th></th>
<th>Tensile strength</th>
<th>Internal diameter</th>
<th>Width at burst</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age</td>
<td>Race</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td>Decreases</td>
<td>Lower in</td>
<td>Decreases</td>
</tr>
<tr>
<td>Ascending colon</td>
<td>NS</td>
<td>NS</td>
<td>*</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Descending colon</td>
<td>NS</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>*</td>
<td>*</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusion: Significant changes more in distal colon. Narrower with age: wider in Africans and thinner (O) in distal colon. Very significant fall in resistance to disruption of the distal European colon.

* P < 0.05; ** P < 0.01; *** P < 0.001; NS = not significant.

found in skin, where there is a deterioration in the ability of the skin to relax after a slight stress is applied to it. However, the presence of an intact blood supply may be necessary to demonstrate the viscoelastic properties of a human tissue.

Various components of the bowel wall experience age changes. Pace (1966) found that the collagen tissue layer between the muscle coat is reduced from 10 years of age, but individual collagen fibers may increase in thickness up to the age of 60. With increasing age the collagen bundles in the submucosa begin to fray. Collagen fibrils become smaller, more numerous, and more tightly packed in the submucosa of the left colon, where they should add to the local strength of the bowel wall (Thomson et al, 1986). Elastin progressively increases throughout life in all layers, individual fibers are shorter, thicker, and less wavy and in the highest group there are hyaline changes. However, Whiteway and Morson (1985) found these changes to predominate in the taeniae coli. Pace (1966) also showed that the reticular fibers increased with age and had degenerative changes in them.

The effects of aging have been studied in blood vessels and there are some parallels with the colon. Young's modulus of the aortic wall increases with age, implying stiffness. The same process might occur in the colon and Iwasa (quoted by Yamada, 1970) stated that the percentage elongation of the bowel or strain at burst was greatest at 20-29 years but had declined greatly in those over 60 years of age. Being a strong, stiff material, collagen is the main load-carrying and stress-bearing element in biologic tissues, whereas elastin is the biologic tissue most resembling an elastic material in that its stress-strain relationship is almost linear. Thus on removal of a load elastin returns to its original dimensions. Muscle changes its mechanical properties as it contracts and relaxes. When relaxed, its Young's modulus approximates to that of elastin, but when active it is much more stiff.
It is possible that aging affects these various components differently in blood vessels compared to the colonic wall. The wall of the aorta may increase in thickness and become stiffer, but may later bulge with aneurismal dilatation, as may the wall of the intestinal tract, as different components—muscle, collagen, and elastin—exert their particular physical properties. Biologic properties are often those of a viscous liquid as well as an elastic solid and are said to be viscoelastic. The advantage of viscoelastic design tissues is a combination of expansibility, strength, and maintenance of shape. If the bowel were made of steel, it would be strong but could not distend. If it were made of rubber, like a balloon, it would change its shape inordinately in response to an increase in pressure. As soon as a cylindrical balloon or tube is subjected to a circumferential strain of 50% or more, the inflation process becomes unstable and the walls will bulge out.

Pace (1966) demonstrated that there is a progressive increase in the thickness of the colon wall with increasing age but that the biggest single growth spurt is in infancy. The changes affect both the circular and longitudinal muscle, which range in thickness from 0.3 mm at 4 months of gestation to 2.6 mm at 5 years of age. Measurements thereafter became, for example, 3.6 mm at 43 and 5.3 mm at 85 years of age. The colon also shows ‘pre-strain’ (Watters, 1983) which is a device to counteract lengthening as the intraluminal pressure rises. If this were not applicable in blood vessels, for example, and they obeyed Hooke’s law, i.e. had a linear stress—strain curve, a 1 mm expansion of the blood vessel diameter would lengthen a blood vessel such as the femoral artery by 25 mm with each pulse pressure rise (Gordon, 1978).

These mechanical principles may modify some aspects of the diverticular disease process. The elastin increase in the taeniae, for example, may be compensation for diminishing muscle activity and a less adequate ‘pre-strain’ resulting from chronic under-filling of the bowel due to a fiber-deficient diet that might also produce an intraluminal pressure rise. These developments might occur slowly and, though related, could vary in their intensity. Successive crops of diverticula seem to stay at around the same size, which suggests that the tension in the wall is not rapidly increasing. Colonic intraluminal pressure may be modified by the ‘propagation’ of the segmentation process, which may explain why pressure measurements do not reliably distinguish between the normal and the diseased state. Perhaps more attention should be paid to the abnormal fast waves of lower amplitude known to be present (Connell, 1975). It also seems that there is a clinical spectrum (Almy and Howard, 1980) from cases of pancolonic diverticula with no evidence of hypermotility or excessive segmentation, to cases with few diverticula, marked muscle thickening and hypermotility at the other extreme. These diverse patterns are apparently the product of two factors, intraluminal pressure change and the weakness of the wall, and these may be present in each patient in quite differing proportions. Mendeloff (1976) has pointed out that a disease affecting complex urban society may well have a multifactorial causation.

‘Normal’ clinical material is thus difficult to derive since patients in the middle years of life who may not have diverticular disease have been exposed to the same dietary background as the diverticular disease subjects. Watters found that the European with a narrower, weaker bowel had these changes,
age for age, whether he had diverticular disease or not. The African who does not have diverticular disease has a wider, stronger, and more distensible colon. The essential difference in the aging European may reside in a combination of a changed wall plus a rise in intraluminal pressure, resulting from fiber deprivation. Many North American and European adults of 50 or 60 years of age without diverticula may be on the threshold of developing them, given sufficient increase in pressure, even if only intermittent, or a further weakening of the bowel wall. The fact that neonatal colons from Africa and Europe were identical in their tensile strength and elastic properties suggests that there is no racial or genetic difference and that the later trends are environmental and could be related, among other factors, to diet.

COMPLICATED DIVERTICULAR DISEASE

Most patients who develop complications have only recently come to be symptomatic; in general, they would be expected by the criteria of Weinreich and Andersen (1976) to have raised intraluminal pressures. The question now changes: can the level of intraluminal pressure which may develop in symptomatic diverticular disease as a result of the colon's own musculature have a critical and adverse effect on the disease process? The rise in intraluminal pressure can, for example, be sufficient to arrest momentarily the circulation through the wall of the bowel. A reduction of oxygenation follows diminished blood flow, and it has been calculated that this becomes critical when it is reduced to a minimum of 20% of average total flow. This reduction favors bacterial growth and allows penetration of bacteria through the bowel wall to establish a peridiverticulitis from which pericolonic abscesses and other complications result. The incidence of inflammatory complications is higher in patients with immune suppression, chemotherapy, radiotherapy, and cytotoxic therapy probably because of interference with the walling off of inflammatory collections, with the leukocyte response, and with the general capacity of the body to maintain resistance against infection. Thus bacteremia may be followed by severe hypotension, disseminated intravascular coagulation, and renal failure before the clinical state is recognized.

The muscle-dependent pressure changes also influence the development of fistulae. Colovesical fistula classically is attributed to peridiverticular abscess which has drained into bowel and bladder. Henderson and Small (1969) found that this form had virtually disappeared and that the presentation had changed. Patients with colovesical fistula are often younger, in the 45-50 age group, and are almost always males with a short segment of diverticular disease. This allows a mobile pelvic colon to fall into contact with the bladder where it becomes adherent, a process prevented in the female by the interposition of the uterus, the exception being posthysterectomy. They further showed that pressure was higher in the bowel than in the bladder. The urinary bladder has a highly developed capacity for accommodation and the pressure may rise and fall off again before the bladder fills to its maximum capacity prior to voiding. The directional flow in the fistula is from the high pressure colon to the lower pressure in the bladder so that it truly is a
COLORECTAL MUSCLE IN DIVERTICULAR DISEASE

CO-EXISTENCE OF DIVERTICULAR DISEASE WITH OTHER CONDITIONS

Dietary fiber deficiency has been advanced as a possible cause of both diverticular disease and colonic cancer. Though the two conditions occur together, diverticular disease has never been regarded as a precursor of cancer of the colon. Small and Smith (1975) estimated that of 100 cancer specimens, 20 will show diverticular disease, while of 100 specimens removed for diverticular disease, two will have cancer. The fact that they have been found together in some series (Boulos et al, 1985) may follow from patients of a middle to elderly age group with diverticular disease being intensively examined. Fiber deficiency may produce increased pressure in the lumen in diverticular disease, but in other individuals it may prolong the transit time and promote the production of fecal carcinogens.

Inflammatory bowel disease and diverticular disease may also occur in the same patient and tend to run a stormy course with a high incidence of infective complications (Jalan et al, 1970). There can be minimal involvement of the right colon in the colitic process so that water is well absorbed, and the left colon, which comes to contain scybalous feces, may be obstructed. The left side is doubly affected with colitis and diverticula and there is a thickened muscular muscle and a raised intraluminal pressure. The clinical problem becomes that of the emptying of the colon and some of these patients require operation for a proximal colonic dilatation, in some instances progressing to toxic dilatation.

One of the most common clinical associations of diverticular disease is gallstones and hiatus hernia in Saint’s triad. The formation of gallstones has been associated with the metabolic consequences of fiber deficiency on the bile-salt pool and cholesterol synthesis, but the link between hiatus hernia and diverticular disease may have a pressure basis. Increased intra-abdominal pressure following the straining caused by the constipation associated with diverticular disease may encourage weakness of the diaphragmatic hiatus or
laxity of the gastroesophageal ligaments. However, part of the problem could relate to changes in the hormonal control of the gastroesophageal sphincter and abnormal release of peptide hormones. Cholecystokinin is known, for example, to have motor effects on the muscle of the colon and on upper alimentary sphincters as well as on the gallbladder itself.

SUMMARY

The muscle abnormality in diverticular disease is seen most often in surgically excised specimens in the sigmoid colon, though a pancolonic form of the disease without muscle thickening also exists in the elderly. In terms of physiopathology, the condition has a raised intraluminal pressure operating on the wall locally, this being most readily demonstrated in symptomatic patients. In Western societies the colon loses its tensile properties throughout life. The anatomical and functional evidence is that the colon is outstandingly strong in infancy in both Africans and Europeans, but later the mechanical properties of the African colon become superior and they remain so throughout ensuing decades. The diminished tensile strength and elasticity of the wall is no different in the diverticular and non-diverticular subjects and this suggests that an additional factor, such as pressure, may be necessary in Europeans to cause the mucosal extrusion which constitutes each diverticulum. Fiber fills the colon with bulkier, moister feces, which necessitates less work, especially as it operates for most of the time as a low-pressure system, only occasionally evacuating by mass peristalsis into the rectum. Cereal fiber binds salt and water and there is evidence that this is mostly a physicochemical process, dependent on particle size. Certain types of fibers undergo chemical degradation in the cecum and increase the bacterial population of the stool.

Population studies show that diverticular disease subjects consume less fiber and in countries where the fiber intake is reduced, fecal output is lessened, transit is slower, and intraluminal pressure may be rising. As a result of the adoption of high-fiber diets and the use of bulking agents elective operations for diverticular disease are less commonly performed. The number of operations in most Western countries may be increasing because of increasing longevity. Complications often arise after a relatively short history; most are explicable on the basis of sudden pressure increments. The recent important finding in this disease is the change in colonic wall compliance, which probably occurs because of a collagen failure. Contraction of the taenia may follow elastosis, which may relate to under-filling; this produces the contracted structure seen in the excised colonic specimen. The strength of the colonic wall diminishes throughout life, due to changes in its composition; some of these changes are hastened by self-imposed stresses, which currently seem to be mainly of dietary origin.

Acknowledgment

The author is indebted to Dr A. Busuttil of the Department of Pathology, Western General Hospital, Edinburgh for Figure 3 and would like to express his thanks to Mr David Waters, FRCS University Teaching Hospital, Zambia for allowing him to quote liberally from his thesis, University of Edinburgh, 1983.
REFERENCES


The Submucosa of the Human Colon

Hugh J. Thomson,* Anthony Busuttil,† Martin A. Eastwood,* Adam N. Smith,* and Robert A. Elton‡

*Gastrointestinal Unit and †Pathology Department, Western General Hospital, and ‡Medical Statistics Unit, University of Edinburgh, Edinburgh, United Kingdom

Received October 29, 1986, and in revised form December 10, 1986

Full-thickness specimens of colon were obtained at operation or autopsy from 20 patients. The submucosa was isolated from the mucosa and muscularis externa, with confirmation by light microscopy. Submucosal specimens were then fixed and prepared for scanning and transmission electron microscopy, with preservation of their orientation. The submucosa was found to consist of a series of layers of collagen fibres, each layer 0.5–2.0 μm thick. The fibres within each layer were co-directionally orientated. The autopsy specimens were comparable in appearance with the operative ones. The mean diameter of the collagen fibrils was 69 ± 13 nm, and the mean fibril count per unit area was 159 ± 58/μm². © 1986 Academic Press, Inc.

It has been recognised for almost a century that the submucosa is the layer of the bowel wall which is most resistant to shearing and stretching forces (Haldsted, 1891). Recent experimental work (Watters, 1983; Watters et al., 1985), based on mechanical stretching of the bowel, has shown that the “bursting strength” and tensile strength of the human colon are dependent on the submucosal layer, which is composed almost entirely of collagen fibres.

The ultrastructure of this important layer has not been studied previously in humans. We describe a method for the isolation and preparation of the colonic submucosa for detailed ultrastructural examination.

MATERIALS AND METHODS

Full thickness specimens were obtained at autopsy from the ascending, transverse, descending, and sigmoid colon of 17 patients (ages 20–96 years, mean 56 years). The specimens were taken within 48 hr of death (mean 22 hr). In addition, fresh operative specimens of normal colon were obtained from 3 patients who underwent colonic resection for intractable constipation.

All specimens were rectangular in shape with their long axis co-directional with the long axis of the colon, so that their orientation could be easily maintained during processing. After paraffin embedding and conventional staining, representative sections from each specimen were examined by light microscopy to exclude any previously undetected abnormality (Fig. 1).

The specimens were washed in tap water and immersed in 10% NaCl solution for 72 hr. This enabled the mucosa to be peeled off, and the specimen was inverted onto a filter paper and the muscularis externa removed by a combination of sharp and blunt dissection (Fig. 2). A segment from the residual portion of each specimen was fixed in 10% buffered formol saline, embedded in paraffin, sectioned, and stained conventionally for light microscopy to confirm that the submucosa had been isolated (Fig. 3). The remainder of the submucosa was divided into two portions, one each for scanning and transmission electron microscopy. These were stretched uniformly in a transverse and longitudinal direction. This was done manually because isolated submucosa is too flimsy to allow mechanical stretching. The specimens were pinned out and postfixed in 5% glutaraldehyde in 0.1 M Na cacodylate for 24 hr.

Scanning electron microscopy. After washing in distilled water, the fixed specimens were dehydrated in increasing concentrations of ethanol from 25 to 100%, and then dried in a Polaron critical point dryer (Polaron Equipment Ltd., Watford, Herts., England). The specimens were mounted on aluminium stubs with Araldite (CY212) (Emscope Laboratories Ltd., Kingsnorth Industrial Estate, Ashforth, Kent, England), sputter coated with gold to a depth of approximately 20 nm in a Polaron SEM coating unit (ES100, Polaron Equipment Ltd.), and examined under the IS1-60 scanning electron microscope (International Scientific Instruments Ltd.).

Transmission electron microscopy. These specimens were cut into 1- to 2-mm-thick slices. After washing with 0.1 M cacodylate-buffered sucrose (pH 7.3), these
Fig. 1. Light micrograph of full-thickness colonic wall. Haematoxylin & eosin, × 260.

Fig. 2. Dissection of the muscularis externa from the submucosa. The mucosa has already been removed.
slices were treated with 1% osmium tetroxide followed by 1% uranyl acetate with a distilled water wash after each, and dehydrated through graded aqueous solutions of ethanol from 50 to 100%. The slices were treated with propylene oxide and immersed in liquid Araldite resin for 24 hr. They were then embedded in fresh Araldite resin which was polymerised for 48 hr at 60°C. Sections 1 μm thick were cut and stained with toluidine blue in 1% borax, and then 60- to 90-nm sections were cut, at 90° to the long axis of the colon, using a Reichert OMU2 ultratome (Reichert-Jung U.K., Slough, England). These sections were mounted on copper grids, stained in saturated uranyl acetate in 50% ethanol followed by Reynolds lead acetate, and examined under the JEM 100 CX11 (Jeol Ltd., Grove Park, Colindale, London). Viewing using the gonioscopic stage at varying angles of tilt produced no appreciable differences in the appearance of the collagen fibrils.

Measurements. The diameters of the collagen fibrils in the fibres cut in cross section from every specimen were measured on visual inspection of the transmission electron micrographs. The maximum and minimum diameters of obliquely cut fibrils were recorded, the minimum being the actual diameter. From the minimum diameters of 10 contiguous fibrils, chosen at random from the middle of a fibre, the mean was calculated for each specimen.

The fibril count per unit area was also determined. To take into account the varying angles at which different fibrils were cut, the ratio of the obliquity of section, y/x, was used to adjust the area for counting fibrils.
Fig. 5. Scanning electron micrograph of colonic submucosa. × 74.

Fig. 6. Scanning electron micrograph of colonic submucosa, showing (A) branching of fibres and (B) fibres interlacing between layers. × 106.
Different collagen fibres had been sectioned, fibrils were counted on the 50 000 x prints (× 2 magnification) within a rectangular area measuring 6 cm on the short side. The long dimension of the rectangle was calculated by multiplying 6 cm by the ratio of the mean maximum to the mean minimum fibril diameter, thus correcting the area for the obliquity of section (Fig. 4). Fibrils overlapping the edge of the designated area were included if more than half of the fibril appeared to be within the area. After the number of fibrils per 36 cm² on the print was counted, the number of fibrils per square micrometer was calculated. All fibril counts and diameter measurements were repeated "blind" by the same observer on each electron micrograph. In addition, reproducibility within an area of the colon was assessed by analysis of five replicates taken from a single specimen.

RESULTS

The structure of the submucosa, on both light microscopy and electron microscopy, appears unchanged up to 48 hr postmortem, despite earlier autolysis of the mucosal and muscular layers of the colonic wall. Degenerative changes in the submucosa under light microscopy were seen only in a prior specimen obtained 60 hr after death, with fragmentation and necrosis of the collagen fibres noted. No significant differences were ob-

Fig. 7. Electron micrograph of colonic submucosa. × 10 600.

Fig. 8. Line drawing to represent the strata in the submucosa of the colon, with fibres running in different directions in each layer.
Fig. 9. Electron micrograph of colonic submucosa. × 21 200.

Fig. 10. Electron micrograph of colonic submucosa. × 106 000.
served between the autopsy (up to 48 hr postmortem) and the operative specimens.

Scanning electron microscopy of the submucosa (Fig. 5) shows a network of collagen fibres orientated largely in two axes. The appearances are not those of an interlacing network, but rather those of a stratified structure, with all the collagen fibres within each individual layer running in approximately the same direction. A small number of fibres appear to branch and cross over between the layers (Fig. 6). Transmission electron microscopy confirms that the submucosal collagen is arranged in strata, 0.5–2.0 μm in thickness (Figs. 7 and 8). The constituent fibrils making up the collagen fibres are seen clearly in the submucosal strata, the characteristic periodicity confirming their identity.

The fibrils seen in cross section (Fig. 9) range from 48 to 104 nm in diameter (Fig. 11). At higher magnifications uneven electron density is noted, leading to a granular appearance (Fig. 10). The diameters and counts are shown in Tables 1 and 2, respectively, along with the repeat measurements. The mean fibril diameter is 69 ± 13 nm, and the mean fibril count is 159 ± 58/μm². The mean coefficients of variation from the replicate data are 4.3% for diameters and 7.3% for counts. The coefficients of variation for the five replicates within one specimen were greater, 5.4% for diameters and 14.1% for counts, suggesting that pure counting and measurement variation within photographs is small in relation to “real” variations.

DISCUSSION

When mechanical properties of the colon in health and disease have been discussed, interest has tended to focus on the muscae-
The submucosa of the human colon is vital to the strength and distensibility of the colon (Watters, 1983; Watters et al., 1985), and little is known about the organisation and fine structure of this layer.

Both type I and type III collagen are found in the intestine (Epstein and Munderloh, 1975), and the submucosa of the colon is composed almost entirely of collagen. While marked degeneration of the muscle was shown to occur soon after death, and during immersion in 10% saline, there are no detectable changes in the submucosa within 48 hr of death, nor after immersion in saline for 72 hr, on either light or electron microscopy. “Delamination” of the bowel wall, as first described by de Carvalho (1973), is facilitated by prior immersion in 10% NaCl solution, and light microscopy confirms successful isolation of submucosa.

The use of hypertonic solutions of NaCl might be expected to produce tissue dehydration, resulting in fibril shrinkage. As all the specimens were treated in an identical fashion, it is to be expected that any resultant morphological variations would be uniform. Another potential area of variation is the stretching and pinning out of the submucosal specimens. This is more likely to affect the fibres than the fibrils.

Several layers of collagen fibres make up the submucosa of the human colon, and this contrasts with the three-layered structure described in the small intestine of rats studied by Orberg et al. (1982) and by Klein et al. (1983). Orberg et al. (1983) suggested that, when the colon is distended, the angles between the collagen fibres alter to accommodate the stretching of the colonic wall. This must entail movement between the submucosal layers, and the presence of fibres which cross between the layers is in keeping with this, as these may anchor the layers together, preventing shearing damage and

### Table 1

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Time after death (hr)</th>
<th>A (nm)</th>
<th>B (nm)</th>
<th>C (nm)</th>
<th>D (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>F</td>
<td>18</td>
<td>75 (74)</td>
<td>77 (69)</td>
<td>60 (57)</td>
<td>75 (75)</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>0</td>
<td>94 (97)</td>
<td>104 (96)</td>
<td>78 (76)</td>
<td>96 (91)</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>24</td>
<td>94 (92)</td>
<td>86 (84)</td>
<td>—</td>
<td>94 (93)</td>
</tr>
<tr>
<td>28</td>
<td>F</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>70 (66)</td>
</tr>
<tr>
<td>33</td>
<td>F</td>
<td>12</td>
<td>78 (74)</td>
<td>75 (79)</td>
<td>73 (75)</td>
<td>56 (56)</td>
</tr>
<tr>
<td>36</td>
<td>F</td>
<td>18</td>
<td>60 (39)</td>
<td>79 (78)</td>
<td>60 (68)</td>
<td>54 (46)</td>
</tr>
<tr>
<td>41</td>
<td>F</td>
<td>24</td>
<td>77 (83)</td>
<td>72 (81)</td>
<td>77 (80)</td>
<td>51 (48)</td>
</tr>
<tr>
<td>45</td>
<td>F</td>
<td>10</td>
<td>71 (72)</td>
<td>64 (61)</td>
<td>56 (49)</td>
<td>72 (78)</td>
</tr>
<tr>
<td>60</td>
<td>F</td>
<td>24</td>
<td>75 (77)</td>
<td>59 (55)</td>
<td>77 (80)</td>
<td>69 (66)</td>
</tr>
<tr>
<td>69</td>
<td>F</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>52 (50)</td>
</tr>
<tr>
<td>72</td>
<td>M</td>
<td>46</td>
<td>63 (69)</td>
<td>71 (71)</td>
<td>57 (68)</td>
<td>49 (56)</td>
</tr>
<tr>
<td>75</td>
<td>M</td>
<td>16</td>
<td>88 (87)</td>
<td>80 (78)</td>
<td>73 (72)</td>
<td>—</td>
</tr>
<tr>
<td>75</td>
<td>F</td>
<td>36</td>
<td>80 (81)</td>
<td>91 (86)</td>
<td>74 (76)</td>
<td>61 (53)</td>
</tr>
<tr>
<td>75</td>
<td>F</td>
<td>24</td>
<td>72 (72)</td>
<td>65 (62)</td>
<td>49 (56)</td>
<td>58 (61)</td>
</tr>
<tr>
<td>77</td>
<td>M</td>
<td>30</td>
<td>69 (72)</td>
<td>49 (49)</td>
<td>66 (67)</td>
<td>58 (58)</td>
</tr>
<tr>
<td>77</td>
<td>F</td>
<td>24</td>
<td>70 (67)</td>
<td>70 (59)</td>
<td>67 (68)</td>
<td>48 (48)</td>
</tr>
<tr>
<td>78</td>
<td>F</td>
<td>18</td>
<td>89 (88)</td>
<td>83 (75)</td>
<td>65 (60)</td>
<td>79 (77)</td>
</tr>
<tr>
<td>81</td>
<td>F</td>
<td>36</td>
<td>78 (85)</td>
<td>62 (59)</td>
<td>56 (64)</td>
<td>58 (75)</td>
</tr>
<tr>
<td>83</td>
<td>M</td>
<td>18</td>
<td>67 (65)</td>
<td>70 (65)</td>
<td>41 (41)</td>
<td>68 (59)</td>
</tr>
<tr>
<td>96</td>
<td>M</td>
<td>48</td>
<td>72 (55)</td>
<td>53 (48)</td>
<td>63 (65)</td>
<td>50 (48)</td>
</tr>
</tbody>
</table>

Note: M, male; F, female. Data are available for (D) only, in two operative patients who had sigmoid colectomy only, and two specimens are missing due to errors in processing.
TABLE II
Details of 20 Patients Showing Counts (per \(\mu m^2\)) of Collagen Fibrils in Ascending (A), Transverse (B), Descending (C), and Sigmoid (D) Colon, with Replicate Data in Parentheses

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Time after death (hr)</th>
<th>Fibril count (per (\mu m^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>F</td>
<td>18</td>
<td>159 (171)</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>0</td>
<td>104 (104)</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>24</td>
<td>78 (75)</td>
</tr>
<tr>
<td>28</td>
<td>F</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>33</td>
<td>F</td>
<td>12</td>
<td>127 (147)</td>
</tr>
<tr>
<td>36</td>
<td>F</td>
<td>18</td>
<td>159 (136)</td>
</tr>
<tr>
<td>41</td>
<td>F</td>
<td>24</td>
<td>104 (84)</td>
</tr>
<tr>
<td>45</td>
<td>F</td>
<td>10</td>
<td>145 (124)</td>
</tr>
<tr>
<td>69</td>
<td>F</td>
<td>46</td>
<td>168 (153)</td>
</tr>
<tr>
<td>72</td>
<td>M</td>
<td>16</td>
<td>116 (107)</td>
</tr>
<tr>
<td>75</td>
<td>M</td>
<td>36</td>
<td>113 (113)</td>
</tr>
<tr>
<td>75</td>
<td>M</td>
<td>24</td>
<td>136 (133)</td>
</tr>
<tr>
<td>77</td>
<td>M</td>
<td>30</td>
<td>165 (171)</td>
</tr>
<tr>
<td>78</td>
<td>F</td>
<td>18</td>
<td>95 (116)</td>
</tr>
<tr>
<td>81</td>
<td>F</td>
<td>36</td>
<td>139 (107)</td>
</tr>
<tr>
<td>83</td>
<td>M</td>
<td>18</td>
<td>234 (208)</td>
</tr>
<tr>
<td>96</td>
<td>M</td>
<td>48</td>
<td>188 (220)</td>
</tr>
</tbody>
</table>

A B C D

- 124 (133) 110 (124) 124 (139)
- 90 (95) 110 (124) 113 (98)
- 87 (78) — — 81 (75)
- 127 (121) 133 (124) 205 (194)
- 133 (130) 176 (179) 197 (246)
- 121 (110) 147 (136) 197 (237)
- 168 (156) 205 (257) 113 (116)
- 173 (185) 263 (173) 324 (303)
- 118 (116) 176 (173) — —
- 110 (110) 124 (130) 191 (223)
- 153 (188) 286 (283) 225 (179)
- 251 (254) 168 (171) 234 (263)
- 165 (173) 168 (197) 266 (283)
- 139 (147) 194 (194) 116 (127)
- 199 (165) 182 (130) 234 (162)
- 165 (173) 168 (197) 165 (179)
- 199 (236) 173 (171) 228 (246)

Note. M, male; F, female. Data are available for (D) only, in two operative patients who had sigmoid colectomy only, and two specimens are missing due to errors in processing.

serving as “ pivots” for rotation of the layers. The diameter of the human collagen fibrils is similar to that found in the rat studies (Orberg et al., 1982), varying from 48 to 104 nm.

The submucosa is an interesting aspect of the anatomy of the colon which is relatively unexplored. The techniques described in this paper have been developed to give insights into the ultrastructure of the submucosa in different areas of the colon.

The authors thank Mr. John Bode, Mr. Lawrence Brett, Mr. David Fairley, and Miss Janis Tocher for preparing specimens for electron microscopy.

REFERENCES

Submucosal collagen changes in the normal colon and in diverticular disease

H.J. Thomson, A. Busuttil, M.A. Eastwood, A.N. Smith and R.A. Elton

1 Gastrointestinal Unit and 2 Pathology Department, Western General Hospital, and 3 Medical Statistics Unit, University of Edinburgh, Edinburgh, Scotland

Abstract. Full thickness specimens of normal colon (n=15), and colon from patients with diverticular disease (n=5) were obtained at operation or autopsy. In the isolated submucosa the ultrastructure of the constituent collagen fibres was examined by transmission electron microscopy. Collagen fibrils in the left colon became smaller (p<0.001) and more tightly packed (p<0.001) than those in the right colon with increasing age. This difference is accentuated in diverticular disease (p<0.01). Factors which contribute to the development of colonic diverticulosis, such as raised intraluminal pressure, may be responsible for premature change in submucosal structure.

The normal colon has both propulsive and storage functions, and is subject periodically to distension and to considerable variations in intraluminal pressure. Increased colonic motility with exaggerated segmentation may be a factor in the aetiology of diverticular disease [1-3]. Although little information is available about structural changes in the colonic wall, Whiteway and Morson [4] have described elastosis in the taeniae coli in this condition, which may be responsible for contracture of the taeniae with corrugation of the circular muscle.

In 1891 Halsted [5] demonstrated that, when the bowel was stretched between clamps, the submucosa remained intact after disintegration of the mucosa and muscularis propria, and concluded that the intrinsic strength of the bowel wall is vested in the submucosa. Mechanical aspects of colonic function were investigated by Watters et al. [6, 7] who showed that the tensile strength and ‘burst strength’ of the human colon are indeed dependent upon the integrity of the submucosa. Lord et al. [8] using scanning electron microscopy, showed an irregular reticular pattern of fine collagen fibres with a varying arrangement at different depths in the submucosa. Nevertheless, detailed examination of this layer of the colonic wall in health and disease has yet to be fully described.

The submucosa consists of a network of collagen fibres. As in collagen elsewhere, these fibres are bundles of collagen fibrils which in turn are composed of tropocollagen molecules covalently bonded together in register, giving the characteristic banded appearance observable on electron microscopy. In this study the ultrastructure of the collagen fibres has been examined in isolated human colonic submucosa. Different regions of the colon have been compared, and the variation of submucosal structure with age and sex examined in both normal colons and in diverticular disease.

Materials and methods

Full thickness specimens were obtained from the ascending (A), transverse (B), descending (C) and sigmoid (D) colon of 20 patients (aged 9–96 years, mean 57 years; see Table 1). Seventeen were autopsy specimens: 8 patients had died of non-colonic malignant disease, 4 from cardiac or cerebrovascular causes, 3 from bronchopneumonia, 1 from encephalitis and 1 from small bowel strangulation. In 12 patients there was no evidence of colonic disease, and 5 exhibited macroscopic changes of diverticulosis. In all the latter patients there were abundant diverticula present, but there were no pericolonic adhesions nor evidence of diverticulitis either macroscopically or histologically, and no record in the case-notes of complications of diverticular disease. All post-mortem specimens were taken within 48 h of death, as preliminary studies had shown loss of integrity of the submucosal collagen structure in specimens removed after longer periods following death. In addition, to ascertain whether the autopsy specimens accurately reflected the ‘in vivo’ situation, fresh operative specimens of colon were obtained from 3 patients who underwent colonic resection for intractable constipation. Our previous experience of such resections was that these colons show no histopathologically discernible abnormalities.

Representative transverse sections from each specimen were embedded in paraffin, conventionally stained, and examined by light microscopy to exclude any abnormality previously undetected. After immersion in 10% saline at 6°C for 72 h, it was possible to dissect out the submucosa from the other bowel coats, as described by De Carvalho [9]; this was confirmed by light microscopy. The submucosal specimens were pinned out and fixed in 5% glutaraldehyde in 0.1 M Na cacodylate for 24 h and then cut into 1–2 mm thick slices and washed with 0.1 M cacodylate for 24 h
Table 1. Details of 20 patients studied, showing diameters and counts of collagen fibrils in ascending (A), transverse (B), descending (C) and sigmoid (D) colon

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Time after death (h)</th>
<th>Fibril diameter (nm)</th>
<th>Count (/3.46 × 10^5 nm^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>18</td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>0</td>
<td>94</td>
<td>104</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>24</td>
<td>94</td>
<td>86</td>
</tr>
<tr>
<td>33</td>
<td>F</td>
<td>12</td>
<td>78</td>
<td>75</td>
</tr>
<tr>
<td>36</td>
<td>F</td>
<td>18</td>
<td>60</td>
<td>79</td>
</tr>
<tr>
<td>41</td>
<td>F</td>
<td>24</td>
<td>77</td>
<td>72</td>
</tr>
<tr>
<td>45</td>
<td>F</td>
<td>10</td>
<td>71</td>
<td>64</td>
</tr>
<tr>
<td>60</td>
<td>F</td>
<td>24</td>
<td>75</td>
<td>59</td>
</tr>
<tr>
<td>69</td>
<td>F</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>75</td>
<td>M</td>
<td>16</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>77</td>
<td>M</td>
<td>30</td>
<td>69</td>
<td>49</td>
</tr>
<tr>
<td>78</td>
<td>F</td>
<td>18</td>
<td>89</td>
<td>83</td>
</tr>
<tr>
<td>83</td>
<td>M</td>
<td>18</td>
<td>67</td>
<td>70</td>
</tr>
<tr>
<td>96</td>
<td>M</td>
<td>48</td>
<td>72</td>
<td>53</td>
</tr>
<tr>
<td>72'</td>
<td>M</td>
<td>46</td>
<td>63</td>
<td>71</td>
</tr>
<tr>
<td>75'</td>
<td>F</td>
<td>36</td>
<td>80</td>
<td>91</td>
</tr>
<tr>
<td>75'</td>
<td>F</td>
<td>24</td>
<td>72</td>
<td>65</td>
</tr>
<tr>
<td>77'</td>
<td>F</td>
<td>24</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>81'</td>
<td>F</td>
<td>36</td>
<td>78</td>
<td>62</td>
</tr>
</tbody>
</table>

| Patients with diverticular disease. Data are available for D only in 2 operative patients who had sigmoid colectomy only, and 2 specimens are missing due to errors in processing (M = male; F = female).|

dylate buffered sucrose (pH 7.3). The slices were treated with 1% osmium tetroxide followed by 1% uranyl acetate, and dehydrated through graded aqueous solutions of ethanol from 50% to 100%. After treatment with propylene oxide, and immersion in liquid araldite resin for 24 h they were embedded in fresh araldite resin which was polymerised for 48 h at 60°C. One-millimetre thick sections were cut and stained with toluidine blue in 1% borax, and then 60-90 nm sections were cut using a Reichert OMU2 ultratome. The orientation of the specimens was preserved during processing such that the final sections were cut perpendicular to the long axis of the colon, and these were mounted on copper grids, stained with saturated uranyl acetate in 50% ethanol followed by Reynolds lead acetate, and examined and photographed under the JEM 100 CX11 (JEOL) transmission electron microscope.

Measurements

The collagen fibrils in the collagen fibres were identified on the electron micrographs by their characteristic cross-banding, and their diameters in cross-section were measured. The maximum and minimum diameters of obliquely cut fibrils were recorded, the latter being considered as the actual diameter. The mean diameter of 10 contiguous fibrils, chosen at random from the middle of a fibre, was calculated from each specimen.

The fibril count per unit area was also determined. In order to take into account the varying angles at which different collagen fibrils had been sectioned, fibrils were counted on the prints at 50,000x magnification within a rectangular area measuring 6 cm on the short side. The long dimension of the rectangle was calculated by multiplying 6 cm by the ratio of the mean maximum to the mean minimum fibril diameter for that specimen, thus correcting the area for the obliquity of section (Fig. 1). Fibrils overlapping the edge of the designated area were included if more than half of the fibril appeared to be within the area. Fibrils were therefore counted per 36 cm² on the print (actual area 3.46×10⁵ nm², taking into account both the microscopic and print magnification).

Statistical methods

Diameters or counts in the different regions of the colon were compared by Wilcoxon signed-ranks tests. The relationships between diameters or counts and other factors were tested by Wilcoxon rank sum tests for binary factors (sex; presence of diverticular disease) or Kendall rank correlation coefficients for quantitative factors (age; time after death). The combined effects of age, time after death and presence of diverticular disease on the diameters and counts were tested by multiple linear regression analysis.

Results

Sample validity in “right” and “left” colon

The data collected on the 20 subjects studied are shown in Table 1. Reproducibility was assessed by analysis of five replicates taken from the same specimen: the coefficients of variation were 5.4% for diameters and 14.1% for counts. Repeat measurements and counts on every specimen gave correlation coefficients of 4.3% for diameters and 7.3% for counts.

The two regions of each side of the colon (i.e. A and B in the proximal colon, and C and D in the
Comparison of right and left colon

There was a significant tendency in all patients for the fibrils to be smaller on the left side of the colon than on the right (mean diameters 66 nm (± 11) and 78 nm (± 11) respectively; \( p < 0.001 \)), and for the fibril counts to be greater on the left side than on the right (58 (± 14)/3.46 \( \times \) 10^5 nm^2 and 46 (± 13)/3.46 \( \times \) 10^5 nm^2; \( p < 0.001 \)) (Figs. 2 to 4). The mean diameter of 73 nm and count of 51/3.46 \( \times \) 10^5 nm^2 in the three operative specimens of sigmoid colon are comparable with the overall left colon figures.

Age and sex comparisons, and time after death

There were no significant differences between the sexes for fibril diameter or count on either the right or left side of the colon, nor was there any significant relationship between time after death and diameter or count. The specimens from the three subjects
operated on for colon inertia showed no difference from autopsy specimens in either diameters or counts. Age showed an inverse correlation with diameter on the right ($p < 0.10$) and left ($p < 0.05$), that on the left being significant (Figs. 5, 6), and a correlation with count ($p < 0.05$ on both sides of the colon) (Figs. 7, 8). Thus the collagen fibrils in the colonic submucosa tend to become smaller and more closely packed together with increasing age.

**Diverticular disease**

On the left side of the colon fibril counts were significantly higher ($p < 0.05$) in those with diverticular disease, and fibril diameters tended to be lower in those with diverticular disease although without reaching statistical significance ($p < 0.10$). There were no corresponding changes in diverticular disease on the right side. In view of the correlations of fibrillar diameter and count with age, colonic site and presence or absence of diverticular disease, multiple regression analysis was applied to ascertain which of these findings remained significant after correction for the effects of the other factors. Fibril diameter and fibril count were significantly related to age on the left side ($p < 0.05$ for both). The findings for diverticular disease were no longer significant when corrected for age. However, the difference between the left and right colon was significantly greater in diverticular disease subjects for both fibril diameters ($p < 0.01$) (Fig. 3) and fibril counts ($p < 0.05$) (Fig. 4). This effect remained significant after accounting for age and time after death in the multiple regression. It is not clear, however, whether this is explained by an increase in diameter in the right colon in patients with diverticular disease, a decrease in diameter in the left colon or a combination of the two effects, since both are seen in
the data (Figs. 5, 6) but to a degree that does not achieve statistical significance. Similar arguments apply to the decrease in count in the right colon and the increase in count in the left colon (Figs. 7, 8).

Fibrillar area

In all the preceding analyses the results for fibril diameters and counts appear to mirror each other, i.e. they show similar but opposite trends, as illustrated by plotting diameter against count (Fig. 9, 10). These relationships follow the shape expected if the 'fibrillar area' (i.e. the percentage of each field occupied by fibrils) was independent of fibril diameter. Fibrillar area (FA) can be estimated by the formula:

\[ FA = \frac{\pi D^2 \times n}{4 \times 3.46 \times 10^5} \times 100\% \]

(D = mean fibril diameter (nm); n = number fibrils/area counted; 3.46 x 10^5 nm² = actual area of field counted taking into account the magnification).

Mean fibrillar areas were 59.8% (± 7.9) in the right colon, and 56.1% (± 7.1) in the left colon (the difference is not significant). The fibrillar areas did not relate significantly to any of the four other factors (age, sex, time after death and presence of diverticular disease), and this supports the idea that fibrillar area is constant regardless of other factors. The curves corresponding to fibrillar areas of 50% and 60% for the right and left sides of the colon are shown in Figures 9 and 10.

Discussion

The wall of the colon is subjected to considerable mechanical stresses, particularly on the left side where stool tends to be solid. It is also in the left colon that the high pressure motility disturbances of diverticular disease have been noted [1-3]. The structure and function of the muscular layers of the colonic wall have received considerable attention, and changes in the muscularis propria have been reported in diverticular disease [4]. The submucosa, however, despite the recognition that it is the strongest part of the colonic wall [5-7] has been less extensively studied. Such an omission may be due to the difficulty of studying the thin submucosal layer.

The technique of 'delamination' of the bowel wall used to isolate the submucosa was first described by De Carvalho [9]. Our successful adaptation of this method [10] was confirmed by light microscopy of the submucosal specimens. The ultrastructural results were reproducible, with no appreciable effects of post-mortem delay, provided this was no greater than 48 h. It was reassuring to find that measurements of fresh operative specimens of colon from patients with chronic constipation did not differ from those found in autopsy patients.

The submucosa consists almost entirely of a network of collagen fibres [8], whose constituent fibrils were easily identified on electron microscopy by their characteristic cross-banding. The diameter of the fibrils in the human colonic submucosa ranged from 41 nm to 104 nm (similar to the diameters found in studies of the submucosa in rats, which varied from 50 nm to 100 nm) [10]. Fibril counts in the human submucosa ranged from 27 to 112/3.46 x 10^5 nm² (78 to 324/µm²). There were no differences between the sexes in submucosal fibril count or diameter. Ageing, however, was associated with smaller, more tightly packed fibrils. There were no differences between ascending and transverse colon nor between descending and sigmoid colon. The fibrils in the left colon were significantly smaller and more closely packed than those in the right colon.
It is possible that these differences are developmental, the right colon being of midgut and the left colon of hindgut origin. However, studies relating the ultrastructure of various animal and human connective tissues to their function have shown that tensile strength and elasticity are related to the diameter of the fibrils which constitute the collagen fibres [12, 13]. This suggests that the structural changes described in this paper derive from the different mechanical stresses to which the connective tissue of each region is subjected. Furthermore the accentuation of the differences in collagen structure between the right and left colon in patients with diverticular disease may reflect the abnormally high pressures found in the colon in such cases. These changes, which are normally associated with ageing, are more pronounced in diverticular disease and may represent premature ageing in these patients.

Acknowledgements. The authors wish to thank Lawrence Brett, John Bode and David Fairley, Department of Pathology, Western General Hospital, and Janis Tocher, Teaching & Research Centre, Western General Hospital, for preparing specimens for electron microscopy.

References


Accepted 17 August 1987
In 1972, an uncontrolled study reported that fibre relieved the symptoms of diverticular disease. It was subsequently shown that it speeded intestinal transit and reduced intraluminal pressure in the diverticular colon. A controlled trial of the treatment of symptomatic diverticular disease with a high-fibre diet confirmed greater relief of symptoms with fibre than with a placebo and other trials have produced similar results. In the decade 1972–82 an increased intake of dietary fibre became widely accepted as the standard management of symptomatic uncomplicated diverticular disease. To determine whether the popularity of fibre treatment has influenced the course of diverticular disease in Scotland, the Scottish hospitals in-patient statistics for diverticular disease have been analysed in a fifteen-year period, the last ten of which fall within the 'bran era'.

METHODS AND DEFINITIONS

Requests were made to the Scottish Office Computer Service for analyses of the 1968–82 Scottish Hospital In-patient Statistics (SHIPS) data, aggregated from the information recorded on the SMR.1 completed for all hospital discharges, transfers or deaths. For convenience these are referred to as ‘admissions’ even though the two terms are not strictly synonymous, e.g. the number of discharges in a year will differ from the number of admissions. Only discharges with a principal diagnosis of diverticular disease were included in the analysis. A waiting list admission is one in which the patient was seen in the clinic and given a date for admission, while a booked admission is one in which the patient was given a date for a repeat admission.

RESULTS

Admission (rate and number) by age and sex

Table 1 shows the numbers and rates of admission, expressed as means over 5 year periods, for diverticular disease in Scotland from 1968 to 1982. The female admission rate per million of the population was 360 from 1968 to 1972, 424 from 1973 to 1977 and rose further to 472 from 1978 to 1982; male admission rates rose slightly from 233 to 246 and then to 248.

An analysis by age and sex shows that almost three-quarters (73 per cent) of female admissions were over 65 years, compared to a little over half (56 per cent) of male admissions. The population over 75 years showed the highest rates (Fig 1 and 2) and increased from 1,800 to 3,000 per million in females (65 per cent) and from 1,200 to 2,200 per million in males (84 per cent). In other age groups only 65 to 74 year old females showed a marginal increased rate. The only group with...
a fall in admission rates was females less than 45 years which decreased from 21.4 to 15.7 per million in the last five-year period but the numbers in the group are small and the finding must therefore be regarded as tentative (Table 1).

**Table 1**

Total numbers and rates of admission for diverticular disease in Scotland 1968-82, by sex and years

<table>
<thead>
<tr>
<th></th>
<th>MALE</th>
<th>FEMALE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Number</td>
</tr>
<tr>
<td>1968-72</td>
<td></td>
<td>584</td>
</tr>
<tr>
<td>1973-77</td>
<td></td>
<td>616</td>
</tr>
<tr>
<td>1978-82</td>
<td></td>
<td>616</td>
</tr>
</tbody>
</table>

**Figure 1**

Female admission rates by age groups over 15 years

**Figure 2**

Male admission rates by age groups over 15 years.
Table 2

Admission rate per million, age 44 years and under in Scotland: by sex and years

<table>
<thead>
<tr>
<th></th>
<th>MALE</th>
<th></th>
<th></th>
<th>FEMALE</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MALE</td>
<td>23.4</td>
<td>25.4</td>
<td>23.6</td>
<td>21.0</td>
<td>21.4</td>
<td>15.7</td>
</tr>
</tbody>
</table>

Admission by specialty and type of admission

Figure 3 shows admission rates for diverticular disease for male and female patients according to the specialty of admission. The majority were admitted under general surgeons. The rate of female surgical admissions rose over the study period, but the proportion of patients admitted as emergencies, waiting list or booked admissions remained constant. About 50 per cent of patients were admitted as emergencies, 25 to 30 per cent as waiting list admissions, and 11 per cent as booked admissions (Table 3).

Table 3

Percentage of patients as emergency, booked, waiting list, or transfer admissions over three 5-year periods

<table>
<thead>
<tr>
<th></th>
<th>MALE</th>
<th></th>
<th></th>
<th>FEMALE</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency</td>
<td>48</td>
<td>46</td>
<td>47</td>
<td>51</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>Booked</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Waiting list</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>26</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Transfer</td>
<td>11</td>
<td>13</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>
Surgery
Male patients had a higher colectomy rate than female patients throughout the study period and in all age groups (Fig 4). The colectomy rate was higher, the younger the patient. Over the years no consistent upward or downward trend could be detected in colectomy rates (Fig 5).

**Figure 4**

**COLECTOMY RATE % ADMISSION**
by age groups, mean 1968-82

**Figure 5**

**COLECTOMY RATE % ADMISSION**
Total population; by year

Admission by Health Board area
Figure 6 shows admission rates for diverticular disease in different Scottish Health Boards. For each Health Board two periods are illustrated, 1968 to 1977 and 1978 to 1982. An increase in the rate of admissions for the latter period is observed in all areas except Grampian. The highest rates were found in predominantly rural areas, e.g. Highland, Tayside and Grampian.

Discussion
These results confirm the trend of earlier reports⁶,⁷ and suggest that the widespread advocacy of high-fibre diets in the treatment of diverticular disease has not had much impact on admission rates. The increase in the rate of admissions in recent years is in keeping with the general increase in admission rates for conditions of comparable severity (those requiring surgical intervention) in the same age groups.

To cover all cases of complicated diverticular disease, admissions for them were grouped.

Surgery
In all areas, diverticulitis was excluded. The marked increase in episodes of diverticulitis in the years leading up to a local epidemic of peri-diverticulitis is not unexpected. Yet only 2% of the major dia-

ucle of diverticulitis were admitted...
DIVERTICULAR DISEASE OF THE COLON IN SCOTLAND OVER 15 YEARS

DIVERTICULAR DISEASE
Admission rates by Health Boards

<table>
<thead>
<tr>
<th>Area</th>
<th>1968-77</th>
<th>1978-82</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCOTLAND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Islands</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dumfries and Galloway</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forth Valley</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tayside</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lothians</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grampian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lanarkshire</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moray</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greater Glasgow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fife</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angus and Orkney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ayrshire and Arran</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>600</td>
</tr>
</tbody>
</table>

Rate per million

Figure 6

has not reduced hospital admissions in Scotland over the past ten years. Both total admissions and admission rates for males and females have increased, but the rise has possibly lessened in the second five-year period after the popularisation of increased dietary fibre. In the larger female population, the increase has been marked and sustained over a ten-year period. The increase is almost completely accounted for by an elderly population aged over 75 years. This group would have been 65 years or above at the time of introduction of high-fibre diets, and a high proportion of them conceivably would have already developed severer forms of diverticular disease. That their hospital admission rates have increased since then may be a reflection of a number of factors, of which a main possibility is that fibre may be more effective in relieving symptoms than in the prevention of complications which could occur more often in the longer living age group (those over 75 years and predominantly female).

To some extent data on diverticular disease in a hospital patient population cover only the more severely symptomatic ones, but include the most complicated forms of the disease. This is supported by the fact that most of the admissions in this period of increase have been surgical ones, and about half of them were admitted as emergency.

Surgical admission, elective or emergency, can be attributed to the need to exclude carcinoma, investigate possible obstruction and abort inflammatory episodes. Thus, a high-fibre diet after the development of diverticulosis may not arrest progress of the disease to the severe symptomatic state, nor prevent the development of complications; bowel hypertrophied from years of adaptation to a low-residue diet, especially if fibrosed from recurrent bouts of peridiverticulitis, is not likely to return to normal on a high-fibre diet.

Yet only 10 per cent of the admissions to surgical beds come to operation as the majority respond to conservative measures. That the proportions of patients admitted as emergencies, booked admissions, waiting list admissions, or transfers
were constant throughout the period examined would tend to imply that the natural history of the disease process itself has not become more aggressive over the period of study and seems also to allow another conclusion that the best criteria for admission have not changed much during the period surveyed. The colectomy rates for diverticular disease have not shown any consistent upward trend over the years is also reassuring. The younger male patient is the most likely to be selected for surgery according to our findings. This may be the result of the tendency of an active wage earner to wish to be rid of his problem rather than to go on a protracted course of medical treatment.

The higher admission rates in rural areas might be due to a lower intake of fresh fruits and vegetables which are transported from central depots. Retail prices of these were relatively high in outlying areas at the time of this survey.

The movement of young people away from rural areas leaving them with a greater proportion of elderly people may in part explain different admission rates for diverticular disease. This begs the question of whether the increase in admissions could be explained by the increase in the proportion of elderly persons in the general population. The increase, however, involved absolute rates as well as admission numbers and is against this explanation. Within the over 75 year age group numbers of those in their 80s or even 90s may have increased disproportionately due to increasing longevity. Our data do not allow for further sub-division of age groups into decades to examine whether the overall rural increase can be accounted for by the admission of more patients in the eighth and ninth decade or by more ready access to hospital admission.

The period covered by the present study may be too short to reveal whether there is any benefit from change of fibre intake. Relatively young patients may be expected to be the ones with a declining incidence of diverticular disease view of its slow onset and presentation at or around 40 or 50 years of age.

It seems clear from our survey, which will be extended, that if there has been a change in fibre intake habits in those over the age of 50 it has not had an effect on the risk of developing diverticular disease nor in reducing complications.

REFERENCES
Colonic Diverticulosis in Patients with Colorectal Cancer and in Controls

A. McCallum, M. A. Eastwood, A. N. Smith & P. M. Fulton
Gastro-intestinal Unit, University of Edinburgh, Western General Hospital, and Dept. of Community Medicine, University of Edinburgh, Usher Institute, Edinburgh, U.K.


The barium enemas of 119 patients with colorectal cancer and 119 age-matched controls were examined for evidence of diverticula. Amongst men, 39.6% of patients with colorectal cancer had diverticulosis, compared with 50% in the control group. In the women, 39.3% of patients with colorectal cancer had diverticular disease, compared with 36% of the controls. There appears to be no significant aetiologic association between the two conditions, since they do not occur together more frequently than in controls, although each is reputedly the result of fibre lack.

Key words: Colorectal cancer; dietary fibre; diverticular disease

Prof. A. N. Smith, M.D., F.R.C.S.Ed., F.R.S.E., Gastro-intestinal Unit, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, U.K.

Colorectal cancer and diverticular disease of the colon are both common diseases in clinical practice. The incidence of the conditions is increasing, and it has been suggested that the aetiology is environmental (1). Nutritional factors may be involved, in that a deficiency of dietary fibre is thought to be a common cause of both problems (2,3). Were such the case, one would expect overlap of the two conditions.

In this study we have looked retrospectively at the co-existence of colorectal carcinoma and diverticulosis in barium enemas performed for colonic carcinoma and compared this with the diverticulosis found in a control group of patients who had had barium enemas in the same hospital at the same period but who did not have colorectal carcinoma as their final diagnosis.

PATIENTS AND METHODS

The barium enema diagnosis of colorectal carcinoma from the Dept. of Radiology was confirmed by histopathology at the Dept. of Pathology at the Western General Hospital. All patients meeting these conditions aged 40 years or more were identified for the years 1980 to 1984. They totalled 126; of these, 2 patients were excluded because they were shown to have a solitary malignant polyp. Four other patients were excluded, three women and one man because the tumour was obstructing and prevented the whole of the left side of the colon from being seen. One further female patient was excluded because of a previous resection, leaving 58 male and 61 female cases.

This group of 119 cases was compared with 119 (58 male and 61 female) control patients who had had a barium enema in the investigation of alimentary symptoms but in whom no carcinoma was shown or diagnosed. The controls were obtained from the 900 barium enemas done in the Dept. of Radiology of the Western General Hospital each year.

Controls were derived by pairing each cancer patient with the next patient whose barium enema showed no carcinoma and who could also be
Table I. Colonic diverticulosis occurring in cancer patients and in controls by age and sex

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cancer</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>75+ years</td>
<td>29/58</td>
<td>22/61</td>
<td></td>
</tr>
<tr>
<td>65-74 years</td>
<td>23/58</td>
<td>24/61</td>
<td></td>
</tr>
<tr>
<td>55-64 years</td>
<td>9/15</td>
<td>7/16</td>
<td></td>
</tr>
<tr>
<td>Under 54 years</td>
<td>8/15</td>
<td>6/16</td>
<td></td>
</tr>
</tbody>
</table>

The barium enema films of both patients and controls were presented to two clinically trained observers who examined each set of films for the presence and extent of diverticula. The criteria for the diagnosis of diverticular disease were 1) obvious multiple diverticula involving the greater part of the colon; 2) multiple localized diverticula; and 3) scattered colonic diverticula and circular muscle hypertrophy of the pelvic colon.

Most patients had obvious diverticular disease characterized by many diverticula in the descending and sigmoid colon.

RESULTS

The results are shown in Tables I and II. In Table I, amongst the men, 23 out of 58, or 39.6%, of the colorectal cancer patients had diverticular disease of the colon, compared with 29 out of 58, or 50%, incidence of diverticulosis in the control group. In the female group, 24 of 61, or 39.3%, of the patients with colorectal cancer had diverticular disease, and 22 out of 61, or 36%, of the control group had diverticular disease. These differences are not statistically significant. McNemar's test was applied to the pairs of patients and controls, and no significant difference was found. There were no significant differences (Table I) in the age groups compared in either sex.

DISCUSSION

The co-existence of colorectal carcinoma and diverticulosis has been examined by identifying matched for sex and age within a 5-year limit. The barium enema films of both patients and controls were presented to two clinically trained observers who examined each set of films for the presence and extent of diverticula. The criteria for the diagnosis of diverticular disease were 1) obvious multiple diverticula involving the greater part of the colon; 2) multiple localized diverticula; and 3) scattered colonic diverticula and circular muscle hypertrophy of the pelvic colon.

Most patients had obvious diverticular disease characterized by many diverticula in the descending and sigmoid colon.

The results are shown in Tables I and II. In Table I, amongst the men, 23 out of 58, or 39.6%, of the colorectal cancer patients had diverticular disease of the colon, compared with 29 out of 58, or 50%, incidence of diverticulosis in the control group. In the female group, 24 of 61, or 39.3%, of the patients with colorectal cancer had diverticular disease, and 22 out of 61, or 36%, of the control group had diverticular disease. These differences are not statistically significant. McNemar's test was applied to the pairs of patients and controls, and no significant difference was found. There were no significant differences (Table I) in the age groups compared in either sex.

The co-existence of colorectal carcinoma and diverticulosis has been examined by identifying paired data comparisons of men and women combined.

<table>
<thead>
<tr>
<th>Colorectal cancer cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diverticulosis</td>
</tr>
<tr>
<td>Controls</td>
</tr>
<tr>
<td>Diverticulosis</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

McNemar's test was applied to the untied pairs; chi-square = 0.075; DF = 1. No significant difference.
the frequency of diverticular disease in a series of
patients with colorectal cancer and comparing it
with that in controls. Clinicians and pathologists
tend to omit diverticulosis when a colorectal carci
noma is present because of the substantially
greater importance of the latter. However, the
distortion and irregularity associated with the
presence of diverticula (4) may also conceal a
carcinoma lurking in the sigmoid or descending
colon. This problem is diminished, however, by
choosing for examination a group who already
have carcinoma of the colon for the assessment
of the accompanying incidence of diverticular
disease. It has been suggested that in the investi
gation of patients with diverticular disease 8% have
unsuspected carcinoma and 23% have polyps that can
only be shown by colonoscopy (5). In the numbers that we have studied such an
error is sufficiently small not to alter the results
and conclusions. None of the patients in the con
trol group who were studied between 1982 and
1983 were subsequently admitted for carcinoma
of the colon.

The study presented several methodologic dif
ficulties, being hospital groups. The patients com
prised only those who had had a barium enema;
other 'concurrent' cancer patients who required
emergency surgery and who therefore did not
have a barium enema for diagnosis are not
included. The controls had to be hospital patients
who had had a barium enema since, for ethical
reasons, asymptomatic subjects from the general
population could not be asked to undergo such a
procedure. They were drawn from patients inves
tigated at hospital but with no major pathologic
bowel findings. Thus a bias towards those with
bowel problems was introduced, although the
main symptoms of the two groups were broadly
similar. If the control group were inadvertently
more likely to have diverticular disease, any
relationship between carcinoma and diverticular
could be diminished.

But if a common nutritional 'fibre lack' were
the cause of the development of colonic cancer
and diverticular disease, a significantly high co
existence of the two problems might have been
expected. Since the prevalence of diverticular
disease in the control group and the colorectal
cancer group is the same in our study, it is unlikely
that there is a common aetiology. Speers & Bacon
(6) reviewed the simultaneous occurrence of
diverticular disease and carcinoma in seven sets
and found that there was co-existence in only 0.4
8.4% of cases. Whatever the particular action of
dietary fibre in each condition, it does not seem
to act as a factor of equal importance in the
presentation of colorectal cancer and diverticular
disease.

REFERENCES

1. Medical aspects of dietary fibre (Report of the Roy
College of Physicians). Pitman Medical, London
1980
2. Painter NS. Diverticular disease of the colon.
Heinemann Medical Books, London, 1975
3. Burkitt DP, Trowell HC. Refined carbohydrates,
fats and disease: some implications of dietary fibre
4. Glerum J, Agenant D, Tytgat GN. Endoscopy 19
9, 228-230
5. Aldridge MC, Sim AJW. Lancet 1986, 2, 833-44
6. Speers CS, Bacon HE. Surgery 1986, 52, 733-76

Received 1 July 1987
Accepted 20 October 1987
Complications of diverticular disease and non-steroidal anti-inflammatory drugs: a prospective study

Previous retrospective studies have suggested an association between consumption of non-steroidal anti-inflammatory drugs (NSAIDs) and the complications of diverticular disease. Ninety-two patients were entered into a prospective study of the complications of diverticular disease over a 3 year period; 31 were taking NSAIDs, compared with only four age- and sex-matched controls from a representative general practice (P < 0.001). A second control group comprised 306 patients with cancer of the colon, in whom NSAID consumption was again significantly lower than in patients with diverticular disease (22 of 306 versus 31 of 92, P < 0.001). Of the 31 patients taking NSAIDs, 19 presented with a perforation or peritonitis. By contrast, only eight of the 61 patients not taking NSAIDs had such complications (P < 0.001). Eleven patients presented with bleeding of whom five were taking NSAIDs and six were not. Patients admitted with complications of diverticular disease have a high incidence of NSAID intake, and it appears that NSAID consumption is associated with a more severe form of the disease.

Keywords: Diverticular disease, complications, non-steroidal anti-inflammatory drugs

Diverticular disease is common in Western society but its complications are relatively uncommon. However, the number of operations performed each year for complications of diverticular disease in Lothian over the period 1980-1988 has increased from 47 to 70. A previous study suggested an association between the consumption of non-steroidal anti-inflammatory drugs (NSAIDs) and bleeding or perforation of the small and large bowel. The number of prescriptions dispensed for NSAIDs in the UK has increased from 76 million in 1987 to 22 million in 1985; this increase in prescribing habits is most marked in women over 65 years of age.

Previous studies suggesting an association between the complications of diverticular disease and NSAIDs were retrospective and thus the accuracy of a history of NSAID consumption and its recording in the case record remains suspect. We have performed a prospective study of all patients admitted to our surgical unit over a 3 year period in whom a final diagnosis of diverticular disease was made. By comparing NSAID consumption in patients with both uncomplicated and complicated disease with appropriate controls, we sought to establish whether a relationship existed between NSAID consumption and the development of a complication of diverticular disease.

Patients and methods

All patients admitted to the Western General Hospital, Edinburgh with abdominal pain were studied prospectively between July 1986 and July 1988. All patients in whom a diagnosis of diverticular disease was considered but who did not come to operation had a colonoscopy and/or barium enema performed. All patients in whom a final diagnosis of diverticular disease was confirmed by these examinations were included in the study. Complications of diverticular disease were confirmed under the headings localized diverticulitis, generalized peritonitis (including perforation) and bleeding. Localized diverticulitis included patients in whom a diagnosis of peridiverticulitis or periostitis was made on the basis of clinical signs in the abdomen supported by a leukocytosis. The diagnosis of perforated diverticulitis was confirmed by laparotomy in each case. Bleeding diverticular disease was diagnosed on the basis of haemorrhage thought to be from the lower gastrointestinal tract with subsequent confirmation of diverticular disease by colonoscopy and barium enema.

Information about drugs being taken by the patients was specifically sought on admission by detailed interview. The indication for NSAIDs together with frequency and duration of intake was recorded in addition to any previous history of symptomatic diverticular disease.

For each patient with diverticular disease an age- and sex-matched control, not known to have diverticular disease, was selected from the hospital catchment area. Current NSAID prescription in these control patients was recorded. A second control group comprised 306 colorectal cancer patients whose clinical details (including NSAID consumption) are recorded as part of a prospective audit. They had an F:M ratio of 1:1 and a median age of 68 years (range 44-85 years). These patients were studied to control for possible bias in NSAID intake caused by the presence of lower bowel symptoms. Statistical analysis between groups was by ^2 test with Yates' correction when groups contained less than ten subjects.

Results

Ninety-two patients (57 women and 35 men, F:M ratio 1:6:1) who fulfilled the diagnostic criteria for complications of diverticular disease were recruited in the study period. The median age was 70.9 years with a range of 35-93 years. At the time of admission, 31 patients (34 per cent) were taking NSAIDs. The indications for NSAID in these 31 patients were osteoarthritis in 32 per cent, rheumatoid disease in 29 per cent, back pain in 16 per cent and other indications in 23 per cent. Patients took 13 different types of NSAID; in 29 cases these were at the dose prescribed by a medical practitioner, while two patients were self-medicating with ibuprofen. The duration of NSAID intake before admission ranged from 4 weeks to 5 years.

Only seven of the 31 patients taking NSAIDs presented with diverticulitis, but 47 of the 61 who were not taking NSAIDs presented in this way (P < 0.001). By contrast, 19 of the 31 patients taking NSAIDs presented with perforation compared with only eight out of 61 not taking NSAIDs (P = 0.001). Of the 11 patients presenting with bleeding, five were taking
NSAIDs and six were not. This difference was not statistically significant. Five patients in the NSAID group had a previous history of diverticular disease, as did 15 in the non-NSAID group. There was no significant difference in age between the NSAID group (median 75 years, range 35–89 years) and the non-NSAID patients (median 67 years, range 43–94 years).

The possibility exists that NSAID consumption might merely be an indicator of rheumatoid disease or corticosteroid consumption, conditions which themselves might be associated with complications of diverticular disease. Ten patients in the NSAID group had rheumatoid disease while none of the 61 patients not taking NSAIDs had this diagnosis. In the NSAID group six patients, all with rheumatoid disease, were on corticosteroid treatment while four in the non-NSAID group were taking steroids. Even with exclusion of these 14 patients from the analysis, patients taking NSAIDs remain significantly more likely to present with perforation (12 of 21) than those not taking NSAIDs (7 of 37). Of the 21 patients taking NSAIDs, four presented with local signs compared with 44 of 37 not taking NSAIDs (P < 0.001). As before, there was no significant difference in NSAID consumption in patients presenting with bleeding.

NSAID consumption was compared between 92 patients presenting with diverticular disease and age- and sex-matched controls. Of the 92 patients with diverticular disease, 31 (34 per cent) were taking NSAIDs. By contrast only four (4 per cent) of the 92 age- and sex-matched controls were taking NSAIDs (P < 0.001). Of the 306 disease-positive controls, 22 (7.2 per cent) were taking NSAIDs at the time of admission to hospital, which is significantly fewer than the patients with diverticular disease (P < 0.001). There was no significant difference in the NSAID intake of the two control groups.

Discussion

This is the first prospective study of the association between NSAID consumption and complications of diverticular disease. Fewer patients with localized diverticulitis were taking NSAIDs at the time of presentation, a finding which gives even greater emphasis to the significant excess of NSAID consumption in patients presenting with perforation. This is the strongest evidence to date for a relationship between NSAID consumption and perforation of diverticular disease. The association between NSAID consumption and upper gastrointestinal bleeding has been the subject of much debate6. Unlike Langman et al.3 we found no association with bleeding diverticular disease, possibly because our study included relatively few of these patients but more probably because their study included patients with haemorrhage from other sites within the intestine.

The proportion of age- and sex-matched control patients taking NSAIDs in our study was 4 per cent compared with 7.2 per cent in our large bowel cancer control group and 9.3 per cent in Langman’s series of hospital controls. Langman et al.3 suggest that some 10 per cent of the population over 60 years of age have recorded NSAID intake. The proportion may be less in our series because 19 of the patients (20 per cent) were less than 60 years of age. All of the age- and sex-matched control patients recorded as taking NSAIDs in our study were over 60.

NSAID consumption as judged by the number of prescriptions written is increasing4, as are the number of operations for perforated diverticular disease in our area5. This study provides further evidence of a causal relationship between these two observations.

Possible mechanisms for NSAID-associated perforation of diverticular disease may be the direct anti-inflammatory action of these agents on the bowel itself or their inhibitory effect on neutrophil function1–7 with a resultant failure of the inflammatory response to localize the disease process.

Our study, in common with previous retrospective studies3,5, has considered only prescribed NSAIDs. Ibuprofen is now available without prescription but only two of our patients were taking this preparation. We have no information about possible ibuprofen consumption in the general practice controls.

NSAIDs produce relief from joint pain and are increasingly prescribed in patients over 60 years of age, about one-third of whom may have diverticular disease. The balance of pain relief against inducing perforation in diverticular disease falls heavily in favour of pain relief. The minority ( < 25 per cent) of patients in this series were known to have diverticular disease at the time an NSAID was prescribed. Given the frequency of joint pain and the relative infrequency of perforated diverticular disease in Western society, it would be inappropriate to withhold NSAIDs even in patients known to have diverticular disease. Nevertheless, the clear association of perforated diverticular disease with NSAIDs should be recognized by all doctors prescribing these drugs.

Acknowledgements

We thank the general practitioners of Stockbridge Health Centre, Edinburgh for allowing access to their records and Mr J. M. Slattery, Department of Clinical Neurosciences, Western General Hospital, Edinburgh for advice on the statistical analysis.

References


Paper accepted 1 July 1990
Strength of the colon wall in diverticular disease

Studies of the aetiology of diverticular disease of the colon have been focused on intraluminal pressure for almost three decades. It is only relatively recently that the mechanical properties of the wall of the colon have been examined. The tensile strength and elasticity of the colon decline with age and this is most marked in the left colon which is the narrowest and thickest part. This review discusses the case that the mechanical properties of the bowel wall are key factors in the development of diverticular disease. The potential role of high fibre diets in reducing the pressure changes which may stress the colon wall in this disease is also considered.

Keywords: Colonic wall, pressure, collagen, fibre, diverticula

Current ideas on the aetiology of diverticular disease focus on the role of intraluminal pressure and only recently has the strength of the colon wall been implicated. The mechanical properties of most tissues change with age and diverticular disease of the colon is particularly common towards the end of life. To most surgeons, the hallmark of diverticular disease is, apart from the diverticulum, a sigmoid colon with a thick muscle coat. But, as is well known to most surgeons, diverticula also occur along the entire length of the thin, atrophic colon which suggests that a raised intraluminal pressure is not a sine qua non.

Further evidence suggests that there are no additional smooth muscle cells in the wall of the bowel in diverticular disease and that the thickened muscle is often the result of the taeniae coli contracting and bunching the sigmoid colon together so that its thick muscle encroaches on the lumen.

This review argues the case for considering the mechanical properties of the bowel wall as important in understanding the "wear and tear" of any pressure changes that affect it, secondary to the narrowing of the lumen, and sees a role for high fibre diets in minimizing or avoiding these changes.

Colonic muscle and the pressure theory of diverticular disease

Diverticular disease is the most common disorder of the human colon and has an important bearing on the health of a large percentage of the elderly Western population. A common change in the wall of the colon is that its muscle coat is markedly thickened, giving rise internally to a narrow lumen, redundant mucosa apparently mildly obstructing it further. The diverticula form in two rows between the mesenteric and antimesenteric taeniae as mucosal extrusions outside the colonic wall. For almost the last quarter of the century since Arfwidsson and Kock and Painter first described raised intraluminal pressure in the sigmoid colon of patients suffering from diverticular disease, attention has been paid to pressure phenomena in the generation of the diverticula.

Moality was first shown to be greater in response to food and cholinergic stimulation in symptomatic diverticular disease, but this is not invariably so since the gastrocolic reflex elicited by food may be absent in severe symptomatic disease and the motility responses are diminished when the pathological features of inflammatory damage are extreme. The increased motility in diverticular disease can be reduced by myotomy and bran, both of which relieve painful symptoms, suggesting that muscle involvement, a raised pressure and symptoms are related.

Excision of the diverticular disease segment, however, does not reduce the motor activity in the remaining distal bowel, suggesting that the muscle abnormality in symptomatic diverticular disease eventually becomes widespread. Confirmation of the wide extent of involvement was provided by Trotman and Misiewicz who positioned pressure sensors high in the left colon with a colonooscope and found that the pressure in the descending colon was higher there than in the more distal sigmoid colon. Others have, however, failed to find consistently raised intraluminal pressure, Trotman and Misiewicz attributed this failure in the study of Weinreich and Anderson to possible displacement of the pressure sensors from the sigmoid colon into the rectum which is not affected by diverticular disease. This seems unlikely in view of the similar finding of Eastwood and his colleagues who also reported a relatively low intraluminal pressure in asymptomatic patients with diverticular disease and it is conceivable that this represents an earlier stage of the disease in which pressure change is not consistently, if at all, present.

Individual constituents of the colonic wall

The predisposition of the distal colon to diverticula formation and the increasing incidence of diverticular disease with age prompted a study of the musculature of the colon by Pace, who showed that the colonic muscle in general increased in thickness with age and became thickest in the distal colon. Little attention has however been paid to the other components in the colonic wall. The mucosa is extremely expansile but weak. Its ability to stretch to many times its original length enables diverticula to form as "balloon" herniations of the relatively elastic mucosa through an otherwise contracted, thickened, inelastic colonic wall. The submucosa consists of collagen fibrils in a matrix of mucopolysaccharide ground substance. Collagen is the most important biological tissue in the colonic wall with a tensile strength of 10^7 Nm^-2 (Reference 16), as opposed to relaxed muscle which is 10,000-fold weaker with a tensile strength of 10^5 Nm^-2. Muscle undergoing contraction can raise the tensile strength to 10^7 Nm^-2 (Reference 17) but, at that, the strength of the muscle still lags behind that of the collagen component.

In the colonic wall the collagen is arranged in a discontinuous criss-cross network which allows for strength and expans-
Colonic wall strength in diverticular disease: D. A. K. Watters and A. N. Smith

bility. The collagen fibrils are smaller in width but increase in number with age in the left colon, a trend which is significantly greater in diverticular disease. Elastin fibrils in the colon also increase in number but deteriorate in quality with age. Whiteway and Morson found no additional muscle cells but an increase of elastin in the thickened taeniae of diverticular diseased colon, the elastin being laid down in a contracted form leading in turn to progressive shortening of the taeniae coli which bunch the circular muscle together and obstruct the bowel lumen, perhaps producing at this stage the increments of pressure which result in increased stress on the bowel wall and the production of symptoms.

Biomechanics of the colon and the effect of ageing

The elastin change also shows qualitative differences, as in skin where there is a fibrous degeneration with age, which reduces the elastic deformation characteristics of skin with age. There are similar age-related changes in the mechanical properties of the colon wall, one of which is a reduced expansibility.

Since diverticula are predominantly found in the elderly, the mechanical properties of the colonic wall might be expected to vary at different ages. Such studies have been carried out on Japanese and on Scots and Ugandans and confirm that the tensile strength of the colon declines throughout adult life in all racial groups and that its expansible properties diminish with age. Both studies examined the stress-strain curve to rupture of the intact colon wall in post-mortem colon. The tensile strength effectively measures the strongest structure in the wall, namely collagen.

Maintenance of form: stress and why the wall bulges

The colon, like other tissues, is under 'pre-strain'. Pre-strain is the phenomenon seen in certain living tissues indicating that they are under varying amounts of stretch and this is demonstrable in the shortening of the colon or of a blood vessel which takes place when it is excised from the body. Pre-strain allows tissues to expand in one direction without unduly altering their length in the other. For example, if blood vessels were like steel then a change in diameter in the femoral artery of 0.5 mm would be associated with a change in length of 25 mm. Such a situation would be incompatible with the maintenance of form.

The maintenance of shape and form under a variety of stresses and strains is a property of what is termed viscoelasticity. Biological tissues behave both like a viscous liquid and an elastic solid at the same time. The stress-strain curve of biological tissues is non-linear, unlike metals such as steel, and reflects their composite nature as fibril of elastin and collagen embedded in a viscoelastic amorphous gel.

Skin and blood vessels are the biological tissues which have been most extensively studied. Daly and Odland demonstrated alterations in the elastic deformity of skin under stress with age. The effects of age could be reproduced in younger skin by removing elastin enzymatically, suggesting that elastin degradation with age might account for the difference. In the aorta the diameter increases with age, as does the wall thickness. However, wall thickness increases more than diameter and the wall shows more stiffness. Such age-related changes may not be peculiar to skin and blood vessels since the colon undergoes similar changes with age which may influence the development of disease in both structures. The colon is essentially a cylindrical tube and its viscoelastic nature allows its dimensions to vary with muscular contraction and distension with faeces and flatus. The stress acting on the wall of a cylindrical structure such as the colon varies according to the intraluminal pressure, the radius and the thickness of the wall being a variant of pressure = (thickness × stress)/radius which is similar to the law of Laplace, which particularly applies to spherical structures. The pressure required to distend the colon is greatest when the radius is small, as when blowing up a balloon, the balloon being hardest to distend when there is no air in it. The greater the intraluminal pressure the greater the stress in the wall of the colon. Thus to allow passage of faeces and flatus, the distal colon, which is narrowest, must experience greater intraluminal pressure and greater stress in its wall. Greater stress in the wall with the passage of time leads to degenerative changes in the collagen and elastin, which could in turn predispose to development of diverticula. As diverticular disease muscle encroachment further narrows the colon, greater intraluminal pressure must be generated to distend and maintain its lumen which could rupture existing diverticula.

The more solid the faeces the greater the pressures required to propel them through the colon. This pressure is generated by the active forces of peristalsis, segmentation and mass contraction throughout the entire colon rather than by a central pump as in the case of the circulation. The more solid the faeces the greater the work done and the stress experienced by the colonic wall. The colon is narrowest in its distal sigmoid part and this segment becomes narrower with increasing age. Thus the ageing pelvic colon is most subjected to stress. Increased stress damages the colon resulting in a loss of tensile strength and elasticity. This has been confirmed by Iwasaki and Watters et al. who found a decline in both properties with increasing age. The proximal colon was much stronger and more expansible than distal colon.

Nutritional factors

Since diverticular disease is prevalent in Western countries but not in Africa and Asia, the African colon should be stronger and more expansible than that of the European. This was shown by Watters et al. who found that the difference was most significant in the distal colon, the area in which a Western population is more susceptible to formation of diverticula. An interesting feature of this study was that the infant African and European colon began with similar properties suggesting that the differences in adult life are environmental and not genetic. Yet if environmental factors, presumably dietary ones, are important in diverticular disease formation, there is no difference in the tensile strength of Edinburgh colons with and without diverticular disease in the over 50 age group studied. Perhaps by 50 years of age the Edinburgh colon population with a lower fibre intake than the African one, might be expected to be prediabetic in status.

Collagen is the most abundant protein in mammals and helps to maintain tissue structural integrity. However, this apparent fails in the colon when exposed to the added stress of propulsion through a progressively narrowing bowel lumen. Collagen is known to remain as a fibre in inter- and intramural cross-links which stabilize it and give mechanical strength to the tissue in which it is situated. Although cross-linking increases with advancing age, the exact position of the cross-links is not known. Collagen may also change qualitatively in a number of tissues being non-enzymatically glycosylated. This increases, for example, in the collagen of the cornea of diabetes mellitus patients. Diabetic patients are prone to diverticular disease an early age suggesting that there might be a defect or increase in the degree of glycosylation of the collagen with advancing age.

There are many studies showing that the raised pressure found in symptomatic diverticular disease can be kept low by fibre added to the diet. The precise mechanism of action of this is still largely unknown. It may act, as far as the distal colon is concerned, mainly by its bulking action, giving rise to a wide lumen, and, by the Laplace law, leading to a lower pressure which in turn lessens the stress in the colonic wall. It would be interesting in this regard to study the stress-strain curve in European subjects who have consistently maintained a high fibre diet to determine whether their colonic wall stays stronger those of their African counterparts. The change from a low to a high residue diet may prevent the taenial shortening and smooth muscle contracture of the pelvic colon.

Reference
Secondary damage

The contraction of the colon which results in a thicker wall may be to a degree a compensatory mechanism for increased stress in the wall, but could also disadvantageously compress the colonic microcirculation and restrict blood flow and tissue oxygenation.

Increased pressure on or in the colonic wall could also influence blood flow, especially at the time when contractions are being maximally exerted as, for example, during segmentation movements, mass contraction or abdominal straining. Reduction in blood flow could hasten the degeneration processes in the colon wall and further affect the tensile strength of the tissues predisposing to the complications of diverticular disease, necrosis, perforation or to the invasion of the colonic wall by infection.

Conclusion

It is a feature of the common form of diverticular disease in Western man that it has a late onset. We envisage its development deriving from years of under filling of the colon from low residue diets in contrast to the situation in the African where the lumen is wider with bulkier faeces and the colon wall remaining for a greater number of years thinner and more elastic. This is quite the antithesis of the narrow lumen with thick contracted muscle of Western man, all of which cause mechanical stress to the colon wall and the loss of its tensile strength. Bulk additives such as fibre oppose these changes and do so by the absorption of water on to non-digestible residues and by increasing the bacterial mass of the stool and its water content. The propulsive effects of motility are easier with moister faeces but this depends on which fibre source is used. Even inert particles stimulate colonic function suggesting that the maintenance of an adequate lumen and the size of the faecal bolus are important in normal colonic physiology, the maintenance of which must finally minimize the wear and tear effects on the colon wall which lead to diverticular disease.

References


Paper accepted 14 September 1989
Current hypotheses on synergistic microbial gangrene

We have reviewed spreading infections of the dermis, with special reference to the importance of synergy in their causation. Evidence for this is accumulating from both clinical studies and from studies in laboratory animals. Necrotizing fasciitis (rapid spread over 24 h) can be caused by β-haemolytic streptococci, sometimes with Staphylococcus aureus, or by mixed infections of aerobes and anaerobes, often of gut origin. Animal studies provide good evidence that S. aureus can potentiate the β-haemolytic streptococcal infection in necrotizing fasciitis. There is also evidence that mixtures of aerobes and anaerobes can act synergistically, but animal models for necrotizing fasciitis have not been developed. Anaerobic cellulitis (variable rate of spread from hours to days) can be caused by mixed aerobes and anaerobes or by mixed clostridial. Animal studies provide good evidence for synergy in the former. Meleneý's synergistic postoperative gangrene (slow spread over weeks) may be cutaneous amoebiasis: the animal model of Brenner and Meleneý relates to the more rapid infections of anaerobic cellulitis.

Keywords: Bacterial synergy, anaerobic cellulitis, cutaneous amoebiasis, Meleneý's synergistic gangrene, necrotizing fasciitis, streptococcal gangrene

For debate

D. Kingston and D. V. Seal

Microbial Pathogenicity Research Group, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ, UK

Correspondence to: Mr D. Kingston

This paper discusses the microbiology of spreading infections of the dermis. This compartment consists of a loose network of fibres containing blood vessels, lymphatics and fat, bounded on one side by the epidermal basement membrane and on the other by the tight connective tissue fascia of the muscle. We wish to draw attention to the evidence that many of these infections seem to be caused by synergy between two or more organisms. By synergy we mean that the mixtures of organisms cause more severe infections than each of the organisms singly. By the term mixed infection we imply that the pathogenic effect is no greater than the sum of the damage caused by infection with each organism alone. Clinical isolates often consist of mixtures of organisms and it is common practice to report only the organism that is regarded as the (single) pathogen. We are therefore accustomed to think only of single pathogens. Although there is much evidence that synergy can be important, it is in practice often disregarded.

What evidence is required to establish the role of synergy in these infections? Firstly competent bacteriology needs to be carried out and all the organisms recorded. Many synergistic infections involve anaerobic bacteria and satisfactory techniques for culturing fastidious anaerobes are of fairly recent introduction and are still far from universal. Our experience has been that homogenization of tissue specimens is also important for culture. Valuable additional evidence can be found from serology1,2 and electron microscopy can show that the tissue contains a mixture of microcolonies of different organisms3. Even if it is established, however, that a genuine mixed culture is generally present in these infections, it can always be argued that there is still only a single pathogen and that the other organisms are irrelevant colonizers of necrotic tissue. Thus it becomes essential to establish a convincing animal model to demonstrate synergy. Satisfactory animal models are not easy to establish and need careful analysis. It is very unfortunate that, in our view, the famous animal model of Brewer and Meleneý (anaerobic streptococci and Staphylococcus aureus) is unrelated to the disease (Meleneý's postoperative 'synergistic' gangrene) which it was developed to explain. Because the crucial difference between the animal model and the disease is the speed of progression of the lesion, we intend to discuss the different clinical syndromes divided into three different rates of progression. Rapidly progressive infections, the first category (e.g. necrotizing fasciitis4-8), have a time course measured in hours, the second, moderately rapidly progressive infections (e.g. anaerobic cellulitis5,9), are measured in days and the third, very slowly progressive infections (e.g. Meleneý's postoperative synergistic gangrene5-9), are measured in weeks. A simplified summary is given in Table 1. It is probable that this grouping of spreading infections of the dermis is an arbitrary division of a continuum. The question also arises as to whether very similar syndromes should be differentiated because they are caused by different organisms (e.g. pneumonia).

Rapidly progressive infection (hours)

Human studies

Swartz4 lists eight syndromes falling under this head of rapidly progressive infections, of which for the present we exclude two as being primarily diseases of the muscle (streptococcal myositis and gas gangrene - clostridial myonecrosis). The remaining syndromes are streptococcal gangrene, necrotizing fasciitis, synergistic cellulitis, non-clostridial anaerobic cellulitis, bacteremic Pseudomonas gangrenous cellulitis and necrotizing cutaneous mucormycosis. These infections are still very serious; Ahrenholz6 provides a table showing that the mortality rate for necrotizing fasciitis remains unchanged at about 40 percent. Further, these rapidly progressive infections usually need early surgical intervention. We intend to discuss the first two in this section, and the remaining four under the head of moderately rapid progression.

Necrotizing fasciitis begins with a patchy erythema of the skin that is swollen and painful. The edge is not raised and demarcated, as in erysipelas, and lym phangitis is absent. The patient is febrile, later becoming toxicemic, with confusion and disorientation. After 24 h, dusky purple areas develop with blistering and bullae, while the erythema and tissue oedema spread further. Rapid necrosis of subcutaneous tissue occurs with deep undermining of ulcerated areas but superficial to the fascial layer. Examination of necrotic tissue shows focal abscess formation with widespread thrombosis of small arteries.
Diverticular Disease of the Colon:
Data Relevant to Management

* A. TORSOLI (Chairman), M. INOUE, O. MANOUSOS, A. SMITH and C.J. VAN STEENSEL

1 Cattedra di Gastroenterologia I, Universita “La Sapienza”, Roma, Italy; 2 Dept. of Health Care, Fukuoka University Medical School, Fukuoka, Japan; 3 University of Crete School of Health Sciences, Div. of Medicine, Crete, Greece; 4 University Dept. Surgery/Urology, Western General Hospital, Edinburgh, UK; 5 Dept. of Surgery, Reiner de Graaf Gasthuis, Delft, The Netherlands

In the present cooperative Report the term diverticulosis was used to indicate the existence of diverticula in the colon, either single or multiple, and that of diverticular disease as a clinical concept including both symptomatic and asymptomatic cases. From epidemiological studies it appears that the disease increased in prevalence after World War II, although with remarkable differences between developed and developing countries. The severity of the disease seems also to have increased, but no significant changes in the mortality rate were recorded. There is evidence that environmental factors, such as a low-fibre diet, are important in the generation of diverticula.

The sigmoid is the site most affected in the West, whereas in Japan and other Far Eastern countries right-sided diverticular disease predominates, especially in the younger age groups. The prominence of muscle dysfunction in symptomatic uncomplicated patients suggests that the disease is basically a neuromuscular disorder. Complications are mainly inflammatory, and the clinical distinction between non-inflammatory (uncomplicated) and inflammatory (complicated) forms is relevant. Histologically, however, focal or non-focal inflammation of the diverticular mucosa is frequent, irrespective of clinical symptoms. Diverticulitis is, therefore, a histopathological finding rather than a specific clinical form of the disease.

According to the classification adopted in this Report, symptomatic uncomplicated disease refers to mild forms, where symptoms are similar to those of the irritable colon. Symptomatic complicated disease includes severe forms (usually due to a diverticular micro-perforation with subsequent serosal inflammation), pericolic abscess, diffuse peritonitis, obstruction, fistula and bleeding. An intermediate group of cases in whom the severity of pain, without systemic signs of inflammation, or the presence of a brief episode of fever with little pain suggest a circumscribed and transient peridiverticular involvement, has been defined as moderate forms.

The symptomatic disease may be acute or chronic (often recurrent), and its course is usually benign. In most cases, including the severe forms, conservative treatment is successful and only a minority of patients actually requires surgery. Surgery may be elective or urgent; occasionally an emergency operation is needed.

INDEX TERMS: Bulk Additives; Diverticular Disease of the Colon: muscle dysfunction, clinical forms, complications, surgical treatment; Low-fibre Diet.

1. INTRODUCTION

When treating a patient with diverticular disease it is often difficult to establish a causal relationship between the presence of diverticula, the associated pathology and clinical symptoms. The severity of the disease has to be assessed but uniform criteria are lacking. Diverticula apparently progress with age, but symptomatic diverticular disease may be reversible either spontaneously or after medical treatment. Predicting the occurrence of complications and their severity is also a problem.

Medical and surgical treatment has to be set against a background of incomplete knowledge of the natural history and geographical differences of the disease, and difficulties in its definition and classification. The clinical distinction between non-inflammatory and inflammatory forms remains ill-established, and radiological appearances are frequently misinterpreted. Despite evidence collected during the last 25 years, physicians and surgeons often consider symptomatic diverticular disease as essentially corresponding to diverticulitis.

The present Report attempts to clarify some of these problems and takes these into account in suggesting approaches for management and in hinting at the need for further investigations. The term diverticulosis has...
### Table I. Prevalence of diverticular disease of the colon based on autopsy studies.

<table>
<thead>
<tr>
<th>Country</th>
<th>Author</th>
<th>No. Exams</th>
<th>No. Pts</th>
<th>Prev (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uganda</td>
<td>Davies et al. 1975 (4)</td>
<td>4000</td>
<td>2</td>
<td>0.0</td>
</tr>
<tr>
<td>South Africa</td>
<td>Keeley et al. 1958 (5)</td>
<td>2367</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>China</td>
<td>Guo-zong et al. 1984 (6)</td>
<td>6896</td>
<td>8</td>
<td>0.1</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>Coode 1985 et al. (7)</td>
<td>200</td>
<td>10</td>
<td>5.0</td>
</tr>
<tr>
<td>Singapore Chinese</td>
<td>Lee et al. 1986 (8)</td>
<td>761</td>
<td>169</td>
<td>22.2</td>
</tr>
<tr>
<td>Malayan Indian</td>
<td>Lee et al. 1986 (8)</td>
<td>99</td>
<td>6</td>
<td>6.1</td>
</tr>
<tr>
<td>Malayan Indian</td>
<td>Lee et al. 1986 (8)</td>
<td>154</td>
<td>19</td>
<td>12.3</td>
</tr>
<tr>
<td>Japan</td>
<td>Sato et al. 1976 (9)</td>
<td>609</td>
<td>6</td>
<td>1.0</td>
</tr>
<tr>
<td>Australia</td>
<td>Hughes et al. 1969 (10)</td>
<td>200</td>
<td>85</td>
<td>42.5</td>
</tr>
<tr>
<td>Hawaii</td>
<td>Stemmermann et al. 1973 (11)</td>
<td>202</td>
<td>105</td>
<td>52.0</td>
</tr>
<tr>
<td>USA</td>
<td>Rankin et al. 1930 (12)</td>
<td>1925</td>
<td>111</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>Ochsner et al. 1935 (13)</td>
<td>447</td>
<td></td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td>Kocour et al. 1937 (14)</td>
<td>7000</td>
<td></td>
<td>2.0-15.2</td>
</tr>
<tr>
<td></td>
<td>Morton et al. 1946 (15)</td>
<td>8500</td>
<td></td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>Pemberton et al. 1947 (16)</td>
<td>47000</td>
<td></td>
<td>8.5</td>
</tr>
<tr>
<td>Norway</td>
<td>Eide et al. 1979 (18)</td>
<td>280</td>
<td>90</td>
<td>32.1</td>
</tr>
<tr>
<td>Malta</td>
<td>Podesta et al. 1975 (19)</td>
<td>119</td>
<td>29</td>
<td>24.4</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Drummond et al. 1917 (20)</td>
<td>500</td>
<td>22</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>Parks et al. 1969 (21)</td>
<td>500</td>
<td>111</td>
<td>37.0</td>
</tr>
</tbody>
</table>

### Table II. Prevalence of diverticular disease of the colon, based on barium enema examinations.

<table>
<thead>
<tr>
<th>Country</th>
<th>Author</th>
<th>No. Exams</th>
<th>No. Pts</th>
<th>Prev (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liberia</td>
<td>Diggs et al. 1975 (22)</td>
<td>300</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>South Africa</td>
<td>Segal et al. 1977 (23)</td>
<td>440</td>
<td>12</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Segal et al. 1977 (23)</td>
<td>250</td>
<td>12</td>
<td>4.8</td>
</tr>
<tr>
<td>Kenya</td>
<td>Calder et al. 1979 (24)</td>
<td>226</td>
<td>15</td>
<td>6.6</td>
</tr>
<tr>
<td>Israel Askenasi</td>
<td>Levy et al. 1977 (25)</td>
<td>618</td>
<td>100</td>
<td>16.2</td>
</tr>
<tr>
<td>Sephardi Arabs</td>
<td>Levy et al. 1985 (26)</td>
<td>823</td>
<td>143</td>
<td>17.4</td>
</tr>
<tr>
<td>Israel Askenasi</td>
<td>Levy et al. 1985 (26)</td>
<td>162</td>
<td>20</td>
<td>12.4</td>
</tr>
<tr>
<td>Sephardi Arabs</td>
<td>Levy et al. 1985 (26)</td>
<td>259</td>
<td>14</td>
<td>5.4</td>
</tr>
<tr>
<td>Jordan</td>
<td>Fatayer et al. 1983 (27)</td>
<td>274</td>
<td>11</td>
<td>4.0</td>
</tr>
<tr>
<td>Iraq</td>
<td>Abu-tabikh et al. 1975 (28)</td>
<td>1000</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>Iran</td>
<td>Dubestani et al. 1981 (29)</td>
<td>556</td>
<td>9</td>
<td>1.6</td>
</tr>
<tr>
<td>Kuwait</td>
<td>Salem et al. 1967 (30)</td>
<td>284</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Thailand</td>
<td>Vajrabukka et al. 1980 (31)</td>
<td>589</td>
<td>12</td>
<td>2.0</td>
</tr>
<tr>
<td>Korea</td>
<td>Kim 1969 et al. (32)</td>
<td>500</td>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>Japan</td>
<td>Sugihara et al. 1987 (33)</td>
<td>1839</td>
<td>244</td>
<td>13.3</td>
</tr>
<tr>
<td>West Indies</td>
<td>Narayansingh et al. 1987 (34)</td>
<td>971</td>
<td>239</td>
<td>24.6</td>
</tr>
<tr>
<td>USA</td>
<td>Mayo et al. 1930 (35)</td>
<td>31838</td>
<td>1819</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>Rankin et al. 1930 (12)</td>
<td>24620</td>
<td>1398</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>Ochsner et al. 1935 (13)</td>
<td>2747</td>
<td></td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>Willard et al. 1936 (36)</td>
<td>463</td>
<td>38</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>Eggers et al. 1941 (1)</td>
<td>428</td>
<td></td>
<td>44.5</td>
</tr>
<tr>
<td>Sweden</td>
<td>Kohler et al. 1969 (37)</td>
<td>3563</td>
<td>546</td>
<td>15.3</td>
</tr>
<tr>
<td>Finland</td>
<td>Kohler et al. 1969 (37)</td>
<td>3125</td>
<td>162</td>
<td>5.2</td>
</tr>
<tr>
<td>Finland</td>
<td>Havia et al. 1971 (38)</td>
<td>1215</td>
<td>296</td>
<td>12.8</td>
</tr>
<tr>
<td>France</td>
<td>Debray et al. 1961 (39)</td>
<td>500</td>
<td>53</td>
<td>10.6</td>
</tr>
<tr>
<td>Greece</td>
<td>Manousos et al. 1973 (40)</td>
<td>1100</td>
<td>59</td>
<td>5.4</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Spriggs et al. 1925 (41)</td>
<td>1000</td>
<td>100</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>Edwards et al. 1934 (42)</td>
<td>1623</td>
<td>25</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Eastwood et al. 1977 (43)</td>
<td>12335</td>
<td>2193</td>
<td>17.8</td>
</tr>
</tbody>
</table>
been used to indicate the anatomical state of having diverticula, either single or multiple. Diverticular disease has been used as a clinical concept including both asymptomatic and symptomatic patients.

2. DIMENSIONS OF THE PROBLEM WORLD-WIDE

An ideal technique for screening the general population for diverticular disease is not available. The easiest way to establish the prevalence of diverticula is the barium follow-through examination, which revealed figures of 7.5% in the United States in 1941 and 19.3% in the United Kingdom in 1967 (1, 2). Other investigations, based on data of autopsy, barium enema examination, colonoscopy, hospital admission, surgery and mortality, are subject to a considerable amount of selection, measurement or interpretation bias (3).

The results of autopsy studies (Table I), and data from barium enema examinations (Table II) and hospital admission show a great variation and are subject to different biases. This is why comparison must be made with great care (4-44). The prevalence of diverticular disease appears to be low in some countries and high in other countries, but relevant differences may also be seen among populations of the same origin when living in different areas (e.g. Chinese and Singapore Chinese). A change in time is also seen. About 20 years ago, diverticular disease of the colon was rarely seen in countries such as Kenya, Zaire, Ghana, Ethiopia, Kuwait and India (30, 45-48). Both an autopsy study in South Africa (23) and a retrospective study of barium enema examinations in Israel (25, 26) revealed an increasing prevalence of diverticular disease of the colon when compared to studies carried out in the same population more than 10 years before.

Recent data on the population of Scotland and The Netherlands showed a significant increase in prevalence in hospitalisation for diverticular disease of the colon, with a mean prevalence of 33-34 per 100,000 person-years. This was mainly due to an increasing hospital admission rate for females over 75 years of age. Although the number of operations did not increase in Scotland, a significant increase was seen in The Netherlands in the same period 1975-1985 (3, 50).

The increase in diverticular disease of the colon with time may reflect changes in the process itself, improved standards of diagnosis, improvement in registration techniques or changes in the definition of the disease. On the other hand the trend may be real. The data need to be corrected for changes in age distribution during the study period. The increase in the prevalence of diverticular disease in The Netherlands series leads to consideration of the following points of interest. The number of cooperating hospitals has not changed since 1980, nor had the diagnostic procedures changed after that period. Therefore, the increase with time after 1980 seems to reflect a real increase in hospitalisation. In the last 20 years no major change has occurred in the indications for surgery. An increase in cases admitted in combination with an increase in surgical rate suggests an increase in severity of the disease with time although this is not reflected in the mortality rate (3).

Fig. 1. Diverticulum of the left colon. The extruding mucosa and submucosa is separated by some thin longitudinal muscle fibres from the outer surface.
collagen of the bowel, which is the main supporting tissue giving it its structural strength and is progressively weakened with age (53). A relevant role of the low-residue diet in the causation of diverticulitis had been suggested same time ago by Burkitt et al. (54), and was confirmed by Gear et al. (55) who found a significantly lower occurrence of diverticular disease in vegetarians compared with non-vegetarians. In a more recent case-control study in Greece (56), a negative relation between diverticula and meat consumption was observed.

The most obvious feature of symptomatic uncomplicated diverticular disease, apart from the diverticula, is usually the thickened muscle of the bowel wall (Figure 3). The increased thickness of the smooth muscle coat has been associated with the "high pressure theory" of diverticular disease. This implies that a diverticulum results from the pulsion forces (high intraluminal pressure), generated by smooth muscle contractions (58). Thickening of the muscularis propria, however, is not invariably present and an alternative concept is that diverticula may represent a developmental stage when the muscle becomes thick as the result of narrowing. Recent work reinforces the concept that the thickening is a bunching together of muscle (myostatic contracture) rather than hypertrophy, and suggests that the muscle may become semi-obstructive, thus eventually producing symptoms (59). The importance of the muscle is supported by the effects of myotomy which lead to reduction of pressure and the temporary disappearance of symptoms (60). Similarly, bulk additives such as bran, which may lower the intraluminal pressure, relieve symptoms. These agents may also act to prevent the contracture of the muscle by ensuring an adequate lumen, through making transit more effective, and by increasing the moisture content of the faeces (61).

Since intraluminal pressures are not necessarily high in the early stages of the disease and muscular changes are not universal (3, 62, 63), pressure phenomena and muscle involvement are not a sine qua non of diverticular disease. High intraluminal pressure has mainly been detected in association with the symptomatic phases. A wide range of pressures was reported by Trotman and Misiewicz (64), who positioned pressure sensors high in the left colon. They found that intraluminal pressures were increased as much as five-fold at this site. Other workers, however, have failed to find consistently raised pressures (3, 65). Prior exposure of some patients to high-fibre diets may have influenced the results of Eastwood and his colleagues who also found normal or low intraluminal pressures in diverticular patients (62).

According to Whiteway and Morson, the muscle process begins as an elastosis of the taeniae which normally act as the supporting ties of the bowel wall, to which are tethered or attached the incomplete rings of the circular smooth muscle coat (63). Each taenia is composed of many fasciculi of smooth muscle cells embedded in the elastin and collagen which pack the interstitial spaces. The elastin, in particular, seems to increase with age. Taeniae are stiffened by this process and go into a state of contracture which the elastin seems to encourage by preventing smooth muscle cells from relaxing. In turn, this leads to a progressive "concertina effect" in the bowel wall. The rings of circular smooth muscle are thus approximated and

![Fig. 2. Intramural diverticulum of the left colon (arrow). The diverticulum is still surrounded by circular and longitudinal muscle fibres.](image-url)

![Fig. 3. Histological appearance of the thickened circular and longitudinal (at the extratranal level) muscle in a sigmoid colon resected for severe diverticular disease.](image-url)
thickened. The tissue between them is herniated outwards to begin a diverticulum.

Shortening of the taeniae also distorts the mesentery and the appendices epiploicae. Diverticula may not be apparent externally as they may be concealed within the appendices epiploicae and pericolic fat. The taeniae stop at the recto-sigmoid junction and below this they splay out as an imperfect external coat to the rectum. Ridges formed by the circular muscle arcs are discontinuous and interdigitate with one another across the lumen as they are pulled together by the taeniae (59). In longitudinal sections, the lumen appears narrow with a sort of step-ladder pattern as though semi-obstructed by a series of baffle plates. The luminal narrowing is exaggerated by the marked redundancy of the mucosa which, in turn, renders the muscle folds even more prominent. Sections of both muscle layers show a marked increase in thickness, with the fasciculi of the longitudinal taeniae being much thicker than those of the circular muscle. Elastic fibres are increased in the taeniae but the elastic content of the circular muscle is unchanged. Collagen fibres retain a normal arrangement and are only increased where there is an accompanying hypertrophy of muscle indicating a degree of obstruction. The origin of the elastin, which may be from muscle cells or fibroblasts, is reminiscent of the age-related changes seen in blood vessels, where there is thickening of the muscle coat in relationship to vascular pressure change with a hypertrophy of the elastic lamina.

Watters and his colleagues (53, 66) examined the tensile strength of the human colon and found that it was greatest in infancy, and then declined throughout life. The tensile strength was greatest in the proximal than in the distal colon. The ability of the colon to stretch increased after the first years of life but then remained constant in the proximal colon and decreased in the distal one. Generally, the human colon develops an ability to stretch at least 150-200% of its original dimensions.

Comparisons have been made between African and European colonic tissue in view of the low incidence of diverticular disease in Africa. There was no difference in the mechanical properties between Ugandan and Scottish colons in neonates, but the Ugandan colons were stronger than the Scottish ones throughout adult life. The distal colon had a greater capacity for stretch in the Ugandan group and this lends strong support to the theory that an environmental factor such as diet may be more important than a genetic one in the aetiology of diverticular disease. That the strength of the colonic wall is lessened in diverticular disease can also be deduced from the distensibility shown by the increased compliance found in balloon distension in the sigmoid area (3).

A muscle thickening comparable to that of advanced diverticular disease (67) may occasionally be found in the absence of obvious or even intramural diverticula, in the condition of idiopathic muscular strictures of the sigmoid colon (68). The muscle thickening leads to a certain degree of obstruction, with slowing of transit, but is not accompanied by local inflammatory complications.

In Western countries diverticula predominate in the left colon and are often localised to the sigmoid alone (Table III). The prevalence of diverticula developing at this site and, in particular, the number of symptomatic diverticula affecting the sigmoid, may be related to the fact that the sigmoid colon is the sector of the large bowel normally having the least internal diameters (Table IV) (69). This, in accordance with the LaPlace formula \( P = \frac{T}{R} \), implies that at equal tensions, the intraluminal pressures will be higher. The sigmoid colon also exhibits the greatest wall thickness (Table V) and the highest intraluminal pressures at rest (Table VI). These conditions favour mucosal herniation and rupture of the diverticular wall (70). The pattern of the spread of the process proximally from the recto-sigmoid junction suggests a functional obstruction at this site, but the presence of a sphincter has never been substantiated.

Focal or non-focal inflammation of the diverticular mucosa is frequent irrespective of clinical symptoms. Inflammatory changes have in fact been seen, in fact, even in asymptomatic patients (71), whereas severe disease symptoms have been associated with a variable degree of diverticulitis or even no diverticulitis at all (72) (Table VII). The pathological background of the most severe and complicated forms is a micro- or macro-perforation of one or more diverticula with subsequent inflammatory involvement of the serosa and pericolic structures (72) (Figure 4). Perforation tends to remain sealed off by the pericolonic fat so that a generalised peritonitis does not usually develop. Diverticulitis is, therefore, a histo-pathological finding rather than a specific clinical form of the disease. Occasionally, however, an isolated diverticular inflammation, usually as a peridiverticulitis or abscess, may produce symptoms of acute diverticular disease.

A pericolic abscess follows rupture of a diverticulum or, alternatively, the spread of inflammation directly through the colonic wall. Acute inflammatory change is often found initially to affect a solitary diverticulum (73) and may spread into the wall of the bowel to produce a phlegmon (74).

4. CLINICAL CLASSIFICATION

The classification of diverticular disease is based on clinical and radiological criteria. In this report four main features have been taken into account: clinical severity, the presence or absence of complications, the course of the disease, and the site of diverticula.

4a. According to clinical severity and the presence or absence of complications, diverticular disease has been classified as follows:

**Asymptomatic Diverticular Disease**

**Symptomatic Diverticular Disease**

- **Uncomplicated**
  - Mild forms
- **Complicated**
  - Microperforation with serosal inflammation
  - Pericolic abscess

...
TABLE III. Site of the diverticula (X-ray examination).

<table>
<thead>
<tr>
<th>Diverticula</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sigmoid colon only</td>
<td>72</td>
</tr>
<tr>
<td>Sigmoid + other segments</td>
<td>108</td>
</tr>
<tr>
<td>Segments other than sigmoid</td>
<td>42</td>
</tr>
<tr>
<td>(Sigmoid or left colonic resection)</td>
<td>24</td>
</tr>
</tbody>
</table>

The Rome GI Unit series of diverticular disease subjects (n=222), showing the site of the diverticula. Although approximately one-sixth of the diverticula were localised outside the sigmoid, surgery was only performed (n=24) for sigmoid diverticular disease (70).

TABLE IV. Calibre of the human colon.

<table>
<thead>
<tr>
<th>Calibre</th>
<th>Ascending colon</th>
<th>Transverse colon</th>
<th>Sigmoid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10.6 ± 0.6</td>
<td>9.1 ± 0.7</td>
<td>5.0 ± 0.5*</td>
</tr>
</tbody>
</table>

Calibre of the colon (in cm) as measured in 10 necropsy specimens fixed in distension and opened after fixation (*p<0.05) (69).

TABLE V. The circular and longitudinal colonic muscle.

<table>
<thead>
<tr>
<th>Muscle Type</th>
<th>Circular</th>
<th>Longitudinal (Extra-taenial)</th>
<th>Taenial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending colon</td>
<td>58.5 ± 37</td>
<td>270.0 ± 12</td>
<td>1057.5 ± 195</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>571.5 ± 36</td>
<td>285.0 ± 30</td>
<td>990.0 ± 88</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>1327.5 ± 112*</td>
<td>568.5 ± 45*</td>
<td>1862.5 ± 112*</td>
</tr>
</tbody>
</table>

Thickness (in microns) of the human colonic muscle in 10 necropsy specimens fixed in distension and opened after fixation (*p<0.05) (69).

TABLE VI. Mechanical activity of the human colon.

<table>
<thead>
<tr>
<th>Mechanic</th>
<th>Proximal colon</th>
<th>Sigmoid colon</th>
<th>Rectum (5 subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure</td>
<td>2.75 ± 1.3</td>
<td>13.49 ± 5.0*</td>
<td>0.50 ± 0.4</td>
</tr>
</tbody>
</table>

Intraluminal pressure of the human large bowel at rest as expressed by the Motility Index in 18 apparently normal subjects (*p<0.05) (72).

TABLE VII. Diverticular inflammatory changes in diverticular disease.

<table>
<thead>
<tr>
<th>Type</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td>9</td>
</tr>
<tr>
<td>Extensive</td>
<td>8</td>
</tr>
<tr>
<td>Periolic inflammation</td>
<td>22</td>
</tr>
<tr>
<td>Muscular thickening</td>
<td>23</td>
</tr>
</tbody>
</table>

The Rome GI Unit series of resected left colons for severe complicated diverticular disease (n=24). Histology revealed the almost constant presence of muscular thickening, periolic (serosal) inflammation and a varying degree of inflammation in one or more diverticula. In three specimens there was no evidence of diverticulitis (72).

FIG. 4. Macroscopic view of a longitudinal section of a resected sigmoid colon in a patient with severe complicated diverticular disease. The thickening of both the circular and longitudinal (extrataenial) muscle is clearly visible, together with the redundancy of the luminal folds, the narrowing of the lumen and (indicated by the arrow) the perforation of a diverticulum.
Mild forms represent non-inflammatory diverticular disease. The severe forms, pericolic abscess, diffuse peritonitis and fistula, are variants of the inflammatory disease. An intermediate group is represented by moderate forms, in which the characteristics of pain or other signs suggest a circumscribed and transient peridiverticular involvement.

According to its course, diverticular disease can be defined as acute or chronic. Acute episodes of diverticular disease may recur (acute recurrent diverticular disease). Chronic diverticular disease may be continuous or intermittent.

According to the site, divertica and diverticular disease can be classified as right-sided, left-sided or diffuse.

5. Diagnosis

The clinical patterns of diverticular disease are independent from the number of diverticula; even a single diverticulum may be responsible for an attack of severe and complicated disease. Diagnosis essentially relies upon symptoms, physical findings, laboratory investigations and radiology. Radiology reveals the existence, number and localisation of diverticula, the thickness of the colonic muscle and various associated pericolonic abnormalities. Repeated examination can also demonstrate the anatomical evolution of the disease. Radiology, however, does not identify diverticular inflammatory changes (diverticulitis). Discrepancies between the X-ray picture and the clinical severity of the disease are not infrequent. The assessment of clinical severity and the course of the disease are based essentially on symptoms, physical examination and laboratory investigations.

There is no significant aetiological association between diverticular disease and cancer, and yet cancer is the main condition to be ruled out. Although a well-performed double contrast enema is usually enough to exclude it, colonoscopy is necessary when neoplasia is suspected.

Radiology Plain abdominal films allow identification of barium deposits in diverticula following recent contrast X-rays, of gas in the bladder in the case of colon-vesical fistula, indirect signs of intestinal obstruction and incidental biliary or urinary stones.

The barium meal and follow-through with observation of the large bowel until emptying of the contrast medium, is the simplest and least invasive method to detect colonic diverticula. Diverticula may not be visible when the colon is fully opacified and, therefore, if diverticula are suspected, a film should be taken 72-96 hours after the barium meal (Figure 5). Repeated small doses of barium sulphate have been shown to visualise diverticula with good sensitivity and reduced body irradiation. The particular sensitivity in revealing diverticula make this investigation suitable for large-scale epidemiological screening.

The double contrast enema is the principal diagnostic method; it provides information which can be summarised as follows:

- Features suggestive of pre-diverticular disease:

- Images of diverticula (single, multiple, diffuse, "en masse");

- Signs of associated muscle abnormalities:
  - increased number and distortion of the folds,
  - reduced length, narrowing and rigidity of the affected segment;

- Signs of complications:
  - pericolic abscess
  - fistula
  - adhesion
  - obstruction;

- Demonstration or exclusion of other colonic diseases.

Laboratory investigations are primarily designed to evaluate the degree of inflammation present. These include haematology, ESR and acute phase reactants, blood protein electrophoresis, urine test and the search for occult blood in the stools.

Endoscopy Diverticula are not mucosal diseases and endoscopy is not exempt from risks (e.g. diverticular perforation following gas distension or injury by the instrument itself). Left or total colonoscopy are not indicated other than in cases of:

- Bleeding (overt or occult);

- Clinical or radiological suspicion of poly(s) or cancer;

- Clinical or radiological suspicion or evidence of an associated inflammatory disease (Crohn's disease, ulcerative colitis, etc.).
Other imaging techniques Abdominal ultrasonography and CT scan may be of value in detecting colonic thickening and abscesses, and incidental biliary and urinary disease. The IV urogram and cholecystography may be indicated in individual patients.

5a. Asymptomatic Diverticular Disease

Diverticula may be seen by chance during X-ray examinations, endoscopy, or surgery performed for other indications. The finding of colonic diverticula, especially when associated with radiological evidence of wall abnormalities, implies that the patients should undergo the faecal occult blood test, haematological and haematochemical tests and abdominal echography.

Although diverticula often remain asymptomatic throughout life, they may increase in number and/or size over time and/or colonic muscle abnormalities may supervene. Therefore, X-ray control examinations at definite time intervals (e.g. five years) may be indicated.

5b. Symptomatic Uncomplicated Diverticular Disease

Mild forms

These are more frequently chronic, continuous or intermittent. Symptoms consist of pain, disturbances of bowel habit and abdominal distension. Pain is mild, i.e. does not require a medical consultation and/or medication. It is usually localised at the left iliac fossa but may affect other parts of the abdomen. It is generally diurnal and often alleviated by the passage of flatus, whereas it may appear or be exacerbated after eating.

Bowel disturbances consist of a variable combination of constipation, diarrhoea or alternating troubles.

FIG. 6. Barium enema examination without (above) and after atropine administration (below). The muscle contraction and diverticula are no longer visible after atropine.

Mucus in the stools and abdominal gas distension are also frequent. An increased consistency of the colonic wall or firmness may be appreciated on palpation but tenderness or guarding are not found on the physical examination of the abdomen nor does the palpation of the involved segment produce acute pain.

X-rays usually show diverticula in the sigmoid and/or descending colon and sometimes also in other parts of the large bowel. Some associated signs of muscle dysfunction (hypertonicity, asymmetry and distortion of the luminal folds) may be associated and are usually recognised as restricted to the left colon. These signs and occasionally the diverticula as well, may disappear after administration of smooth muscle relaxants (Figure 6). There is no evidence of pericolonic involvement.

Moderate (intermediate) forms

These may present as acute episodes or exacerbations of mild forms. They principally differ from the mild forms by the characteristics of pain and the objective examination of the affected area. Pain is severe, although short-lasting, i.e. usually requires a medical consultation and medication. Some tenderness is found in the left iliac fossa, and palpation exacerbates pain. However, there are no systemic signs of inflammation or definite urinary symptoms. In other instances, especially in the elderly, a brief episode of fever is accompanied by constipation and leucocytosis, with very little pain.

In all these cases, remission is usually rapidly achieved and the hospital admission is only occasionally advisable.

5c. Symptomatic Complicated Diverticular Disease

5c.1 Microperforation with serosal inflammation

More acute presentations are mostly due to a diverticular microperforation with subsequent serosal inflammation. These may or may not recur and be preceded or followed by the mildest of symptoms or no symptoms at all. The clinical picture is that of “left-sided acute appendicitis”.

Pain is severe and more frequently located in the left iliac fossa. It can last for hours or days, and is not easily brought to remission. There is local peritonism or guarding and systemic evidence of inflammation (fever, leucocytosis, increase of ESR and acute-phase reactants). Fever is generally moderate, of remittent type, and lasts for one or several days. Typically, it follows the pain onset some hours or one day later. Bowel motion are occasionally suspended for one or two days but there may be diarrhoea. Hospital admission is advisable and often necessary. The body temperature, the state of the abdomen and the main laboratory tests should be monitored. Blood cultures should be performed. Echography and CAT are indicated in order to detect pericolonic abnormalities. Additional examinations may include urogram and upper abdominal echography (to exclude urinary or biliary disease). A double contrast enema should be performed once pain and the other symptoms of the acute phase have subsided.
Fever (temperatures of 38°-39°C), tenderness and guarding in the left iliac fossa with rebound pain are the major features. The leucocyte count also rises (30-50,000/ml). A palpable mass may become apparent if the local tenderness and guarding do not prevent detection and may be suggested on plain radiographs by a soft tissue shadow or the appearances of extraluminal bubbles of gas or a fluid level. Ultrasound or CT scanning may also show not only the thickened wall of the bowel but adjacent loculi suggesting an abscess.

5c.3 Generalised peritonitis

If pus builds up in a diverticular sac, or adjacent to it in a pericolic abscess, this may be followed by rupture of the abscess into the peritoneal cavity. The features then become those of a generalised purulent peritonitis with spread of abdominal tenderness and rigidity. Such patients become very ill with tachycardia, hypotension and oliguria progressing to severe shock with anuria (75). Rupture of a diverticulum may also produce a faecal soiling of the peritoneal cavity (faecal peritonitis). The event is a sudden one and is commonly associated with severe shock if the faecal soiling is widespread. A varying degree of pneumo-peritoneum occurs.

5c.4 Fistula

Fistula sometimes occurs post-operatively though the record of such an event is rarer than with Crohn's disease (77). By the process of draining the abscess content into an adjacent viscus, a fistula is at once formed and may in a sense be partially cured. But the potency of its track as the communication between two adjacent structures remains. The commonest and most important of these fistulae is the colon-vesical fistula, but fistulous tracks also form into the vagina or uterus or into the skin surface or into other loops of bowel particularly into the small intestine (78-83).

5c.5 Obstruction

Acute diverticular disease can produce "inflammatory bands" of the large or small bowel but mechanical obstruction can also be caused by the adhesion of a small bowel loop to the colon (84). Obstruction can also occur in the late stages of the disease when the bowel is affected by a muscle stenosis due to 'contracture' (85) of the thickened muscle coat or to a general fibro-fatty degeneration affecting its wall and encroaching on the lumen. CT scanning again may delineate the rings of thickened muscleature and the irregular lumen.

5c.6 Bleeding

Anastomosing rings of blood vessels surround the neck of diverticulum, and faecaliths within diverticula may erode into these vessels (86, 87). There is a higher incidence of bleeding in patients on non-steroidal anti-inflammatory drugs which are known to interfere with reparative processes (88). Bleeding from diverticular disease is actually rare and usually arises in the sigmoid colon as a result of erosion of a fairly large vessel closely related to the diverticular neck (89, 90). It thus induces a brisk haemorrhage with all the features of an arterial source as a profuse and copious 'bright and red blood' discharge per rectum. The lesion may be difficult to find at laparotomy unless there is confirmatory mass of blood clot in the culprit diverticulum. The situation may be one of critical haemorrhage with rapid hypotension requiring control by proper monitoring and the immediate restoration of the blood volume.

For moderate cases, apparent as mixed blood and faecal losses, a more proximal site may be a possibility. An origin in angiodysplasia may be thought of even if the patient is known to have diverticular disease.

A third clinical type of bleeding from diverticular disease is represented by occult blood losses suggesting a damaged mucosa and resulting in various degrees of anaemia. Such patients need investigation to exclude a coexisting neoplasm and require colonoscopy since a polyp or carcinoma may lurk in the zone of diverticular disease.

6. ADDITIONAL FACTORS AFFECTING THERAPEUTIC DECISIONS

6a. Patient’s history

A positive family for colonic diverticula should be investigated. The early development of diffuse diverticula is sometimes seen in members of the same family. The patient should also be questioned about other co-existent colonic disease. The relatively frequent associations of hiatal hernia and gallstones with colonic diverticula (Saint’s triad), may justify a systematic search for disorders of the oesophageal-gastric junction and gallbladder disease.

6b. Site and extent of diverticular changes

Very few studies have examined the clinical significance of the site of diverticula. Parks (91) found that prognosis was no worse in patients with diverticular disease of the whole colon than in the localised forms. In the Oxford study, no appreciable difference in the risk of dying from diverticular disease was found whether the diverticula were left-sided or generalised. The risk of brisk rectal bleeding appeared to be directly proportional to the number of diverticula. The more extended the diverticular involvement of the colon, the greater was the chance of developing severe bleeding (92).

6c. Patient’s age, sex, ethnic group and socioeconomic condition

The prevalence of diverticula and diverticular disease of the colon increases with age (Table VIII). Patients with many diverticula are usually older than those with a few but a progression of the disease (Figure 7) is apparent only in a part of the cases (92).

In Western countries, diverticular disease is most common in persons over 70 years of age, and the disease is infrequent in persons under the age of 40 (3, 25, 26, 49). However, diverticular disease behaves
Table VIII. Age distribution of patients with diverticular disease of the colon given as a percentage of the total patient population.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Africa, 1977</td>
<td>Segal et al. (23)</td>
<td>16</td>
<td>31.2</td>
<td>25</td>
<td>31.2</td>
<td>12.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Israel, 1977</td>
<td>Levy et al. (25)</td>
<td>100</td>
<td>–</td>
<td>2</td>
<td>14</td>
<td>46</td>
<td>38</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Ashkenasi</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>12.5</td>
<td>37.5</td>
<td>50</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Sephardi</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>50</td>
<td>–</td>
<td>50</td>
<td>–</td>
</tr>
<tr>
<td>Israel, 1985</td>
<td>Levy et al. (26)</td>
<td>143</td>
<td>–</td>
<td>2.1</td>
<td>16.1</td>
<td>26.6</td>
<td>55.2</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Ashkenasi</td>
<td>20</td>
<td>–</td>
<td>–</td>
<td>10</td>
<td>35</td>
<td>55</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Sephardi</td>
<td>14</td>
<td>–</td>
<td>–</td>
<td>21.4</td>
<td>35.7</td>
<td>42.9</td>
<td>–</td>
</tr>
<tr>
<td>Jordan, 1983</td>
<td>Fatayer et al. (27)</td>
<td>35</td>
<td>11</td>
<td>23</td>
<td>29</td>
<td>26</td>
<td>11</td>
<td>–</td>
</tr>
<tr>
<td>Iran, 1981</td>
<td>Debestani et al. (29)</td>
<td>9</td>
<td>22.2</td>
<td>22.2</td>
<td>44.4</td>
<td>–</td>
<td>11.1</td>
<td>–</td>
</tr>
<tr>
<td>Singapore, 1986</td>
<td>Lee et al. (8)</td>
<td>169</td>
<td>9.8</td>
<td>17.0</td>
<td>27.3</td>
<td>21.6</td>
<td>17.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Thailand, 1980</td>
<td>Vajrabukka et al. (31)</td>
<td>15</td>
<td>33.3</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>Vajrabukka et al. (31)</td>
<td>12</td>
<td>4.2</td>
<td>4.2</td>
<td>33.3</td>
<td>41.7</td>
<td>16.7</td>
<td>–</td>
</tr>
<tr>
<td>Japan, 1980</td>
<td>Inoue et al. (134)</td>
<td>1163</td>
<td>19.2</td>
<td>23.1</td>
<td>23.7</td>
<td>21.2</td>
<td>12.7</td>
<td>–</td>
</tr>
<tr>
<td>Hawaii, 1973</td>
<td>Stemmermann et al. (11)</td>
<td>105</td>
<td>2.9</td>
<td>14.3</td>
<td>31.4</td>
<td>30.5</td>
<td>21.0</td>
<td>–</td>
</tr>
<tr>
<td>The Netherlands, 1989</td>
<td>Van Steensel et al. (3)</td>
<td>38497</td>
<td>0.4</td>
<td>3.1</td>
<td>8.6</td>
<td>15.1</td>
<td>29.0</td>
<td>43.7</td>
</tr>
<tr>
<td>United Kingdom, 1975</td>
<td>Kyle et al. (49)</td>
<td>359</td>
<td>6.9</td>
<td>39.6</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

more aggressively in the younger age group. Ouriel and Schwarz (93) demonstrated that under the age of 40, medical treatment of acute inflammatory diverticular disease failed within 27 months in 50% of the patients.

In the hospital admissions during the period 1958-1961, Kyle found a male preponderance in the younger age group and a female preponderance in the elderly (44). Ten years later this difference had disappeared (49). In recent data from Scotland, the total patient population showed a shift from an almost equal distribution in 1968-1972 to a male preponderance in 1978-1982 (94), although no proof exists that this occurred in the era when the use of bran was advocated.

A migration study showed that the Japanese population of Hawaii exhibits a higher prevalence of diverticular disease, whereas the prevalence in Japan was low at that time (11). Similar changes have been noted in Israel, Singapore and Fiji (8, 25, 26, 44).

6d. Short- and long-term outcome of treatment

Most studies on uncomplicated diverticular disease are short term and show that bulking agents provide symptomatic relief. They also suggest that such agents may protect from the development of complications.

In severe diverticular disease the published evidence indicates that short-term results are good. The great majority of patients recovered without requiring surgical intervention, however, a tendency to develop further complications remains and a significant proportion of those patients will undergo surgery in the future (92). In various centres surgery is advocated after the second episode of acute severe diverticular disease (95), but this policy has not been validated prospectively.
Elective surgery is more debatable for patients suffering only from chronic bowel symptoms. Approximately 30% of the patients surgically treated for the relief of such symptoms had recurrent symptoms and occasionally developed serious complications (92). Indeed, in recent years the need for elective surgery for symptomatic diverticular disease has dropped dramatically. The number of elective operations in Edinburgh hospitals, which 10 years ago numbered about 40, has dropped to about five operations per annum in the last five years.

6e. Surgical risk

The death rate for elective diverticular disease surgery is lower in each age group than that for colonic cancer surgery. The mortality rises sharply, however, with complications, and is currently 5.7% in Edinburgh compared with a figure of 3.7% for cancer of the colon. This is principally attributable to increase in sepsis, particularly from faecal peritonitis in elderly subjects. Lower mortality figures are quoted, as 2.7%, from special proctology centres (94). Prior antibiotic preparation and appropriate use of defunctioning colostomy and parenteral feeding help to keep it low.

6f. Associated disease

Irritable Bowel Syndrome (IBS)

The problem of aetiological associations of the two disorders has been extensively studied during the past 20 years (65). Colon motility and transit times in patients are similar to those with IBS (96, 97, 98). A recent review concluded that, although the occurrence of IBS and colonic diverticula in the same individual is likely to be coincidental, a common aetiology is not precluded (99).

Polyps and carcinoma

In countries where colon cancer is rare, diverticular disease of the colon is also rare. There is no evidence that diverticular disease leads to cancer or polyps, so the coexistence of these two relatively common conditions is to be considered incidental (100, 101).

Angiodysplasia

In case of bleeding in patients with diverticular disease, colonoscopy can establish the correct diagnosis and, if present, angiodysplasia can be treated. If surgical treatment is indicated, angiography may be needed to lead to a better focus for treatment (89).

Ulcerative colitis

Both ulcerative colitis and Crohn’s disease of the colon may render the course of diverticular disease more serious and increase the tendency to major complications. Although some found a high mortality in the combination of diverticular disease and ulcerative colitis, this was not confirmed by others (102, 103, 104). The prevalence of diverticular disease of the colon in patients with ulcerative colitis, varies between...
25 and 29%, which is not as high as reported from the general population (104, 2, 40, 101).

When the coexistence of ulcerative colitis is suspected, colonoscopy is mandatory (105). The fact that acute colitis may be missed, because diverticular disease is so obvious radiologically, might be more important than the worsening effect of either two conditions. Ulcerative colitis, in fact, requires a more extensive resection than does diverticular disease (106). However, in a small series in older patients a limited resection, as for diverticular disease, had good results (107).

**Crohn's colitis**

Not infrequently, patients with clinical suspicion of inflammatory forms of diverticular disease actually appeared to have Crohn's colitis on histological examination of the resected specimen (108, 109, 111). Missing the diagnosis of Crohn's colitis leads to an increased morbidity and in a number of cases subsequent colectomy for "intractable" Crohn's disease had to be performed (108, 112).

**Ischaemic colitis**

Ischaemic colitis with fever, leucocytosis and tenderness in the left side of the abdomen may simulate acute diverticular disease. A plain radiograph may give some help by indicating that the obstruction is mainly at the splenic flexure, and a subsequent barium enema may show the feature of "thumb printing", as an indentation of the barium-filled lumen by patchy mucosal swelling.

**Diverticular disease, hiatus hernia and gallstones (Saint's triad).**

These three conditions are common in Western society. However, no relation between them could be demonstrated (32). In the series of Hughes, the combination of gallstones and diverticular disease was no greater than might be expected (10); others found a higher incidence of gallstones in patients with diverticular disease (47, 48, 113).

**Extra-intestinal manifestations**

Arthritis and pyoderma grangrenosum have been described in association with inflammatory diverticular disease, but the prevalence is very low when compared to ulcerative colitis and Crohn's colitis. Total relief from these extra-intestinal symptoms can be obtained by resection of the diseased colon segment (114).

**Ischaemic heart disease**

Both diverticular disease of the colon and ischaemic heart disease are common in Western countries. A barium follow-through in a population matched for age, sex and social class, showed a significant higher prevalence of diverticular disease in the ischaemic heart disease group as compared to controls (115).

7. **MEDICAL TREATMENT**

Therapeutic decisions depend largely on the stage of the disease process. Although some centres use surgical treatments often, studies of the natural history of the disease show that only a small percentage actually require surgery (116).

7a. **Asymptomatic Diverticular Disease**

The available data, although derived from short-term studies, suggest that the administration of agents that increase the bulk of stools is justified. Bran was shown to decrease intracolonic pressures especially after meals, and to increase stool weight appreciably (117). Similar changes in physiological parameters were observed after the administration of ispaghula (118).

7b. **Mild (and Moderate) Diverticular Disease**

Chronic mild symptoms that afflict patients with colonic diverticula are usually treated according to the same criteria followed for the irritable bowel syndrome. Bulk forming agents have been found effective (119). Spasmolytics in the form of anticholinergics or muscle relaxants are used extensively, but there are no data as to their real efficacy (120). Occasionally the symptoms become more severe and an inflammatory component may be clinically suspected. In this case, even if the laboratory indices are not clear-cut, a course of antibiotics, such as metronidazole, is advisable.

7c. **Severe (Complicated) Diverticular Disease**

The approach to this form is basically conservative at first, but it is imperative that a surgeon be consulted. Nothing by mouth, naso-gastric suction, measures for pain relief, control of fluid balance and antibiotics are the main foundations of treatment. Antibiotics should be employed systematically in cases of septicemia. Most patients respond to those measures (121). If the clinical state worsens, catheterisation of the bladder is imperative and central venous monitoring should be instituted.

8. **SURGICAL PROCEDURES AND RESULTS**

8a. **Elective patients**

The decision as to when to operate, is made by the failure of medical treatment. Surgery must be considered when inflammatory attacks do not settle. Repeated attacks of inflammatory disease produce obstruction or settle but often at the cost of a fistula. The need for surgery may be coloured by uncertainty in the diagnosis especially if problems of ischaemia, inflammatory bowel disease or carcinoma have to be considered.

The second decision is to know when to resect. This is imperative when the wall of the bowel is compromized by perforation or fistula. The soiling of the abdominal cavity may be local and a resection may be easily performed if the contamination is minimal or the inflammation local. Alternatively, inflamed colon may be adherent to other viscera such as the small intestine.
uterus, bladder or the wall of the pelvis. There may be overlapping by omentum, free pus or even faeces. In such patients, most surgeons agree that it is preferable to resect the damaged tissue quickly. Proximal colostomy is then performed and the distal rectal stump closed off (Hartmann’s operation).

In the more deliberate resection of the elective case, the surgeon should plan to divide below the recto-sigmoid junction since it is at the recto-sigmoid that the process appears to subside.

In the face of major peritoneal contamination, either from an extending inflammatory diverticular disease and purulent peritonitis, or from necrotic perforation of the bowel wall producing a faecal form of peritonitis, most surgeons will choose to perform a Hartmann’s resection and postpone anastomosis to a later date (122). The prognosis of this procedure may be worsened, however, by the repeated operation required to re-anastomose. When the contamination has been minimal, experienced surgeons aim to perform immediate anastomosis (one-stage procedure), especially after the cleansing effect of abdominal lavage and with the protection afforded by systemic antibiotics and good resuscitative measures, including the protection from colostomy or ileostomy temporarily.

Twenty to 30% of resected patients are said to have residual symptoms but this lessens with the pursuance of high-fibre diets and recourse to bulk additives. There is no evidence that more extensive resections of the left colon are any different (123), nevertheless a formal left hemicolectomy may be appropriate in case of extended disease. Post-operative studies have shown (124) that intraluminal pressures in resected patients can be high, but long continued high-fibre diets may lead to a better outcome. There is also little direct evidence of recurrence of diverticula, even in spite of the long maintained surgical trend to perform limited resections which may not remove all affected bowel bearing diverticula on it.

A British trial led by surgeons based at St. Mark’s Hospital, London, provided evidence that colon surgery is markedly operator-dependent and requires special training and expertise (125). Multicentre trials efforts have also been made in the UK to reduce the morbidity and mortality of colonic operations through the employment of standardised protocols for operative selection and management and by the encouragement of the surgical reporting of results by audit (126).

8c. Surgery for fistulas and bleeding

Many patients with a colon-vesical fistula present with a short history. The site of adherence and the fistulous track can often be readily recognised and few patients require staged operations compared with the time when the fistula was passage from the bowel to the bladder through a complex abscess cavity (129). The two structures can usually be easily separated and locally closed, the bladder being protected from dehiscence temporarily by continuous drainage via a Foley catheter.

Concerning bleeding, its site has to be identified at angiography or colonoscopy. At the time of bleeding, particularly in urgent episodes, arteriography is the more conclusive procedure for achieving the definition of the bleeding site. An exception to this is when copious blood is expelled per rectum indicating true diverticular bleeding from the distal colon and the patient runs the risk of becoming exsanguinated.

8d. Surgery for right-sided diverticular disease in Western subjects

True right-sided diverticular disease is rare in Western Europe and North America and is most often part of a generalised extension of the disease. It is not infrequent in elderly subjects and is commonly unassociated with muscle thickening of the bowel wall. Indeed, the colon is thin and atrophic, the entire picture being in keeping with one of failure of supportive structures such as the collagen of the bowel wall, reminiscent of the diverticular disease of Marfan’s or the Ehlers-Danlos syndrome (131).

A solitary diverticulum of the ascending colon may be congenital. It occurs on the anterior wall above the insertion of the ileum at the ileo-colic junction. The diverticulum may become inflamed and simulate appendicitis. A diverticulum full of faecal material may also twist into a local volvulus which may infarct the bowel wall. Some inflammation of the diverticulum may
also exist and cause an inflammatory tumour. Very occasionally, localised diverticular disease in the right colon mimics the pattern found in South-East Asia and Japan (132).

9. DIVERTICULA AND DIVERTICULAR DISEASE IN FAR EASTERN COUNTRIES

9a. Prevalence and anatomical distribution
In Far Eastern countries diverticular disease is remarkably less common than in Western countries (Table IX), and right-sided disease predominates (Table X).

9b. Japanese studies
The prevalence of diverticular disease in Japan before 1969 was less than 2%. However, the diagnosis has been made much more frequently since then (132). A cooperative study in different areas (Aomori, Niigata, Tokyo, Misinomiya and Fukuoka) (133, 134) showed that the average prevalence of diverticular disease had increased about three times from 1975 to 1986, and the average prevalence in 1986 was 14.5%. The prevalence was higher in males than in females (1.9:1), and in large cities. The prevalence in Tokyo was 2.5 times as high as that in Aomori in which the prevalence was the lowest.

When the disease was classified as right-sided, left-sided and bilateral, the proportion of each group was 73%, 13% and 15% of all cases, respectively. Right-sided diverticular disease predominated (more than 90%) in the age group under 39, increased sharply until 50 years of age, and thereafter the increase was slight. Left-sided and bilateral diverticular disease began to increase after 40 years of age, and the increase was especially remarkable after 60 years. No difference in the location of diverticula was found between the different regions of Japan, or between native Japanese and the Japanese Hawaiians in whom the disease was 4-5 times as frequent. These results suggest a genetic modulation of whatever environmental event is responsible for the generation of diverticula (135).

Cases with a solitary diverticulum, those with two to nine diverticula, and those with more than 10 diverticula were 32%, 48% and 20% of the whole series, respectively. In the right-sided form, the proportion of the cases with solitary diverticulum, with two to nine diverticula, or with more than 10 diverticula was almost the same among age groups. However, in the left-sided diverticular disease, the proportion of the cases with solitary diverticulum decreased and the cases with more than 10 diverticula increased in the older age groups (133, 134).

9c. Pathology and pathophysiology
Pathological studies on diverticular disease in the Far Eastern countries are scarce. Clinically significant colonic diverticula in Japan are mostly of the acquired type. In patients with sigmoid diverticula, low grade muscle abnormalities have been often observed. In right-sided disease, muscle abnormalities were noted, but these were less frequent and milder than those of sigmoid disease (136, 137). In right-sided diverticular disease intraluminal pressure of the right colon was significantly greater than that of normal controls and persons with left-sided disease, both basally and after neostigmine (138, 139). A correlation was found between the basal intraluminal pressure in the right colon and the number of the right-sided

Table IX. Prevalence of diverticular disease in the Far Eastern countries.

<table>
<thead>
<tr>
<th>Country</th>
<th>Method</th>
<th>Year(s)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korea</td>
<td>Ba. enema</td>
<td>1980-82</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1980-87</td>
<td>1.3</td>
</tr>
<tr>
<td>China</td>
<td>Autopsy</td>
<td>1921-83</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Colonoscopy</td>
<td>1974-83</td>
<td>0.33-1.2</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>Autopsy</td>
<td>1981-85</td>
<td>5.0</td>
</tr>
<tr>
<td>Chinese</td>
<td>Autopsy</td>
<td></td>
<td>24.0</td>
</tr>
<tr>
<td>Singapore</td>
<td>Surgery, X-rays</td>
<td>1972-76</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Ba. enema</td>
<td>1978-79</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Table X. Site of the diverticula as a percentage of the total patient population.

<table>
<thead>
<tr>
<th></th>
<th>No. Pts</th>
<th>Right-sided</th>
<th>Bilateral</th>
<th>Left-sided</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>5545</td>
<td>72.8</td>
<td>14.5</td>
<td>12.7</td>
<td></td>
</tr>
<tr>
<td>Korea</td>
<td>19</td>
<td>73.7</td>
<td>5.3</td>
<td>21.1</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>18</td>
<td>61.1</td>
<td>11.1</td>
<td>16.7</td>
<td>11.1</td>
</tr>
<tr>
<td>Singapore</td>
<td>194</td>
<td>70.1</td>
<td>7.7</td>
<td>9.2</td>
<td>12.9</td>
</tr>
<tr>
<td>Bangkok</td>
<td>27</td>
<td>63.0</td>
<td>11.1</td>
<td>26.0</td>
<td></td>
</tr>
</tbody>
</table>
Fibre intake in the Japanese diet decreased rapidly after the Second World War paralleling the remarkable increase of diverticular disease (140, 141). In five different regions there was a negative correlation between the fibre intake and the prevalence of diverticular disease. In two case control studies fibre intake of patients with diverticular disease was significantly lower than that in normal controls (142, 143). These findings suggest that a low fibre intake may be a predisposing factor in the right-sided diverticular disease also.

9c. Natural history
Forty to 50% of patients whose barium enema showed colonic diverticula complained of abdominal symptoms, such as abdominal pain or distension (133, 134). However, many of the symptoms could not be ascribed to the presence of diverticula. By repeated barium enemas, progression in number and distribution of diverticula was observed in 30-50% of the cases (144).

Definite acute inflammatory disease occurred in 2-4% of the cases. Right-sided inflammatory diverticular disease was more frequent in those under the age of 40, but in those above 40 years of age with left-sided disease. Acute inflammatory diverticular disease of the left colon recurred more frequently than that of the right colon (33, 145). The prevalence of diverticular haemorrhage was 1.1-3.1%. Diverticular haemorrhage was more frequent in the older age groups, and also in left-sided or bilateral disease.

9d. Guidelines for treatment
Symptomatic right-sided diverticular disease is generally mild and uncomplicated; in most cases, conservative treatment is successful. When surgery is performed laparotomy discloses an inflamed colonic wall with normal appendix; drainage of the inflamed area results usually adequate (145).

10. SUGGESTIONS FOR FUTURE STUDIES
Prospective long-term studies are needed to see whether manipulation of the diet can prevent the formation of diverticula and their complications, and whether there is any difference in recurrence rates between conservative sigmoid resections as against more "radical" procedures, such as left hemicolectomy. The efficacy, if any, of other therapeutic measures (e.g. muscle relaxants or intermittent antibiotic treatment) in chronic disease also remains to be established. Studies in the Far East should be designed to clarify the aetiology and pathogenesis of this local form of diverticulitis and so shed light on the disease in general.

11. SUMMARY
Diverticula of the colon, both in the Western and Eastern countries, are mostly false, and are of the acquired type. The term diverticulosis has been used in this Report to indicate the state of having diverticula, either single or multiple, whereas the expression of diverticular disease has been used as a clinical concept including both asymptomatic and symptomatic cases.

Epidemiological studies from various continents have shown that the disease has a low prevalence in some countries and a significantly higher prevalence in others; sometimes with significant differences among populations of the same ethnic origin but living in different areas. The disease shows everywhere an increasing prevalence, and yet is rarely listed as a cause of death. The changing prevalence may be attributed to a change in the dietary habits, suggesting that environmental factors are of prime importance in the genesis of diverticula.

The most obvious feature of uncomplicated disease, apart from the diverticula, is the thickened muscle of the colonic wall. The muscular abnormality probably begins with an elastosis of the taeniae which is accompanied by a reduction of the tensile strength. In Western countries "symptomatic" diverticula predominate in the sigmoid colon, which is the segment of the large bowel having the minimal internal diameter (implying that at an equal tension of the wall intraluminal pressure is higher). In Japan, where diverticula mostly affect the right colon, intraluminal pressures were also found to be elevated in the right-sided disease. Diverticular disease is to be seen, therefore, primarily as a neuro-muscular disorder with a secondary deterioration of supporting collagen in the colonic wall.

Complications are mainly of an inflammatory nature, and the distinction between non-inflammatory (uncomplicated) and inflammatory (complicated) diverticular disease has great clinical relevance. The clinical signs of inflammation usually appear when the serosa and pericolic structures are affected by the inflammatory process, most frequently as a result of a diverticular (micro- or macro-) perforation. Focal or non-focal signs of inflammation of the diverticular mucosa appear to be frequent, irrespective of the clinical symptoms. Diverticulitis is, therefore, a histopathological finding rather than a specific clinical form of the disease.

Diverticular disease may be acute or chronic (often recurrent) and, according to its severity and the presence or absence of complications, it has been classified in this Report as (a) asymptomatic, (b) symptomatic uncomplicated, and (c) symptomatic complicated. In this classification, symptomatic uncomplicated diverticular disease refers to the mild forms, symptomatic complicated diverticular disease includes the severe forms (usually due to a localised peritonitis) and other complications such as pericolic abscess, diffuse (purulent or faecal) peritonitis, fistula, obstruction and bleeding. Moderate forms represent an intermediate group where the characteristics of pain or other symptoms suggest a circumscribed and transient peridiverticular involvement.

Diagnosis relies upon symptoms, physical findings, laboratory investigations and radiology. Radiology is the method of choice for detecting diverticula and the associated muscle dysfunction as well as some of the complications. Echography and CT-scan are of value in selected cases. Endoscopy is not indicated unless in case of bleeding (ovet or occult), the suspicion of cancer, polyps, or concomitant inflammatory bowel
disease.

Therapeutic decisions are influenced by the site and extent of diverticular changes, the patient's age and socio-economic condition, the suspicion of one or more concomitant disease, and data about the short- and long-term outcomes of medical and the surgical treatment.

Surgery may be elective or urgent. In elective patients, the one-stage resection of the pelvic colon and colo-rectal anastomosis beyond the recto-sigmoid junction has had good results, thus confirming that (in the Western countries) the sigmoid is the most intense site of the disease process. A left hemicolectomy may however be indicated for extensive disease. Although 20–30% of resected patients are said to have residual symptoms, this lessens with the pursuance of high-fibre diet and the recourse to bulk additives.

Surgery becomes urgent in case of a gross abscess cavity or diffuse peritonitis. Laparotomy and drainage may be a first measure, then a Hartmann resection with a left iliac fossa colostomy and closure of the rectal stump is the procedure of choice. Special operations may be necessary for other complications such as fistula and bleeding. The recent progresses in interventional radiology and endoscopy may, however, render surgery for bleeding less necessary.

In the Far Eastern countries, the disease is remarkably less common than in the West, although its prevalence is increasing. It predominates in the right colon, especially in people under the age of 40. Studies of the pathology and pathophysiology of the Far East disease are scarce, but in Japan low-grade muscle abnormalities have been shown both in the right-sided and left-sided diseases. The prevalence of inflammatory disease is low, and the conservative treatment is successful in the great majority of cases.

ACKNOWLEDGMENTS

The authors wish to express their gratitude to Dr Enrico Corazzari, Rome, for his assistance and contribution during the preparation of the Report, and to Miss Stefania Crisari and Mrs Clara Ghigarelli for typing the various editions of the manuscript.

The Report was made possible by a Special Educational Grant from GIULIANI S.p.A, Milano, Italy.

REFERENCES

APPENDIX I

The papers presented in Part 1 (mainly on diverticular disease of the colon) derive from a prior interest in gastrointestinal motility (i) and its normal and abnormal features. Kinins had shown the possibility of explaining vasomotor (ii), peristaltic (iii) and inflammatory features (v) of the dumping syndrome, the carcinoid state and had been found in the wall of the colon in inflammatory bowel disease (v). One particular form of chronic ulcerative colitis with constipation rather than diarrhoea (faecal stasis) had been contrasted with diverticular disease and had overlapping motility features (iv). Kinin release was absent in diverticular disease, in spite of supposed inflammatory features (v). The introduction of myotomy as an operation, though short-lived, had been proposed as a therapeutic procedure for correction of the muscle disorder of diverticular disease and gave an opportunity to investigate the thickened muscle of the diverticular state. With the subsequent introduction of fibre diets (mainly bran) this enabled one to use this as a tool to investigate the aetiology of this common colonic disorder.

(i) Smith A N, Hogg D. Effect of gastrin II on the motility of the gastrointestinal tract. Lancet 1966; i: 403-404


(iii) Zeitlin I J, Smith A N. 5-hydroxyindoles and kinins in the carcinoid and dumping syndromes. Lancet 1966; ii: 986-991


(v) Zeitlin I J, Smith A N. Mobilisation of tissue kallikrein in inflammatory disease of the colon. GUT 1973; 14: 133-138
EFFECT OF GASTRIN II ON THE MOTILITY OF THE GASTROINTESTINAL TRACT

The isolation and properties of gastrin I and II were described by Gregory and Tracy. They specifically mentioned, apart from the well-documented acid-secretory activity, a motor action of these peptides on the stomach and intestine of the dog. Maklouf et al. reported the potent action of gastrin II on acid gastric secretion of man. Bennet reviewed the motor action of gastrin on isolated smooth-muscle preparations, taken from the rat and guineapig, and demonstrated that gastrin II caused contraction of the stomach and colon of the rat, and, in particular, of the ileum of the guineapig. It is the purpose of this preliminary communication to outline some effects of pure gastrin II (hog) on the motility of the human gastrointestinal tract.

METHODS

The experiments were done on adult males who were fasting and at rest. Motility in the proximal alimentary tract was recorded by a swallowed pressure-sensitive telemetering capsule with a thread attached to it; recording started when the capsule passed distally to the zone of the gastrointestinal tract chosen for study—the jejunum, ileum, or proximal colon. When released from its attached thread the capsule later passed distally. The motility of the distal (pelvic) colon and rectum was studied by the sigmoidoscopic insertion of triple, narrow-lumen polyethylene tubes, 3 mm. in diameter, with small terminal balloons. The tubes placed in the upper and lower pelvic colon and rectum were linked to standard recording apparatus operating on the condenser-manometer principle (Statham transducer no. 23D; Cardiac Recorders Limited).


Gastrointestinal motility (cm. water) after injections of gastrin; and the effect of atropine (0.6 mg.).

The first injections of gastrin were given over a period of one minute; later injections were given more slowly to avoid possible side-effects. G = gastrin II.
TABLE I—AMPLITUDES AND DURATION OF WAVES AFTER INJECTIONS OF GASTRIN INTRAVENOUSLY SLOWLY OVER FIVE MINUTES, COMPARED WITH THE RESTING PERIOD, IN 1 SUBJECT

<table>
<thead>
<tr>
<th>Site</th>
<th>Mean amplitude (cm. water)</th>
<th>Mean duration (sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resting Gastrin (25 µg.)</td>
<td>Gastrin (50 µg.)</td>
</tr>
<tr>
<td>Jejunum</td>
<td>8-4</td>
<td>9-1</td>
</tr>
<tr>
<td>Ileum</td>
<td>7-8</td>
<td>8-2</td>
</tr>
<tr>
<td>Colon</td>
<td>10-5</td>
<td>12-8</td>
</tr>
<tr>
<td>Rectum</td>
<td>11-0</td>
<td>14-2</td>
</tr>
</tbody>
</table>

The difference between mean values after gastrin and at rest were significant at the following levels: 10% (*), 5% (†), 2% (‡), and 1% (§).

RESULTS

Gastrin II was given intravenously in each case in 5 ml. of sterile water at doses of 5 µg. and 15 µg.; these produced no effect on the stomach. 25 µg. stimulated the onset of antral contractions and a greater contractile response was elicited with 50 µg. This response was greatly reduced by the prior injection of atropine (0.6 mg.) (see accompanying figure).

Intestinal motility was assessed by recording a five-minute resting-period before the gastrin injection and comparing the mean amplitude of the wave forms in cm. water pressure and their duration in seconds over a similar period, measured from the onset of motor activity after slow injection. Since the effects diminished slightly if injections of gastrin were made rapidly after one another, and to avoid the possible side-effects of these relatively large doses, all later injections were spaced out by a time interval of at least fifteen minutes.

Table I lists the resting-amplitudes and the duration of wave forms recorded by the telemetering capsule in the jejunum, ileum, and colon, consecutively in 1 subject; motility of the rectum was examined using the tube method.

TABLE II—INDEX OF CONTRACTILE FORCE IN TWO GROUPS OF 4 SUBJECTS GIVEN DIFFERENT DOSES OF GASTRIN

<table>
<thead>
<tr>
<th>Dose of gastrin (µg.)</th>
<th>Subject no.</th>
<th>Index of contractile force * in:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Jejunum †</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resting</td>
</tr>
<tr>
<td>25</td>
<td>1</td>
<td>40-4</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>26-3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>24-1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>37-5</td>
</tr>
<tr>
<td>50</td>
<td>5</td>
<td>42-8</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>38-8</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>28-8</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>36-1</td>
</tr>
</tbody>
</table>

* For calculation of index, see text.
† The difference between the mean contractile forces after gastrin and at rest was significant at the 1% level (subjects 1–4) and at the 0.5% level (subjects 5–8).
‡ Significant at 2% level (subjects 1–4) and 1% level (subjects 5–8).
TABLE III—EFFECT OF ATROPINE ON THE INDEX OF CONTRACTILE FORCE PRODUCED BY GASTRIN

<table>
<thead>
<tr>
<th>Subject</th>
<th>Index of contractile force in ileum after:</th>
<th>Index of contractile force in rectum after:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gastrin (50 μg.)</td>
<td>Gastrin (50 μg.) and atropine</td>
</tr>
<tr>
<td>9</td>
<td>119.8</td>
<td>76.5</td>
</tr>
<tr>
<td>10</td>
<td>97.6</td>
<td>58.2</td>
</tr>
<tr>
<td>11</td>
<td>92.8</td>
<td>51.1</td>
</tr>
<tr>
<td>12</td>
<td>112.2</td>
<td>58.7</td>
</tr>
</tbody>
</table>

The effect of atropine on the contractile force produced by gastrin was significant at the 1% level for both ileum and rectum.

25 μg. gastrin II and 50 μg. gastrin II were repeated for each zone studied. Throughout, there was a greater response with the 50 μg. dosage. In the jejunum the effect, with the repeated doses, on wave duration was more significant than the rise in amplitude of the waves. These effects were more striking in the ileum. In the proximal colon the wave amplitude was not affected significantly by 25 μg. nor was the wave duration prolonged. With the 50 μg. dose the effect on amplitude reached a high level of significance. In the rectum the mean amplitude was more significantly affected than the duration with the 50 μg. dose.

The mean effects of gastrin for 4 subjects are compared in table II with their motor activity at rest. The area of each wave has been calculated as $\frac{1}{2} A \times D$, where $A$ is the amplitude and $D$ is the duration. The total area per unit of time was calculated by multiplying by $n$ (the number of waves) and dividing by $t$ (the duration in minutes of the period of observation). The total boundary area produced by motor activity of the observed waves per unit of time may be hypothetically taken as an index of the "contractile forces" producing a motor response:

$$\text{Index} = \frac{A \times D \times n}{2t}$$

This index has been used for comparison before and after gastrin in 4 subjects given 25 μg. gastrin and a further 4 given 50 μg. gastrin. The motility was more significantly affected in the jejunum than in the rectum, and more so by 50 μg. than by 25 μg. gastrin II. The significance of the difference of the responses in these groups of patients had been compared and $p$ was evaluated from a $t$ test. The effects were notably lessened by 0.6 mg. atropine sulphate (table III) given before a second injection of gastrin which was given fifteen minutes after the first to avoid tachyphylactic reductions.

CONCLUSION

Gastrin exerts an effect on gastrointestinal motility but the threshold for pronounced measurable effects is higher.
than that for the secretory effects, since the amounts used here are approximately ten times those used to elicit acid gastric secretion. Large doses, short of those inducing possible toxic effects, were used intentionally to demonstrate effects. This does not exclude the possibility that smaller amounts influence the motility of the gastrointestinal tract, especially if gastrin is released slowly and continuously. The effects on the small bowel, colon, and rectum were all readily demonstrated but, perhaps due to greater scatter in the wave forms in the distal gut, the effects did not reach such a high level of statistical significance. A variable inhibition or cessation of motility was observed in the sigmoid colon; the conditions under which this occurs are not clear but are being investigated.

The findings are consistent with observations already made by other workers who have injected gastrin clinically for the estimation of acid gastric secretory responses; there may be audible borborygmi occasionally associated with discomfort or even pain. Most subjects pass flatus at some time after gastrin injections and in our experiments, the rectum, empty at the time of insertion of the motility recording tubes, was often filled with faeces at the completion of the procedure. The reduction in motor effects by atropine is in keeping with the recorded in vitro effect described by Bennet, and with a comparable reduction described in vivo by Gregory and Tracy.

**SUMMARY**

The effects of gastrin II on gastrointestinal motility have been measured in the jejunum, colon, ileum, and rectum. Pronounced increases in motility were obtained with doses of 25 µg. and 50 µg. intravenously; these doses are large when compared with those used to elicit acid gastric secretion. When atropine (0.6 mg.) is given, the effects are notably reduced.

The gastrin II in these experiments was given by Prof. R. A. Gregory of Liverpool, to the Gastrointestinal Unit of the Western General Hospital, Edinburgh.

Department of Clinical Surgery,
University of Edinburgh, and
the Gastrointestinal Unit,
Western General Hospital,
Edinburgh

A. N. SMITH
M.D. Glasg., F.R.C.S.E.
D. HOGG
M.B. Queensland, F.R.A.C.S.
Certain patients, experiencing the post-gastrectomy symptoms commonly known as dumping, react by showing manifestations of this such as an initial pallor followed by flushing, perspiration, nausea, weakness, and abdominal features such as borborygmi, abdominal discomfort, and diarrhoea. It is the intention of this preliminary paper to show that the vasoactive peptide substance bradykinin, or a bradykinin-like substance, is released during some of these dumping manifestations and may contribute to the symptomatology.

The work was carried out because of the description in recent years of the participation of 5-hydroxytryptamine in the production of features of the dumping syndrome. 5-Hydroxytryptamine (5-HT) had interested various workers as a possible mediator of this syndrome in view of the similarity between symptoms of patients with the carcinoid syndrome, in which 5-HT has a major role, and those of dumping. Peskin and Miller (1962) have advanced the role of 5-HT in the dumping syndrome and Johnson, Slop, Joseph, and Harkins (1962) have furthermore shown that 5-HT (serotonin) antagonists were beneficial in experimental and clinical dumping. Drapanas, McDonald, and Stewart (1962) suggested that a possible site for serotonin release was the proximal intestine and that this could be elicited by the instillation of hypertonic glucose.

There are, however, two basic difficulties in attributing the symptoms and signs of dumping solely to 5-HT release. First, the 5-HT formation in the carcinoid syndrome is vastly in excess of that which has been demonstrated in dumpers. Secondly, 5-HT may not be the sole cause of the features of the carcinoid syndrome. Oates, Melmon, Sjoerdsma, Gillespie, and Mason (1964) have shown that a kinin peptide is found in the systemic circulation in this syndrome and proposed that it was a bradykinin-like substance, rather than 5-HT, may be the causal agent of the flushing attacks in the carcinoid state.

Table I.—Release of Kinin in 4 Carcinoid Syndrome Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Severity of Symptoms</th>
<th>Kinin Precursor (Bradykinin Equivalents)</th>
<th>Free Kinin (Bradykinin Equivalents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Continuous lobster colour</td>
<td>10.6 (ng./ml. plasma)</td>
<td>53.7 (ng./ml.)</td>
</tr>
<tr>
<td>2</td>
<td>Transient flushing</td>
<td>4.9 (ng./ml. plasma)</td>
<td>26.3 (ng./ml.)</td>
</tr>
<tr>
<td>3</td>
<td>Non-flushing</td>
<td>6.6 (ng./ml. plasma)</td>
<td>2.0 (ng./ml.)</td>
</tr>
<tr>
<td>4</td>
<td>Transient flushing</td>
<td>7.0 (ng./ml. plasma)</td>
<td>24.3 (ng./ml.)</td>
</tr>
</tbody>
</table>

Kinin the dumping syndrome which were artificially induced by the ingestion of hypertonic glucose (Machella, 1949).

METHODS

The methods used for the estimation of bradykinin and its precursor utilized the smooth-muscle contracting powers of this compound. Extraction was performed from 6-ml. samples of venous blood. The method used is based on the solubility of kinin in ethanol and the assay is performed on the oestrus rat uterus. The precursor may be determined by allowing trypsin to act on the precursor plasma protein and assaying the free kinin produced. All assays were done against a pure standard preparation of bradykinin. Inactivation of the activity demonstrable in the blood samples by chymotrypsin confirmed that a polypeptide substance was present. Parallel assay showed that the polypeptide was bradykinin-like and not substance P or gastrin.

RESULTS

1. Kinin Levels in the Carcinoid Syndrome.

—Table I shows the release of kinin in 4 carcinoid cases: in each instance the vasomotor state is recorded as flushing or non-flushing at the time of examination. There is no rise in kinin level in patients without vasomotor symptoms, but kinin is increased at the time of flushing in patients with this feature of the carcinoid syndrome.
2. Release of Bradykinin during provoked Attacks of Vasomotor Dumping.—Dumping attacks were provoked by glucose in 4 fasting subjects, and the bradykinin precursor and kinin levels assayed during the sequence of an attack. All 4 subjects complained of post-prandial malaise, rapid

flushing, and sweating, with headache, weakness, and prostration and abdominal discomfort following Polya partial-gastrectomy for duodenal ulcer. Blood-levels were examined before the provocation of dumping, at the height of an attack, which usually occurred 10–15 minutes following glucose administration, and later when the patient began to feel free of the uncomfortable symptoms. In each case the duration of the flush and the severity of it were recorded, and the pulse-rate and blood-pressure recorded in the upright posture.

The level of kinin was found to rise at the height of an attack but fell very rapidly, and normal levels were found at the completion of an attack (Fig. 1). The active formation of bradykinin was demonstrated by a rapid fall in the precursor bradykininogen (Fig. 2) at the time of maximum kinin formation and the most severely recorded symptoms. These experiments were repeated in 4 subjects and increased amounts of kinin were found in each case, though the extent of the increase varied greatly. Control

![Fig. 1](image1)

*Fig. 1.—The production of free kinin after dumping shown as a histogram (for each of two tests, in one of which there was no free kinin in the control and final samples).*

![Fig. 2](image2)

*Fig. 2.—The kinin precursor, examined concurrently to the free kinin changes in Fig. 1, shows a fall in the middle (10-minute) period, the period of kinin production.*

![Fig. 3](image3)

*Fig. 3.—The release of kinin is illustrated in 4 cases. Cases 1, 2, and 3 show a marked release. Case 4, though less, is above the control and normal levels.*

![Fig. 4](image4)

*Fig. 4.—The blood-pressure and pulse-rate changes in the 4 cases of Fig. 3 are shown, averaged for each occasion of dumping provocation. The least affected subject is Case 4, who released the smallest amount of kinin.*

tests were carried out giving 2 patients a large volume of fluid (250 ml.) suitably sweetened by saccharin; neither subject showed the release of kinin in these control tests. Normal subjects, on whom no gastric surgery had ever been performed, did not release kinin when given dumping provocation with hypertonic glucose solution (Fig. 3).

Each of the 4 patients was graded in severity by estimation of the duration of flush and the effect on
Humoral factors in the dumping syndrome have attracted the attention of various workers. Raised levels of catecholamines and of 5-HT have both been found in this syndrome. In comparison with the carcinoid syndrome, to which there is in most cases a general clinical similarity, the amount of 5-HT released is usually slight (Zeitlin and Smith, unpublished observations). Howe (1964) found that 5-HIAA production formed from released 5-HT related not to the dumping features but to changes in blood-volume, suggesting that the role of 5-HT in dumping may be a secondary one. The use of the serotonin antagonists in dumping can also be criticized on the ground that many of them are non-specific, having actions not only of 5-HT antagonism but others which are sympathine-like and adrenolytic. Several humoral factors may be released into the circulation.

Because of the formation of bradykinin in the circulation in carcinoid cases with features remarkably similar to those of dumpers, we were stimulated to search for the presence of this substance in dumping attacks. Our results confirm the work of Oates and others (1964) concerning raised free kinin levels in the blood-stream in the carcinoid syndrome. The level of free kinin appears to be related to the degree of flush seen. One patient had a continuously severe flush and the highest level of free kinin. Two patients, flushing transiently, had lesser amounts; one examined during a vasomotor attack had an increment of free kinin and a fall in the precursor substance.

All the patients exhibiting dumping with vasomotor features released kinin and concomitantly showed a diminution of the precursor substance. The amounts released were as great as in carcinoid cases and appeared to be related to the severity of the dumping attack. Control examinations did not reveal a change in kinin or kinin precursor when attempts were made to provoke this phenomenon using saccharin-sweetened fluid.

The site of the release of kinin has not been established. It may be a local release from the intestinal tract, which had been shown to have rich stores of kinin-forming enzymes (Amundsen and Nustad, 1965), but its formation may be activated in the circulation or in other tissues elsewhere in the body. Bradykinin formation in carcinoid cases is thought to result from release of the kinin-forming enzyme from the carcinoid tumour itself (Oates and others, 1964). Catecholamines may release kinin from certain tissues (Hilton and Lewis, 1956) and the secretion of adrenaline or nor-adrenaline may be factors indirectly promoting the general formation of bradykinin, in addition to the role already claimed directly for such substances in the dumping syndrome.

SUMMARY

1. We have confirmed that bradykinin is formed in the carcinoid syndrome and is present when flushing is intense.
2. A kinin similar to bradykinin in its pharmacological reaction is released in vasomotor dumping attacks; kinin precursor has been shown to fall in the circulation at this time.
3. The rival claims of 5-HT and kinins as mediators of the dumping clinical features have been outlined.

REFERENCES

5-HYDROXYINDOLES AND KININS IN THE CARCINOID AND DUMPING SYNDROMES*

I. J. Zeitlin
B.Sc. Edin.
RESEARCH ASSISTANT, DEPARTMENT OF PHARMACOLOGY,
UNIVERSITY OF EDINBURGH

A. N. Smith
M.D. Glasg., F.R.C.S.E.
READER, DEPARTMENT OF CLINICAL SURGERY, UNIVERSITY OF EDINBURGH,
AND CONSULTANT SURGEON, GASTRO-INTESTINAL UNIT, WESTERN
GENERAL HOSPITAL, EDINBURGH

From the Departments of Pharmacology and Clinical Surgery, University of Edinburgh, and the Gastro-Intestinal Unit, Western General Hospital, Edinburgh

There have been many hypotheses to explain the post-prandial intestinal and vasomotor symptoms, known as the "dumping" syndrome, which appear in some patients as a sequel to gastric surgery. The syndrome may be provoked by a meal or, experimentally, by ingestion of a hypertonic glucose solution (Machella 1949). The symptoms vary widely in different individuals, but generally they include borborygmi, nausea, vomiting, and diarrhoea as the intestinal component, and dizziness and pallor, followed by flushing, tachycardia, sweating, and weakness.

One hypothesis relates these symptoms to the release into the bloodstream of 5-hydroxytryptamine (5-H. T.) from the small intestine (Duthie and Irvine 1965). But while the release of intestinal 5-H. T. might explain the intestinal symptoms it does not adequately explain the vasomotor changes. The carcinoid syndrome bears many similarities to the dumping syndrome in both its intestinal and vasomotor features. The involvement of 5-H. T. in the

* Some of the results given in this paper were presented to the annual meeting of the Association of Surgeons of Great Britain and Ireland in Edinburgh, March 31 and April 1 and 2 (Smith and Zeitlin 1966).
carcinoid state is well known (Smith 1965, Stacey 1966), but it may not be the sole causative agent of the patients' symptoms since Oates et al. (1964) demonstrated the appearance of a kinin-like polypeptide in the hepatic venous blood of patients during the carcinoid flush.

The kinins are a group of related polypeptides of which the best known is the nonapeptide, bradykinin. They are extremely potent, vasodilator, hypotensive substances which are normally present in the blood-stream in minute amounts. However, blood contains relatively vast quantities of inactive kinin precursor protein (kininogen), from which free kinin may be released, by the action of readily activated proteolytic enzymes also present in blood, the plasma-kallikreins. Once released, the free kinins are rapidly destroyed by plasma-peptidases.

We have confirmed that raised levels of bradykinin-like activity are found in the blood of carcinoid patients, and demonstrated a release of bradykinin-like activity in the blood of patients during the flushing phase of the dumping syndrome.

Clinical Features and Procedures

Clinical Features

We investigated eight cases of postcibal dumping. All patients had previously had a Polya partial gastrectomy. They were males aged 30-55. They were investigated at least 6 months after operation, and were selected because they were exhibiting, in particular, the vasomotor features of the dumping syndrome.

Four patients were investigated because of features of the carcinoid syndrome. Patient 1 (Kinloch, Webb, Eccleston, Zeilin 1965) and patient 2 (no. 1 in the series of Smith et al. [1965]) have been described elsewhere. Patients 3 and 4 presented with histories of diarrhoea and abdominal discomfort. They were said by the referring doctor to have had repeated attacks of flushing. In patient 3, investigation revealed a raised 5-hydroxyindoleacetic acid (5-H.I.A.A.) in the urine (255 mg. per 24 hours) and the liver-biopsy specimen showed anaplastic tumour. The blood-5-H.T. outside the flush phase, was 0.35 µg. per ml. Necropsy revealed a bronchial carcinoma of the oat-cell variety. Patient 4 had a laparotomy which disclosed tumour tissue of carcinoid type in mesenteric lymph nodes and liver. At this time his 5-H.I.A.A. excretion was within normal limits (9-3 mg. per 24 hours). The primary tumour was never identified but was thought possibly to be in the duodenum. Later, the patient began to have intermittent flushing attacks, mainly postcibal. These attacks varied and could be regularly induced by injection of adrenaline (10 µg. intravenously). Blood-5-H.T. before and during one of these attacks was 0.35 µg. per ml.
Clinical Procedures

Four patients with dumping provoked by ingesting 50 g. glucose in 250 ml. warm water had venous blood-samples examined for 5-H.T. content before, during, and after their attacks. The urinary excretion of 5-H.I.A.A. in the patients was calculated for 24-hour periods during which repeated attacks, three or four times per day, had been provoked by normal food intake.

Another group of four patients had dumping attacks similarly provoked by hypertonic glucose and samples of blood were taken for kinin and kininogen assay before, during, and after each attack. Blood-pressure and pulse-rate were examined while the patients were standing. The dumping features usually reached a peak between 10 and 20 minutes after ingestion of the glucose solution.

As a control experiment, a placebo of 250 ml. water, sweetened with saccharin comparable to the hypertonic glucose dumping stimulus, was administered to three of these patients. As a further control, 250 ml. of hypertonic glucose were administered to 4 healthy volunteers. In both control experiments, blood-samples were taken before and after the dumping stimulus, and assayed for kinin and kininogen content.

Methods

5-H.T. and 5-H.I.A.A. were determined by the methods of Crawford, Ashcroft, Eccleston, and Smith (1965) and McFarlane et al. (1956), respectively.

Kinin and kininogen assay.—6 ml. blood-samples were taken from an arm vein, and assayed for free kinin activity and kininogen concentration, as described by Zeitlin and Brocklehurst (1966). The routine kinin assays were carried out using isolated oestrus rat uterus (Gaddum et al. 1949).

Characterisation of kinin-like activity.—In some of the samples in which free kinin-like activity was detected, its polypeptide nature was demonstrated by its inactivation when incubated with chymotrypsin (250 μg. per ml.) at pH 7.4 for 60 minutes.

In some samples the similarity of the extracted activity to the kinins was shown using the isolated rat duodenum (Gaddum and Horton 1959) which contracts to acetylcholine, 5-H.T., histamine, substance P, gastrin, and other pharmacological substances, but is only known to relax to the kinins and the catecholamines. One sample was assayed against bradykinin on isolated rat uterus, rat duodenum, and guineapig ileum, and the index of discrimination was calculated (Gaddum 1955).

Statistics

The 5-H.T. and 5-H.I.A.A. results were analysed using the Student's t test. The kinin and kininogen values were analysed using non-parametric techniques. Paired results were tested using the Wilcoxon signed-ranks test.
Table I—Whole-Blood 5-H.T. and Urinary 5-H.I.A.A. in Dumping Patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Whole-blood 5-H.T. (μg./ml.)</th>
<th>Urinary 5-H.I.A.A. (mg./24 hr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-dumping control</td>
<td>Dumping peak</td>
</tr>
<tr>
<td>1</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>2</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>4</td>
<td>0.08</td>
<td>0.1</td>
</tr>
</tbody>
</table>

The mean of values in seven healthy volunteers—7.1, 2.9, 6.1, 7.1, 3.8, 4.2, and 11.1—was 6.0 mg. urinary 5-H.I.A.A. per 24 hours.

Table II—Whole-Blood 5-H.T. and Urinary 5-H.I.A.A. in Carcinoid Patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Severity of symptoms</th>
<th>Whole-blood 5-H.T. (μg./ml.)</th>
<th>Urinary 5-H.I.A.A. (mg./24 hr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Continuous lobster colour</td>
<td>0.82</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>Transient flushing</td>
<td>2.00</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>Non-flushing</td>
<td>0.37</td>
<td>255</td>
</tr>
<tr>
<td>4</td>
<td>Transient flushing</td>
<td>0.35</td>
<td>9.3</td>
</tr>
</tbody>
</table>

Results

Blood-5-H.T. Levels and 5-H.I.A.A. Excretion in Dumping and Carcinoid Patients

Whole-blood 5-H.T. levels were measured in the venous blood of four dumping patients before and during experimentally provoked dumping (table I). For these patients, the mean concentration at the dumping peak was not significantly greater than the mean pre-dumping control value (p > 0.05).

For these same patients, the urinary excretion of the 5-H.T. metabolite 5-H.I.A.A. during a 24-hour period in which postcibal dumping occurred, was measured (table I). The mean value for the four patients (15.5 mg.) was compared with the mean 24-hour 5-H.I.A.A. excretion of seven healthy people of 6.0 mg. The dumping patients excreted more 5-H.I.A.A., and this difference was highly significant (p < 0.01).

The whole-blood 5-H.T. levels obtained after flush provocation, and 24-hour urinary 5-H.I.A.A. levels for the four carcinoid patients were also known (table II). These values show no clear relationship to the severity of the symptoms, the 5-H.I.A.A. levels in fact decreasing with increasing severity in three of the patients. The values are compared in fig. 1 with those obtained from the dumping patients.
Fig. 1—Venous whole-blood 5-H.T. and 24-hour 5-H.I.A.A. in carcinoid and dumping patients.

(a) Levels of venous whole-blood 5-H.T. in four carcinoid patients after flush provocation, and in four patients before and at the height of vasomotor dumping.

(b) 24-hour excretion of 5-H.I.A.A. in the urine of four carcinoid patients, four dumping patients, and seven healthy volunteers.
### TABLE III—KININ PRECURSOR AND FREE KININ IN FOUR CARCINOID PATIENTS

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Severity of symptoms</th>
<th>Bradykinin equivalents of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Kinin precursor (µg./ml.)</td>
</tr>
<tr>
<td>1</td>
<td>Continuous lobster colour</td>
<td>16.6</td>
</tr>
<tr>
<td>2</td>
<td>Transient flushing</td>
<td>4.9</td>
</tr>
<tr>
<td>3</td>
<td>Non-flushing</td>
<td>6.6</td>
</tr>
<tr>
<td>4</td>
<td>Transient flushing (appr. 3.5)</td>
<td>7.0 (control)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.8 (height of flush)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.5 (after flush)</td>
</tr>
</tbody>
</table>

**Carcinoid Patients: Plasma Kinin and Kininogen Levels**

Kininogen and free kinin levels were measured in the venous blood of four carcinoid patients who showed symptoms of varying severity (table III). In only one of these (patient 4) was it possible to obtain samples before, during, and after the flush.

Patient 1, a terminal case, showed very severe symptoms, and was a continuous lobster colour. His free kinin level was 15.6 times the mean level found in healthy people (Zeitlin and Brocklehurst 1966).

Patients 2 and 4 showed the typical transient flush of the carcinoid syndrome. At the height of the flush (provoked by 10 µg. adrenaline intravenously) we found levels of free kinin of 9.4 and 8.7 times normal, respectively. Patient 4 (fig. 2) showed normal free kinin levels before flush provocation, and showed levels approaching normal as the flush subsided. The kinin-precursor level fell steadily during the onset and subsidence of the flush in this patient, indicating a continuous release of kinin throughout the syndrome.

Patient 3, although showing other features of the carcinoid syndrome, could in no way be provoked to flush. His free kinin level was at all times a little below the mean normal value.

Thus the levels of free plasma-kinin measured in these four patients increased with increasing severity of their symptoms.

**Dumping Patients: Plasma Kinin and Kininogen Levels**

Free kinin and kininogen levels were estimated in the venous blood of four dumping patients before and during experimentally provoked dumping. With patient D, one dumping provocation was carried out; with each of patients A and C, dumping provocation was carried out twice on
separate days. With patient B one of the dumping experiments gave unusually high control and dumping peak free kinin levels, and a third experiment was carried out with this patient.

The results are shown in table IV. In every case we found a striking increase in free plasma-kinin during the syndrome (fig. 3). The peak levels showed wide scatter, but averaged 37 times the mean pre-dumping control level. In every case too, a simultaneous fall in kininogen level was measured (fig. 4). The mean level at the dumping peak was 75.8% (range 36.7-98.4%) of the pre-dump control. Both of these changes were highly significant (p < 0.01). The increase in free kinin-like activity was coincident with a flushing phase and a transient hypotension (fig. 5), usually occurring about 20 minutes after provocation. The maximum levels of free plasma-kinin measured in these patients at the height of their symptoms were at least as great as those measured in the carcinoid patients (fig. 6).

To assess whether the kinin release was truly related to the dumping syndrome in these patients, and was not merely a non-specific response produced by ingesting

---

**FREE KININ**

<table>
<thead>
<tr>
<th>Bradykinin Equivalents</th>
<th>% of Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.50</td>
<td>100</td>
</tr>
<tr>
<td>2.25</td>
<td>90</td>
</tr>
<tr>
<td>2.00</td>
<td>80</td>
</tr>
<tr>
<td>1.75</td>
<td>70</td>
</tr>
<tr>
<td>1.50</td>
<td>60</td>
</tr>
<tr>
<td>1.25</td>
<td>50</td>
</tr>
<tr>
<td>1.00</td>
<td>40</td>
</tr>
<tr>
<td>0.75</td>
<td>30</td>
</tr>
<tr>
<td>0.50</td>
<td>20</td>
</tr>
<tr>
<td>0.25</td>
<td>10</td>
</tr>
</tbody>
</table>

**KININOGEN**

<table>
<thead>
<tr>
<th>Bradykinin Equivalents</th>
<th>% of Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.50</td>
<td>100</td>
</tr>
<tr>
<td>2.25</td>
<td>90</td>
</tr>
<tr>
<td>2.00</td>
<td>80</td>
</tr>
<tr>
<td>1.75</td>
<td>70</td>
</tr>
<tr>
<td>1.50</td>
<td>60</td>
</tr>
<tr>
<td>1.25</td>
<td>50</td>
</tr>
<tr>
<td>1.00</td>
<td>40</td>
</tr>
<tr>
<td>0.75</td>
<td>30</td>
</tr>
<tr>
<td>0.50</td>
<td>20</td>
</tr>
<tr>
<td>0.25</td>
<td>10</td>
</tr>
</tbody>
</table>

**CARCINOID SUBJECT**

- **Patient 4 (carcinoid):** levels of free kinin and kininogen in the venous plasma before, during, and after the flush provoked by 10 μg. intravenous adrenaline.

---

**Fig. 2**—Patient 4 (carcinoid): levels of free kinin and kininogen in the venous plasma before, during, and after the flush provoked by 10 μg. intravenous adrenaline.
<table>
<thead>
<tr>
<th>Kinin precursor (µg/ml)</th>
<th>Bradykinin equivalents of:</th>
<th>Free kinin (µg/100 ml)</th>
<th>Dump peak</th>
<th>After dump</th>
<th>Pre-dump control</th>
<th>After dump</th>
<th>Pre-dump control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dumping patients (provocation)</td>
<td>A</td>
<td>7.6</td>
<td>3.9</td>
<td>5.8</td>
<td>0.24</td>
<td>7.50</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>8.4</td>
<td>4.7</td>
<td>9.0</td>
<td>0.35</td>
<td>261.50</td>
<td>3.85</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>6.9</td>
<td>5.6</td>
<td>6.5</td>
<td>0.15</td>
<td>151</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>8.1</td>
<td>4.8</td>
<td>7.2</td>
<td>0.37</td>
<td>153</td>
<td>0.37</td>
</tr>
<tr>
<td>Healthy volunteers (provocation)</td>
<td>E</td>
<td>3.7</td>
<td>3.5</td>
<td>3.4</td>
<td>0.17</td>
<td>10.1</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>4.5</td>
<td>4.6</td>
<td>4.5</td>
<td>0.37</td>
<td>261.50</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>2.9</td>
<td>2.8</td>
<td>2.5</td>
<td>0.37</td>
<td>220</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>2.1</td>
<td>2.0</td>
<td>2.1</td>
<td>0.37</td>
<td>151</td>
<td>0.37</td>
</tr>
</tbody>
</table>

* Provocation by hypertonic glucose. + Saccharin.
250 ml. of fluid, or produced perhaps by the emotional stress of sample taking, a sham experiment was carried out with three of the four patients. Provocation was attempted with a placebo consisting of 250 ml. of saccharin-flavoured water. In no patient was an increase in plasma-kinin activity, or a significant fall in precursor level detected (see table IV and figs. 3 and 4).

Finally, to determine whether the kinin release found in the dumping patients was directly related to their dumping syndrome, and not merely an unrelated effect of ingesting hypertonic glucose, we administered hypertonic glucose 250 ml. to four healthy volunteers. Again, in these

---

**Fig. 3**—Levels of venous free-plasma-kinin measured before and at the height of vasomotor symptoms of the dumping syndrome.

Interrupted line represents the level above which symptoms are usually seen.

(a) Levels in dumping patients A–D; dumping provoked by ingestion of 250 ml. hypertonic glucose.

(b) Levels in dumping patients A–C (○), after ingesting 250 ml. hypotonic saccharin placebo and in healthy controls E–H (●), after ingesting 250 ml. of hypertonic glucose.
individuals, no change in free kinin or kininogen level was detected (table IV and figs. 3 and 4).

Characterisation of Free Kinin-like Activity from Carcinoid and Dumping Patients

Although the changes found in plasma-kinin levels were dramatic, the quantities involved were minute, making it difficult to apply several characterisation tests to the same sample.

Carcinoid patients.—The free-kinin extracts obtained from carcinoid patients 1 and 2 relaxed the isolated rat duodenum (fig. 7). The rat duodenum was found to contract to 5-H.T., substance P, histamine, gastrin, and acetylcholine, and to relax to adrenaline and to bradykinin. The extracts also contracted rat uterus in the presence of atropine and a 5-H.T. antagonist (BOL-148, 2-bromo-lysergic acid diethylamine, Sandoz). The rat uterus is relaxed by adrenaline, so the activity could be distinguished

---

Fig. 4—Kinin-precursor levels in venous plasma at the height of and the cessation of the vasomotor symptoms of the dumping syndrome.

(a) Levels in dumping patients A–D, dumping provoked by ingestion of 250 ml of hypertonic glucose.

(b) Levels in dumping patients A–C (Θ), after ingesting 250 ml. of hypotonic saccharin placebo; and in healthy controls E–H (●), after ingesting 250 ml. hypertonic glucose.
from adrenaline and from the other substances mentioned, but was indistinguishable from bradykinin.

*Dumping patients.*—Free-kinin activity from samples taken at the dumping peak in two patients was destroyed on incubation with the peptidase chymotrypsin, indicating the polypeptide nature of the substance involved. The activity from two samples relaxed the isolated rat duodenum (fig. 7). Since the active principle also contracted rat uterus in the presence of atropine and BOL, it was shown to be bradykinin-like. In addition, the activity from one sample was assayed against synthetic bradykinin, using three different isolated tissues—oestrus rat uterus, rat duodenum, and guineapig ileum. The values found for the kinin content of the extract were in the ratios of 1.1/1.0/1.0 for the three tissues respectively. This is strong pharmacological evidence for the close identification of the extracted activity with bradykinin.

**Fig. 5**—Systolic blood-pressures and pulse-rates measured in dumping patients A-D in the standing position, before and after dumping provoked by ingestion of 250 ml of hypertonic glucose.

Hatched areas represent clinical assessment of the severity of symptoms.
**Bradykinin Equivalents**

\[ \text{\(\mu g/100\text{ml Plasma}\)} \]

<table>
<thead>
<tr>
<th>Carcinoid Subjects</th>
<th>Dumping Subjects (Mean flush peak Values)</th>
<th>Normal Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 6—Highest free-kinin levels in the venous plasma of carcinoid patients 1-4 after provocation of symptoms, and in dumping patients A-D and healthy volunteers E-H, after ingestion of 250 ml. of hypertonic glucose.

Fig. 7—Smoked-drum tracing showing characteristic relaxation of isolated rat duodenum by bradykinin-like activity in ethanol extracts from the venous blood of flushing carcinoid and dumping patients.

BK = Standard bradykinin.
SP = Substance P.
D = Dumping sample.

\(C_1\) and \(C_2\) = Samples from two carcinoid patients.
The fact that in both the carcinoid and dumping syndromes the appearance of the raised bradykinin-like activity was associated with a fall in plasma-kininogen levels, indicated that this activity originated from a kinin-precursor protein in the plasma.

Discussion

Various workers have shown that in vitro, 5-H.T. is released by guinea pig small intestine in response to distension (Bülbring and Lin 1958, Bülbring and Crema 1959). An increase in 5-H.T. levels in the venous blood draining the small intestine has been found by several workers during dumping in dogs (Drapanas et al. 1962, Peskin and Miller 1962, Sloop et al. 1962, Walker et al. 1962). But the released 5-H.T. is rapidly metabolised and none of these workers reported raised levels in peripheral blood. Walker et al. (1962) were unable to detect raised 5-H.T. levels in even the portal venous blood during dumping in dogs, without prior administration of an amine-oxidase inhibitor to prevent destruction of 5-H.T. In man, no consistent relationship has been found between the symptoms of dumping patients and either blood 5-H.T. levels or the excreted 5-H.T. metabolite, 5-H.I.A.A. (Howe 1964, Silver et al. 1965).

Thus, whether or not 5-H.T. release is involved in the production of the dumping syndrome, the changes in blood-5-H.T. level, where detectable, are very small. They are unlikely to account for the frequently severe vasomotor changes seen in this condition—i.e., postural hypotension, increased heart-rate and peripheral vasodilatation (Hinshaw et al. 1957, Castenfors 1961, Cox and Allan 1961, Christoffersson 1965). In particular, a release of 5-H.T. alone would not account for the flush, and vasodilatation of the skin vessels frequently seen during the dumping syndrome (Hinshaw et al. 1957) since infusion of 5-H.T. in man produces striking cutaneous vasoconstriction (Fox et al. 1961).

Many features of the dumping syndrome are similar to those of the carcinoid syndrome. Both are often provoked by similar types of stimulus and are characterised by very similar intestinal, and vasomotor symptoms. An involvement of 5-H.T. in the carcinoid syndrome is well established, and grossly raised levels of blood-5-H.T. and urinary 5-H.I.A.A. are diagnostic of the condition (Smith 1965, Stacey 1966). Yet not even the vasomotor symptoms of the carcinoid syndrome are adequately explained by the release of 5-H.T. (Lancet 1962). Oates et al. (1964) showed that raised blood-levels of a plasma-kinin-like polypeptide
were associated with the appearance of the flush of carcinoid patients. Our results support this finding.

In our carcinoid patients, although abnormally high levels of both blood-5-H.T. and urinary 5-H.I.A.A. excretion were seen, there was no obvious relationship between the size of the abnormality and the severity of the symptoms. But there was a clear relationship between the release of free kinin into the circulation and the appearance and severity of flush in these patients.

Investigation into the dumping syndrome indicates a picture similar to that seen in the carcinoid syndrome. Although no change in blood-5-H.T. was detected in patients during dumping symptoms (possibly owing to the small number of patients examined), their 24-hour urinary excretion of 5-H.I.A.A. was more than twice as great as normal. In these patients, however, the vasomotor symptoms of dumping (manifested as facial flushing, and transient hypotension) were found to be clearly related to the appearance of raised levels of free kinin in the circulation. These levels of free kinin were at least as great as those measured in patients during the carcinoid flush.

Infusion of bradykinin in healthy individuals reproduces vasomotor symptoms seen in both carcinoid and dumping patients—flushing and cutaneous vasodilatation, transient hypotension and increase in pulse-rate (Fox et al. 1961, Bishop et al. 1965). In carcinoid patients, while grossly abnormal indole metabolism is generally observed, such abnormality is not consistently related to their vasomotor symptoms. Our results support the claim that these vasomotor changes are mediated by the release of vasoactive kinins into the circulation (Oates et al. 1964). In dumping patients, abnormal indole metabolism, although present, is barely detectable, and is not likely to be responsible for the frequently severe vasomotor changes seen in this condition. The release of plasma-kinin, as indicated by these results, could reasonably account for the vasomotor symptoms of the dumping syndrome.

Summary

The “dumping” syndrome consists of both intestinal and vasomotor symptoms, and in this respect it is similar to the carcinoid syndrome. Release of 5-hydroxytryptamine (5-H.T.) into the bloodstream could account for the intestinal symptoms, but not, consistently, the vasomotor changes. In some carcinoid patients the release of bradykinin-like activity into the circulation during flushing is confirmed. Abnormally raised blood-levels of 5-H.T.,
and increased urinary excretion of 5-hydroxyindoleacetic acid (5-H.I.A.A.) were also observed in these patients.

Dumping patients showed no significant increase in circulating 5-H.T. during the vasomotor symptoms, although their 24-hour 5-H.I.A.A. excretion was raised. But during the vasomotor symptoms of dumping, a release into the circulation of a bradykinin-like polypeptide, and a concomitant fall in plasma-kininogen was observed.

The work of one of us (I. J. Z.) was supported by a grant from the Scottish Hospitals Endowment Research Trust, under the supervision of Prof. W. L. M. Perry and Dr. W. E. Brocklehurst, and forms part of a thesis submitted for the degree of Ph.D., University of Edinburgh. We thank Sir John Bruce and the physicians and surgeons of the Gastrointestinal unit for their interest and cooperation; Dr. H. Holgate of Sandoz Ltd. for a gift of bradykinin; Dr. I. Laszlo for a sample of substance P; and Prof. R. A. Gregory who gave a sample of gastrin II to the Gastrointestinal unit.

Requests for reprints should be addressed to A. N. S., Department of Clinical Surgery, The University, Teviot Place, Edinburgh 8.

REFERENCES
Lancet (1962) i, 576.

The Lancet Office, 7, Adam Street, Adelphi, London, W.C.2
Faecal stasis and diverticular disease in ulcerative colitis

K. N. JALAN, R. J. WALKER, R. J. PRESCOTT, S. T. G. BUTTERWORTH, A. N. SMITH, AND W. SIRCUS

From the Gastrointestinal Unit, and the Department of Pathology, Western General Hospital, Edinburgh, and the Computer and Statistics Section, Department of Social Medicine, University of Edinburgh

SUMMARY The incidence of faecal stasis and of diverticular disease has been studied in a group of 399 patients with ulcerative colitis. Sixty-one patients had faecal stasis and 23 patients had diverticular disease. Pathological studies demonstrated an increase in the thickness of the inner spiral muscle in colitis patients with faecal stasis. The thickening was not as great as that seen in diverticular disease. Preliminary studies on the motility patterns in patients with faecal stasis show a higher mean activity in the pelvic colon than in normals but not as great as that seen in diverticular disease. Pressure studies in patients with faecal stasis have shown hypotonia in the proximal colon associated with dilatation.

The possible significance of these results is discussed. It is suggested that ulcerative colitis may initiate a motility disturbance which leads to muscle thickening similar to that in diverticular disease. Diverticula associated with ulcerative colitis are usually not involved in the mucosal inflammatory process.

It is recognized that constipation may occur in patients with proctocolitis (Royal Society of Medicine, 1969; Sim and Brooke, 1958; Nezger and Acheson, 1963; Goligher, de Dombal, Watts, and Watkinson, 1968), and in up to one third of patients with proctitis (Lennard-Jones, Cooper, Newell, Wilson, and Jones, 1962a). Constipation as a prominent disability was described in six patients with distal proctocolitis all of whom had severe disease with retention of faeces in the proximal colon (Lennard-Jones, Langman, and Jones, 1962b). Constipation is recognized as a prominent disability in up to one third of patients with proctitis (Lennard-Jones, Cooper, Newell, Wilson, and Jones, 1962a).

We have studied this association as part of a retrospective survey involving 399 patients with ulcerative colitis (Jalan, Prescott, Sircus, Card, McManus, Falconer, Small, Smith, and Bruce, 1969). In view of the possibility that the cause of the constipation could be in disordered motor activity of the large bowel, we have examined the incidence and possible significance of diverticular disease when this occurred in association with ulcerative colitis. Differences have been sought in the clinical and pathological features of those colitis patients with constipation, both with and without diverticular disease, from those of the remainder of the series. Large bowel motility was studied in a small number of patients.

Method

The retrospective study covers the period 1961 to 1967 (inclusive). The primary source of data was the case records, the information being transferred to cards and the material analysed by Atlas computer.

The diagnosis of faecal stasis in colitis was made when a change of bowel habit occurred becoming less frequent than normal and the need for laxatives. Radiological evidence of faeces in the proximal colon was usually observed. Barium often persisted in the right half of the colon a week or even a month after a barium enema (Figs. 1 and 2). Diverticular disease was diagnosed on the presence of one or more diverticula with or without radiological evidence of motor or inflammatory abnormality in the colon. In the whole series there were 173 males and
Faecal stasis and diverticular disease in ulcerative colitis

Fig. 1 Barium mass in the ascending colon in a patient with faecal stasis one day after barium enema.

Fig. 2 Same patient as in Figure 1. Barium mass still present 18 days later.

females. One hundred and ninety-one patients were in a first attack of colitis and 208 in relapse.

MOTILITY STUDIES
Motor activity of the proximal colon was assessed in eight patients and four controls using a radiotelemetering capsule (Solartron capsule); pressure waves were recorded from the frequency change, 'movement activity' from the signal strength, and progression from the change in the 'edge' of the radiomagnetic field (Smith and Ridgway, 1962).

Pressure activity in the sigmoid zone and rectum was examined in five patient's with faecal stasis, 29 patients with uncomplicated diverticular disease, and in 14 control subjects by peranal passage of miniature balloons on air-filled polythene tubes. These were connected by Statham transducers to electromanometers within a photorecording device; basal tone was recorded and meals or prostigmine (0-5-1 mg) were used as stimuli.

PATHOLOGY
Histological material from 15 patients with faecal stasis was available for study. Studies of the colons of 26 patients with ulcerative colitis but without faecal stasis served as controls. The intact specimens of resected colon were not available at the time of this study, but the pathologists' original reports of the microscopic appearances of these were analysed and considered, together with a review of the remaining blocks and sections from known sites in the colon. An eye-piece micrometer was used to measure the maximum thickness of the circular muscle coat in sections from the descending and sigmoid colon.

Results

CLINICAL ASSESSMENT

Incidence
Faecal stasis was present in 15·8% of patients with ulcerative colitis. In some cases constipation was the major source of disability and such patients correspond to those described by Lennard-Jones et al (1962b). Of 79 patients with disease confined to the rectum, 21 had stasis. This incidence of 26·6% is similar to that reported by Lennard-Jones and his colleagues (1962a) in proctitis. It is rare in the young (Fig. 3).

We also confirmed the commoner incidence of faecal stasis in females (Table I). Five out of the six cases of stasis described by Lennard-Jones et al (1962b) were female.

Previous history
Twenty per cent of the patients with faecal stasis reported constipation before the onset of colitis compared with 5·3% of the patients without stasis. It is emphasized that a history of
Sex Faecal Stasis

<table>
<thead>
<tr>
<th></th>
<th>With</th>
<th>Without</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>18</td>
<td>155</td>
</tr>
<tr>
<td>Female</td>
<td>43</td>
<td>183</td>
</tr>
</tbody>
</table>

Table I Sex incidence in patients with faecal stasis

\[ \chi^2 = 4.98, \text{df} = 1, 0.025 < p < 0.05. \]

constipation is subjective. Frequencies shown are of visits to the lavatory (Table II). Faeces are not always passed on each occasion but often only mucus, mucopus, or blood without faeces.

<table>
<thead>
<tr>
<th>No. of Motions</th>
<th>Faecal Stasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With</td>
</tr>
<tr>
<td>0-4</td>
<td>17</td>
</tr>
<tr>
<td>5-8</td>
<td>33</td>
</tr>
<tr>
<td>9+</td>
<td>11</td>
</tr>
</tbody>
</table>

Table II Frequency of bowel motion in patients with faecal stasis

\[ \chi^2 = 6.00, \text{df} = 2, 0.025 < p < 0.05. \]

Length of history
Stasis is relatively more common in patients with disease of short duration (Table III), and incidence is the same in the first attacks as in relapses and in colitis of gradual or sudden onset.

Severity, extent, and prognosis
A scoring procedure was used to classify patients into three grades of severity: mild, moderate, and severe (Jalan et al., 1969). The variables used were fever, number of bowel movements, and eosinocyte sedimentation rate. A significant relationship between stasis and severity of disease was not established (Table IV). A larger proportion of patients with faecal stasis had a normal barium enema or partial ‘left-sided’ colitis as compared with the remaining patients (Table V). Faeces, stasis was observed in only seven subjects with extensive involvement of the colon. Likewise the incidence of colonic stricture and of colonic dilatation was less than that found in the wide without stasis (Table VI). Not surprisingly therefore, the outcome in patients with faecal stasis is good so that the phenomenon is probably an expression of the better prognosis of patients with distal involvement regardless of the severity of the attack (Table VII). Furthermore a smaller proportion of patients with stasis showed decrease in severity with time, and a smaller number of patients had continuous disease as compared with the stasis group.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Faecal Stasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With</td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
</tr>
<tr>
<td>Female</td>
<td>43</td>
</tr>
</tbody>
</table>

Table III Length of history in patients with faecal stasis

\[ \chi^2 = 5.25, \text{df} = 2, 0.05 < p < 0.1. \]

<table>
<thead>
<tr>
<th>Severity</th>
<th>Faecal Stasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With</td>
</tr>
<tr>
<td>Mild</td>
<td>34</td>
</tr>
<tr>
<td>Moderate</td>
<td>15</td>
</tr>
<tr>
<td>Severe</td>
<td>12</td>
</tr>
</tbody>
</table>

Table IV Severity of colitis in patients with faecal stasis

\[ \chi^2 = 3.72, \text{df} = 2, 0.10 < p < 0.20. \]

<table>
<thead>
<tr>
<th>Extent</th>
<th>Faecal Stasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With</td>
</tr>
<tr>
<td>Normal</td>
<td>21</td>
</tr>
<tr>
<td>Partial left</td>
<td>31</td>
</tr>
<tr>
<td>Entire</td>
<td>7</td>
</tr>
<tr>
<td>Not known</td>
<td>2</td>
</tr>
</tbody>
</table>

Table V Extent of bowel involvement (radiology) in patients with faecal stasis

\[ \chi^2 = 24.56, \text{df} = 3, p = < 0.0005. \]

\[ \chi^2 = 6.00, \text{df} = 2, 0.025 < p < 0.05. \]
Faecal stasis and diverticular disease in ulcerative colitis

<table>
<thead>
<tr>
<th>Faecal Stasis</th>
<th>With</th>
<th>Without</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic stricture</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>No colonic stricture</td>
<td>60</td>
<td>321</td>
</tr>
<tr>
<td>Toxic dilatation</td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>No toxic dilatation</td>
<td>58</td>
<td>286</td>
</tr>
</tbody>
</table>

Table VI Toxic dilatation and colonic stricture in relation to faecal stasis

\[ p > 0.1 \text{ (exact test)} \]
\[ x^2 = 3.93, df = 1, 0.025 < p < 0.05. \]

Table VII Outcome of first referred attack in patients with faecal stasis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Faecal Stasis</th>
<th>Without</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission</td>
<td>53</td>
<td>211</td>
</tr>
<tr>
<td>Improved</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Surgical survivors</td>
<td>5</td>
<td>74</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical treatment</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>After surgery</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>338</td>
</tr>
</tbody>
</table>

Twenty-three patients in whom colitis and diverticular disease coincided were similarly analysed. Seven of these had faecal stasis. The incidence of faecal stasis in patients with colitis and diverticular disease is not different from the rest of the population of colitis. In respect of sex, age at onset, previous bowel habit, site of attack, onset of colitis, extent of involvement, severity, and prognosis, no differences emerge from those characteristics in the group of colitics without diverticular disease.

**Pathology**

The incidence of pericolicitis, submucosal fibrosis, and destruction of ganglion cells was the same in the two groups of patients with and without stasis. As already shown in the clinical assessment, the proportion of patients with limited or distal colitis was much greater in the group of patients with faecal stasis and proximal dilatation of the colon was much commoner. In the latter subjects, the mucosa of the proximal colon tended to be rather thin, but only in three was this a notable feature (< 0.3 mm); all had associated diverticular disease.

It is of interest that in three patients the inflammatory changes of ulcerative colitis were slight or absent in the mucosal portion of the diverticula (Figs. 4 and 5). Of six patients with colitis and with diverticular disease and faecal stasis, in only three was the diagnosis of diverticular disease made by radiology. Only one patient had an organic obstruction, a kink in the bowel apparently caused by pericolic fibrosis.

**Fig. 5**

Figs. 4 and 5 Diverticulum (left) in a case of ulcerative colitis. Inflamed mucosa and granulation tissue can be seen at the neck, but the inflammation does not extend into the compressed diverticular mucosa (× 15, haematoxylin and eosin). Magnified (above) view of junction of compressed and inflamed areas. (× 75, haematoxylin and eosin).
Thickness of muscle layers

Information on the thickness of the circular muscle (Fig. 6) of the colon in colitis patients with faecal stasis, in diverticular disease associated with faecal stasis, and in two control groups of patients with ulcerative colitis without faecal stasis and patients with diverticular disease but no ulcerative colitis is summarized in Table VIII. The last group (diverticular disease) were patients operated upon for the disease. No significant difference appears in the mean values for circular muscle thickness among patients with faecal stasis associated with ulcerative colitis whether diverticular disease was present or not ($t = 1.00, 0.3 < p < 0.4$) but the patients with faecal stasis alone showed a greater variance ($t = 5.86, 0.01 < p < 0.05$). The combined group of all patients with faecal stasis in ulcerative colitis shows a highly significant increase in muscle thickness over the control patients with uncomplicated ulcerative colitis. The second control group of patients with diverticular disease alone show a highly significant increase in muscle thickness as compared with that of the patients with faecal stasis and colitis. An increased variance of muscle thickness was also present in this group.

Table VIII  Circular muscle thickness in ulcerative colitis in patients with faecal stasis and diverticular disease

<table>
<thead>
<tr>
<th>Group</th>
<th>1 (Control) Ulcerative Colitis Only</th>
<th>2 Faecal Stasis with Ulcerative Colitis</th>
<th>3 (Control) Diverticular Disease Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>26</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Muscle thickness (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0-6-2-1</td>
<td>0-8-2-8</td>
<td>1-2-2-5</td>
</tr>
<tr>
<td>Mean</td>
<td>1-18</td>
<td>1-63</td>
<td>3-26</td>
</tr>
<tr>
<td>SD</td>
<td>0-40</td>
<td>0-52</td>
<td>1-28</td>
</tr>
<tr>
<td>Test on variances</td>
<td>$r = 1.69, p &gt; 0.05$</td>
<td>$r = 6.11, p &lt; 0.01$</td>
<td></td>
</tr>
<tr>
<td>Test on means</td>
<td>$t = 3.07, 0.001 &lt; p &lt; 0.005$</td>
<td>$t = 4.55, p &lt; 0.001$</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 6  Descending colon in a case of ulcerative colitis and faecal stasis, but without diverticular disease, to illustrate the thickness (1.8 mm) of the muscular coat ($\times 40$, haematoxylin and eosin).

Table VIII  Circular muscle thickness in ulcerative colitis in patients with faecal stasis and diverticular disease

1Including six patients with diverticular disease and faecal stasis. Range; 1-1-1-9, mean 1-48, SD 0-26.
2Welch's modification of $t$ test for different variances applied.
Faecal stasis and diverticular disease in ulcerative colitis

Fig. 7 Telemetering capsule passing from the terminal ileum into the caecum faintly outlined by previous administration of barium most of which by this time had been evacuated.

Left colon
The mean motility index, defined as the product of the mean wave height in millimetres of water and the percentage duration of waves occurring during the recorded period, was calculated in 14 control subjects. It was found to be 166 in the basal state, 322 for the gastrocolic reflex stimulation, and 806 after prostigmine injection. In five patients with colitis and faecal stasis the mean motility index was 204 in the basal state, 668 after gastrocolic reflex stimulation, and 1,400 after prostigmine. The mean responses to prostigmine in faecal stasis lay between the values for normal subjects given above and for the diverticular disease cases (prostigmine response = 2,856) reported by Attisha and Smith (1969); the gastrocolic response was much less in both groups (mean motility index in faecal stasis 668 and in diverticular disease 740).

Discussion
Our findings confirm those of Lennard-Jones and his colleagues (1962b). The essential feature in these patients is the hold-up of faeces in the right half of the colon although all patients pass frequent stools consisting in the main of blood and mucus. Plain abdominal films in patients in whom the frequency of passage of faeces has fallen usually show evidence of stasis in the proximal colon. Stasis produces disability deserving of treatment in itself. We have found both liquid paraffin and oral diocetyl sodium sulphasuccinate to be helpful.

In our experience constipation due to stasis in proctocolitis is usually a transient affair which remits when the inflammation is brought under control but tends to recur with each exacerbation of the disease. In one patient in whom the colitis remained active over a long period barium was still present in the right half of the colon three months after a barium enema.

The incidence of stasis in our series was greatest in patients with limited distal involvement of the colon. This fits the concept discussed by Lennard-Jones et al (1962b) that the cause is a functional obstruction to the passage of
Of diverticular disease to ulcerative colitis could explain the constipation or, alternatively, in the absence of diverticular disease, it seemed possible that ulcerative colitis could bring about a similar disordered motility. On this hypothesis muscle changes might be expected in colitis, and, similar to those seen in early diverticular disease, possibly result in the formation of diverticula.

In the Oxford area the radiological incidence of diverticular disease is in the region of 30% in subjects over the age of 60 (Manousos, Truelove, and Lumsden, 1967) and compares with the 25% incidence in our patients with ulcerative colitis over the age of 60. In the age group 40-59, the incidence of diverticular disease in the Oxford area was 18.5% compared with 14.3% for our ulcerative colitis patients in this age group. These figures appear to favour an incidental association of the two diseases in our patients but there are certain difficulties with this interpretation. The diagnosis of diverticular disease in the presence of ulcerative colitis is not easy (Berenbaum, Yaghmai, and Berenbaum, 1961).

In our six pathological specimens in which the two diseases coexisted diverticula were demonstrated radiologically in only three. It may be relevant that before 1958 only one of 30% of our patients with colitis was recognized to have diverticular disease, in the following two years nine out of 61 were recognized, and up to the end of the study, 13 out of 235 cases had been recognized to have the disease. We feel, therefore, that this is due to more accurate radiological diagnosis. The true incidence of diverticular disease may be higher than our radiological based overall figure would suggest.

Although Collins (1961) reported a good prognosis in patients with ulcerative colitis complicated by acute diverticulitis, we have not encountered this association.

The pathological study supports the concept that a motility disorder similar to that seen in diverticular disease accounted for the faecal stasis because significant thickening of the inner spiral muscle of the colon was demonstrated. In diverticular disease this is accompanied by a marked thickening of the taenia which, it has been suggested, causes bunching of the colonic wall. The true incidence of diverticular disease may be higher than our radiological based overall figure would suggest.

Although Collins (1961) reported a good prognosis in patients with ulcerative colitis complicated by acute diverticulitis, we have not encountered this association.

The pathological study supports the concept that a motility disorder similar to that seen in diverticular disease accounted for the faecal stasis because significant thickening of the inner spiral muscle of the colon was demonstrated. In diverticular disease this is accompanied by a marked thickening of the taenia which, it has been suggested, causes bunching of the colonic wall. The true incidence of diverticular disease may be higher than our radiological based overall figure would suggest.

Although Collins (1961) reported a good prognosis in patients with ulcerative colitis complicated by acute diverticulitis, we have not encountered this association.

The pathological study supports the concept that a motility disorder similar to that seen in diverticular disease accounted for the faecal stasis because significant thickening of the inner spiral muscle of the colon was demonstrated. In diverticular disease this is accompanied by a marked thickening of the taenia which, it has been suggested, causes bunching of the colonic wall. The true incidence of diverticular disease may be higher than our radiological based overall figure would suggest.

Although Collins (1961) reported a good prognosis in patients with ulcerative colitis complicated by acute diverticulitis, we have not encountered this association.

The pathological study supports the concept that a motility disorder similar to that seen in diverticular disease accounted for the faecal stasis because significant thickening of the inner spiral muscle of the colon was demonstrated. In diverticular disease this is accompanied by a marked thickening of the taenia which, it has been suggested, causes bunching of the colonic wall. The true incidence of diverticular disease may be higher than our radiological based overall figure would suggest.
Faecal stasis and diverticular disease in ulcerative colitis

muscle in colitis was suggested by the work of Garrett, Sauer, and Moertel (1967), who showed significant hyperactivity of the pelvic colon in patients with mild or moderate proctocolitis after oral administration of 15 minims of tinct. opii compared with normal controls.

Other motility studies have demonstrated decreased motor activity in patients with ulcerative colitis (Spriggs, Coder, Bargen, Curtiss, and Hightower, 1951; Kern, Almy, Abbott, and Bogdonoff, 1951). Kern and his colleagues (1951) had shown an inverse relationship between the frequency of bowel habit and the total activity of the record. Chaudhary and Truelove (1961), on the other hand, suggested that the mean total activity was greater in patients with severe colitis, but Connell (1962), in a discussion of this report, pointed out that this was probably a false interpretation as the results were significantly affected by one patient with abnormally high activity and after excluding this case, the mean total activity for the remainder was less than normal. There has been great variation in the results for individual patients, but in most studies there has been no attempt to divide them on the basis of bowel frequency, and most of the patients studied have had diarrhoea. Kern et al (1951) studied the motility of the distal colon in non-specific ulcerative colitis, and hyperactive records were obtained in four patients, three of whom had constipation. Our own finding of increased activity, mainly after prostigmine stimulation in the left colon in ulcerative colitis associated with faecal stasis in the right colon, is in accord with this, and apparently agrees with our pathological study in that the mean total activity in the sigmoid colon after cholinergic stimulation for these patients fell between that of normals and that found in diverticular disease. The observation of atony and non-propulsion in the proximal colon is in keeping with the proximal dilatation observed in resected specimens and presumably reflects a passive response to the distal functional obstruction; the basal pressure fell at the ileocecal junction when a rise might have been expected if active obstruction, without atony, had been present. The observations are taken from patients in whom the orientational position of the capsule had not changed and in whom the capsule to aerial radio link had not varied, as indicated by the stability of the strength of the signal received from the capsule. An interesting histological finding was that the mucosa in many of the diverticula did not share in the inflammatory response of the surrounding mucosa, but we can offer no explanation for this unless disordered motility has some aetiological significance in colitis, as diverticula, being largely free of muscle, can have little share in the motility responses of the rest of the colon.

Our evidence suggests that when ulcerative colitis is associated with faecal stasis a muscular abnormality exists which may be indistinguishable from that seen in prediverticular disease and the irritable colon syndrome. It is possible that this in some cases leads to the formation of diverticula but loss of mucosal tissue due to ulceration would otherwise limit the process.

We wish to thank Mrs L. Lockerbie and the staff of the Computer and Statistics Section of the Department of Social Medicine, University of Edinburgh, for valuable technical assistance.

Dr K. N. Jalan was supported for this work initially by the Scottish Hospital Endowments Research Trust and later by Pharmacia (Great Britain) Ltd during the tenure of a research fellowship. Dr W. Sircus is an external member of the scientific staff of the Medical Research Council. Mr A. N. Smith was supported by a grant for motility studies by the Scottish Hospital Endowments Research Trust. We wish to thank Dr Shirley Clarke for assistance with the motility studies.

References


Mobilization of tissue kallikrein in inflammatory disease of the colon

I. J. ZEITLIN AND A. N. SMITH

From the Wolfson Laboratories, Gastrointestinal Unit, Western General Hospital, and the Department of Clinical Surgery, University of Edinburgh

SUMMARY Colonic tissue was taken at operation from 10 patients with active ulcerative colitis and three patients with uncomplicated diverticular disease but with severe symptoms. Levels of kininogen, kallikrein, and kallikrein precursor were measured in blood-free tissue samples. In normal colon tissue a kininogen occurred in the muscle and none was detected in the mucosa. Kallikrein and its precursor were found in mucosa but not in muscle. In acutely inflamed tissue from ulcerative colitis patients relatively high levels of active kallikrein were detected in the underlying colonic muscle. There was little change in the level of kallikrein in inflamed mucosa or of kininogen in the muscle of these patients. No kallikrein was found in colonic muscle from patients with diverticular disease and the mucosal kallikrein level in these patients was unchanged. The findings suggest a mechanism for the formation of kinins in the wall of the colon which is present in ulcerative colitis but not in diverticular disease.

Recent studies have shown that the gut wall contains a kallikrein-forming enzyme which is stored as an inactive precursor and which can be found in the mucosa at every level of the gut (Zeitlin, 1970, 1971, and 1972; Seki, Nakajima, and Erdős, 1972).

Kininogens are considered to be likely mediators of the inflammatory reaction (Lewis, 1963). They are potent vasodilators, enhance capillary permeability, produce pain, and their destruction is inhibited at a slightly acid pH, such as occurs in inflamed tissue. In the gut, kinins contract most longitudinal muscle while inhibiting circular muscle (Elliott, Horton, and Lewis, 1966; Fishlock, 1966). The presence, therefore, of a kallikrein-forming enzyme in the gut tissue makes it clearly of importance to determine whether this enzyme plays a role in inflammatory diseases of the gut, particularly where motility disorders are also present.

Free kinins, once they are formed, are rapidly destroyed by peptidases occurring in the blood and tissues. However, owing to their great potency, marked local effects can be caused by the occurrence of free kallikrein within tissue in quantities too minute to produce any detectable systemic changes. Their labile nature makes it impractical to look for free kinins in the gut tissue in clinical situations. In the present study, levels of relatively stable kallikrein-forming enzyme have been determined in colonic tissue from patients with ulcerative colitis or diverticular disease.

Preparation of Tissue

METHODS

Tissue was obtained from patients who were having operations for acutely active ulcerative colitis and for uncomplicated diverticular disease but with severe symptoms. In the ulcerative colitis group the operation was a proctocolectomy so that tissue was obtained from several segments of the colon. In diverticular disease the operation was more restricted (partial left hemicolectomy). In the colitis group the tissue was obtained from patients who mainly had the left and distal colon affected with minimal involvement of the proximal, ie, right colon. A main vessel was cannulated for perfusion of a diseased and a normal segment of bowel (mainly left and right colon respectively). In diverticular disease the operation specimen contained mainly the sigmoid colon with or without part of the left colon. The bowel was perfused via the sigmoid and left...
colic artery and diseased tissue excised from the sigmoid colon and normal tissue from the upper (left or descending colon) end. The perfusions were performed as soon as possible after the operative excision with heparinized (10 units/ml) Krebs-Henseleit solution at 37°C to flush out blood. If the solution was too cold, vasoconstriction prevented adequate removal of blood. With care it was possible to produce small areas of blood-free tissue which could be cut out. The tissue samples were then further washed in Krebs-Henseleit and stored in this solution at 4°C for up to one hour until transport to the laboratory for kininogen or kallikrein assay.

In the initial studies whole-thickness tissue was taken for kininogen estimation. In subsequent studies, the mucosal layer was dissected away from the muscle and the two tissues were assayed separately for kallikrein or kininogen content.

**KININOGEN ASSAY**

The tissue was washed in fresh Krebs-Henseleit solution, dried by briefly blotting with filter paper, and weighed. The available tissue per sample was usually about 0.5 g. The tissue was homogenized in 80% ethanol (about 10 ml/g) in a ground glass homogenizer. The ethanolic suspension was placed on a boiling water bath for 10 minutes to inactivate enzymes and to ensure kininogen precipitation. The homogenate was centrifuged to remove the ethanol and the precipitate was washed twice with distilled water and resuspended in distilled water. Aliquots of freshly shaken suspension were incubated with trypsin as described by Brocklehurst and Zeitlin (1967) to activate kininogen. The released kinin was compared with standard synthetic bradykinin (Sandoz) using the isolated oestrous rat uterus.

The unit of kininogen referred to in the text is the amount of kininogen releasing the equivalent of 1 µg of synthetic bradykinin when treated as described.

**KALLIKREIN ASSAY**

The tissue was washed in fresh Krebs-Henseleit solution, dried by briefly blotting with filter paper, and weighed. The weight of tissue in each sample was usually about 0.1-0.5 g. The tissue was homogenized in exactly 10 ml of fresh distilled water per gram, using a chilled ground-glass homogenizer. The homogenate was tested for unsatisfactory blood removal using Hemastix which has a detection limit of 50 µg haemoglobin per litre. Samples were then allowed to incubate under toluene for 20 hours at 20°C to allow activation of the kallikrein. The homogenates were centrifuged to remove cell debris (about 2000 g). To determine the kinin-forming activity of the supernatant, aliquots were incubated for 15 minutes at 37°C with excess of the stable substrate of Amundsen, Nustad, and Waaler (1953) in Krebs-Henseleit solution at pH 8.0. Orthoperanthonine (0.001 M) was present to inhibit kininase. The enzymic action was stopped by heating on a boiling water bath (10 min), and the incubates were rapidly frozen for storage. Extract and substrate incubated separately were included as controls. The released kinin was compared with standard synthetic bradykinin (Sandoz) using the isolated oestrous rat uterus. Where enzyme inhibitor studies were to be carried out, the extract was preincubated with inhibitor for 10 min before the addition of substrate.

The unit of kallikrein referred to in the text is the amount of kallikrein releasing the equivalent of 1 µg of synthetic bradykinin in 15 minutes when incubated as described.

**BIOASSAY**

Routine kinin assays were carried out using the atropinized isolated oestrous rat uterus (Brocklehurst and Zeitlin, 1967). With some samples, a parallel bioassay was carried out using both isolated rat uterus and the isolated rat duodenum (Gadduni and Horton, 1959) in the presence of atropine sulphate (1 µg/ml) and 2-bromoelyseric acid diethylamide (BOL-148, Sandoz) (0.5 µg/ml). Only kinins known to contract the isolated rat uterus are relax rat duodenum under these conditions.

**STATISTICS**

The Wilcoxon matched pairs signed-ranks test was used to test differences for statistical significance.

**RESULTS**

**TISSUE KININOGEN IN ULCERATIVE COLITIS**

Blood-free gut wall contains a kinin precursor which may be activated by incubation with trypsin. The kininogen content was estimated in diseased whole-thickness tissue from five patients with colitis. The level was found to be significantly raised (p < 0.05) when compared with a control sample of an adjacent area of 'normal' tissue (Fig. 1).

**DISTRIBUTION OF COLON TISSUE KININOGEN AND KININ-FORMING ENZYME IN ULCERATIVE COLITIS**

An increase in kininogen level can indicate a variation in production or consumption of kininogen. If the kininogen were not uniformly distributed through the gut wall, a loss of one of its components, such as the mucosa in ulcerative colitis, could produce an apparent increase in tissue kininogen content. In a further series of five patients, the mucosa was separated from the colonic muscle. In two of these patients sufficient blood-free tissue was obtained for assay both simultane-
Mobilization of tissue kallikrein in inflammatory disease of the colon

The muscular tissue (Table), while none could be detected in mucosa. Furthermore, with the mucosa removed, there was very little difference in kininogen level between the normal and diseased portions of tissue.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Kininogen (Units/g tissue)</th>
<th>Kallikrein (Units/g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal Muscle 0.51</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Normal Mucosa 0.49</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>Diseased Muscle 0.49</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Diseased Mucosa 0.53</td>
<td>2.1</td>
</tr>
<tr>
<td>2</td>
<td>Normal Muscle 0.53</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Normal Mucosa 0.55</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Diseased Muscle 0.55</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>Diseased Mucosa 0.55</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Table: The distribution of kallikrein and kininogen in normal and diseased colonic tissue from two patients with ulcerative colitis.

The kinin-forming activity was also not continuously distributed throughout the colon wall. In the normal tissue, the kinin-forming enzyme was present only in the mucosa (mean = 0.84 Units/g) while none could be detected in the colonic muscle (mean < 0.02 Units/g) (Table and Fig. 2). However, in the diseased segment, considerable kinin-forming activity could be detected in every case in the muscular tissue (mean = 3.4 Units/g) (Fig. 2), the values ranging from more than two to 25 times that found in the normal mucosa. When the enzyme levels in diseased and normal muscle were compared, the increase from zero occurred more often than could be accounted for by random variation (p = 0.05). The level of enzyme in the diseased mucosae (mean 1.8 Units/g) had increased when compared to the mean normal mucosa level but this was not statistically significant (p > 0.05); however it may be relevant that in colitis the mucosal layer is being destroyed and there may have been therefore an unmeasured loss into the bowel lumen.

In two patients, kinin-forming activity was estimated immediately on receipt of the tissue samples in the laboratory, and then following autolytic activation (see Methods). The results indicated that the enzyme present in the diseased muscle was entirely in the active state, while some 50% of the mucosal enzyme was in the active state. However, whether this represented the state of activation of the enzyme in vivo could not be satisfactorily determined, since activation during surgical manipulation and the necessary delay between excision and assay could not be excluded.
LEVELS OF KININ-FORMING ENZYME IN COLONIC TISSUE IN DIVERTICULAR DISEASE

Uncomplicated diverticular disease is considered nowadays to be a condition of the large bowel in which a disorder of its musculature is initially a more important feature than inflammation. Tissue was examined from patients with this condition in order to see whether kallikrein occurred in colonic muscle in an uninfamed condition, for example, secondary to motor changes, and also to provide an additional control for the colitis study. In the colitis group, diseased tissue from the left colon was being compared with normal tissue from the right colon and the changes found could have been due to regional variation. The diverticular disease specimens were samples from normal and diseased tissue in the left colon; the normal samples would act as the controls for diverticular disease but would act as a further control for the colitis cases since they were from the same colonic site of origin. In patients with diverticular disease no kinin-forming enzyme could be detected in either normal or diseased muscle (Fig. 3).

CHARACTERIZATION OF ENZYMIC ACTIVITY

It was necessary to determine whether the activity appearing in the diseased muscle tissue from ulcerative colitis patients was indeed a kinin-forming enzyme and also to show that it was not merely the result of contamination with trypsin or plasma kallikrein.

Enzyme-containing extract from the diseased muscle of two ulcerative colitis patients was pooled. Incubations were carried out as described for the kallikrein assay. When extract or human plasma substrate were incubated separately, no smooth-muscle stimulant activity was formed (Fig. 4). When extract and substrate were incubated together, activity appeared in the incubate which contracted the rat uterus and relaxed rat duodenum in the presence of atropine and 2-bromolysergic acid diethylamine, a 5-HT antagonist (Fig. 4). The extract thus contained an enzyme which released plasma kinin-like activity (see Methods). This kinin-forming enzyme was almost completely inhibited (96.8%) by Trasylol (100 Units/ml) but only slightly inhibited (4.5%) by soybean trypsin inhibition (100 µg/ml). A similar response to these inhibitors was shown by the kinin-forming enzyme present in the normal mucosa. The enzyme thus differed from trypsin and plasma kallikrein which are inhibited by both inhibitors. It should be noted in this respect, however, that Sei

<table>
<thead>
<tr>
<th>MUCOSA</th>
<th>MUSCLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>DISEASED</td>
</tr>
<tr>
<td>K</td>
<td>L</td>
</tr>
<tr>
<td>K</td>
<td>L</td>
</tr>
</tbody>
</table>

Fig. 3 Total kinin-forming enzyme in colonic tissue from three patients with diverticular disease. Samples were taken from diseased and normal colonic tissue nearby. The values are plotted on a logarithmic scale.

Fig. 4 Parallel bioassay on rat uterus and rat duodenum, of activity formed when activated extract of diseased colonic muscle from ulcerative colitis patients is incubated with kinin-forming substrate (S). All doses are added 0.1 ml.; dilutions shown in figure. Contact time one minute for the rat uterus (drum stopped between doses), two minutes for the rat duodenum (drum ran continuously).
Mobilization of tissue kallikrein in inflammatory disease of the colon

et al (1972) report that purified human colonic enzyme is partially inhibited (47%) by the soybean inhibitor. The kinin-forming activity was not distinguished from human pancreatic kallikrein by these tests. However, the fact that the activity was not continuously distributed through the gut wall and could not be detected in normal colonic muscle was a reasonable indication that the measurable activity was not merely the result of contamination from gut contents, blood, or lymph.

Discussion

There have been few studies on intrinsic kinin-forming activity in the wall of the alimentary tract. Twelve years ago, Werle and his colleagues (1960) reported that a hypotensive substance can be liberated from human and animal gut wall by incubation with trypsin. Homogenates of intestinal mucosal cells from rats and rabbits were subsequently shown to contain kinin-forming activity (Amundsen and Nustad, 1965; Burger, Lembeck, and Wagner, 1968). The kinin-forming enzyme of the rat gut wall occurs as an inactive precursor and has properties similar to some glandular kallikreins (Zeitlin, 1971 and 1972). Recently Erdös and his colleagues (Seki et al, 1972) have purified kallikrein from normal human, monkey, and dog colonic mucosae. These workers found that the purified human enzyme behaved more like plasma kallikrein than a glandular kallikrein. No previous studies have related intestinal kinin-forming enzyme or its precursor to the aetiology of human alimentary disease, nor has the presence of a kininogen in human gut wall been previously reported.

In the present investigation it was found that the human colon wall contained both a kinin-forming enzyme and a kininogen. In normal tissue, the kinin-forming enzyme and its precursor were present only in the mucosa while the kininogen occurred only in the muscle. When diseased tissue was compared with adjacent relatively normal tissue from patients with ulcerative colitis, it was found that while no kinin-forming enzyme or its precursor was present in normal muscle, considerable quantities of active enzyme could be detected in the diseased muscle. The enzymic activity found in both normal mucosa and diseased mucosa and muscle was distinguished from trypsin and plasma kallikrein and was not due to contamination from these sources. No similar infiltration of kinin-forming enzyme into the muscular tissue was found to occur in patients with diverticular disease of the colon.

Studies with isolated strips of human taenia coli have shown that this muscle has a complex response to contact with bradykinin. Taenia coli strips from some donors give a biphasic response with relaxation at low doses and contraction at higher doses of bradykinin (Fishlock, 1966) while strips from other donors react only with contraction to as little as 10 ng/ml (Fishlock, 1966; Zeitlin and Smith, 1971). Circular muscle strips from the human colon respond only with relaxation to bradykinin (threshold = 5 ng/ml) (Fishlock, 1966). In situ, human colonic motility is inhibited by intravenous infusion of bradykinin (Murrell and Deller, 1967).

Ulcerative colitis is a disease of the colonic and rectal mucosa and the inflammation does not generally extend beyond the submucosal layer, yet abnormalities in the smooth muscle of the bowel and disordered motility are characteristic of the disease. Colonic motility is generally reduced in patients with ulcerative colitis (Spriggs, Code, Bargen, Curtiss, and Hightower, 1951; Kern, Almy, Abbot, and Bogdonoff, 1951; Bloom, LoPresti, and Farrar, 1968; Jalan, Walker, Prescott, Butterworth, Smith, and Sircus, 1970), while notable features of the condition (Lennard-Jones, Lockhart-Mummery, and Morson, 1968), are the striking shortening of the colon with loss of the haustra which are normally maintained in part by an action of the circular muscle of the colon, which also becomes thickened. The smooth x-ray appearance of the colonic wall at barium enema examination has been explained on this basis, but no biochemical differences have hitherto been demonstrated between diseased and normal muscle which satisfactorily explain these changes. It has now been shown that the diseased muscle differs from healthy muscle in containing active kinin-forming enzyme; it also contains a kininogen, as does the normal muscle. Although the kininogen level in the diseased muscle is not decreased, it has previously been noted in carcinoid patients that while transitory kinin release results in a fall in plasma kininogen levels, chronic over-production of kinin may be accompanied by abnormally high kininogen levels (Zeitlin and Smith, 1970). The release of kinins within diseased colonic muscle would reasonably explain the shortening of the colon and the inhibition of motility seen in ulcerative colitis.

It is not difficult to imagine a mechanism by which the enzyme protein may pass from the mucosa into the muscle tissue. In the severely inflamed mucosae of ulcerative colitis, the abnormal release of permeability increasing factors such as 5-HT, histamine, or even excessive activation of mucosal kinin formation could permit the enzyme protein to pass through cellular membranes adjacent to the inflammation. Some could pass into the muscle tissue, the remainder would be flushed away by the blood. Although in terms of local tissue concentration the amounts of enzyme involved are large, in terms of whole body physiology, the total amount of active
enzyme is small. The chronic leakage of minute amounts of the enzyme into the circulation is unlikely to produce any marked systemic vasomotor changes. If the formation of kinins represents part of an inflammatory reaction in the wall of the colon in ulcerative colitis, by these pharmacological criteria diverticular disease is affected by a dissimilar type of process.

This work was supported by a Medical Research Council temporary research grant to Dr W. Sircus and by S.H.E.R.T. grant no. 291 to A. N. Smith.

References


PART 2 - Studies on motility disorders of the ano-rectum

The use of intra-rectal pressure measurement to evaluate functional ano-rectal disease needed the development and validation of further means of the registration of pressure changes (39), compliance and sensory change by proctometrography (41) and of conduction in the distal spinal cord and pudendal nerve (40). In the latter case recourse was made to the development of non-invasive methodology (47), assessed against standard invasive techniques.

At the time that the work presented here began there was interest in adjuvant treatment by radiotherapy in the surgical management of rectal cancer. An MRC trial, of which I was National Secretary, was instituted to examine and report on the pathological and clinical results (see Appendix II, i - iv). Aspects of radiation damage to bowel in the treatment of advanced pelvic malignancy were also studied by my group (Appendix II, v). Evaluation was therefore begun of the changes produced by pelvic irradiation in ano-rectal function (42, 43). This was extended to an assessment of the main operations performed for radiation damage such as colo-anal sleeve anastomosis (44), the results of which were vastly superior (49) to the same operation performed for localised inflammatory disease (Appendix II, vi). One of the conclusions was that the radiation lesion was not solely a 'proctitis' but that it had a neurological component as well.

Subsequent studies focussed on distal spinal cord function both in normals and in faecal incontinence (47) and on genuine female stress urinary incontinence (52). In both types of incontinence this established a neurogenic basis, in part at least, for the condition. It was soon realised that maintained pudendo-anal reflex stimulation could be used for neuro-muscular stimulation of the pelvic floor. Original apparatus was constructed for this purpose and was applied to and assessed in subjects with faecal incontinence (56). Ano-rectal function, particularly the neurogenic aspects, was also studied in young female subjects with intractable constipation (53), as was the abnormal bowel function of the elderly (50). Ano-rectal and pelvic floor function was reviewed (54) but, in particular, in respect of neural pathways, in a chapter on anal reflexes (65).
The study of external stimulators was complemented by another on the effects of surgically implanted devices to stimulate distal spinal cord function in paraplegics (46, 48). The severe constipation of the paraplegic was first quantified by studies on oro-anal transit, stool frequency and the water content of the faeces; as was the relative return of abnormal parameters to normal after use of the Brindley implanted device (62). The motility effects of stimulating the parasympathetic innervation of the left colon (55), the ano-rectum and pelvic floor (60) were also documented and confirmed that this innovative approach to the treatment of this form of constipation in the disabled could produce a return of 'normal' physiological function. The motility effects of the pro-kinetic agent 'cisapride' were also assessed (51) in spinal injury subjects.

Hysterectomy patients occasionally experience most obdurate constipation and a series of such patients was examined for any bowel disturbance (57). A hard core had marked disturbance of both bowel and bladder function (58), suggesting a common denervation lesion in the pelvis. Further investigation (59) revealed evidence of pelvic denervation in the most severely affected of these patients and this could be the main cause of the condition. Neural factors in disorders of distal bowel function as investigated and treated as suggested above were subsequently reviewed (64).

Clinical investigation into pelvic physiology was now extended by developing a cannula-electrode means for EMG recording from the pelvic floor musculature, particularly in regard to its non-relaxation or even contraction during defaecation (61); anal endosonography was also applied to the evaluation of sphincter thickness (67) and the effect of the probe size evaluated (70). Isotope proctography was also developed for the estimation of the ano-rectal angles, pelvic floor movements and for the rate and adequacy of rectal evacuation (68). This technique was subsequently used to assess differences in both idiopathic constipation (69) and in obstructive defaecation or anismus (75). Outlet obstruction causing anismus was further characterised (76) and managed by biofeedback (63) which aimed to correct the defaecation reflex through its re-education (74). The changes shown, however, need evaluation by a controlled clinical trial to determine how rewarding these measures are clinically as the effects may in part be induced by the mere act of treatment; the anismus effects may also be exaggerated by the investigative measures used, in this case non-ambulatory ones. Solitary rectal ulcer, which is associated clinically with obstructive defaecation, was treated by biofeedback measures (61) as well as by surgery with enhanced results over surgery alone.
Anal endosonography was used to delineate the external and internal anal sphincters and to show how they complement one another mechanically, while also showing interdependence in function (70). The same technique was used to demonstrate changes which follow ageing and are associated with faecal incontinence (72), of which the predominant ones are a lessening of the width of the external sphincter but a paradoxical increase in the width of the internal sphincter; but this could represent loss of smooth muscle and replacement by fibro-fatty change. Repetitive stimulation of the pelvic floor, using the pudendo-anal reflex pathway (56), reversed manometric abnormalities in incontinence (73) and improved the pelvic floor movement but did not change the ano-rectal angles, though increasing importantly the functional length of the anal canal. Neuro-stimulation as a therapy for some cases of faecal incontinence and its modes of action were reviewed (77). The work of an ano-rectal physiological measurement unit had been described shortly after its establishment (45) and a further audit for an eight-year period (71) is presented and analysed.
studies on motility disorders of the ano-rectum


Anorectal profilometry with the microtransducer

The reproducibility of anal sphincter manometry has been evaluated in 17 patients with a continuous pull-through technique using a miniature transducer mounted on a 2 mm diameter Dacron catheter. Comparison was made with a conventional station pull-through technique using a 4 mm diameter water-filled microballoon connected to an external transducer. Parameters measured with the microtransducer (maximum resting pressure, squeeze pressure, functional sphincter length, area under high pressure zone, amplitude of rectosphincteric reflex) showed mean coefficients of variation from 3.2 to 5.7% per cent. Pressures measured with the microballoon were uniformly higher than those obtained with the microtransducer. The functional sphincter length was significantly shorter when measured with the microballoon (P < 0.001). The microtransducer provides a highly accurate and reproducible method of anorectal profilometry that avoids many of the drawbacks associated with fluid-filled systems.

Keywords: Anorectal manometry, microtransducer, continuous pull-through technique

Patients and methods

Anorectal manometry was performed in 17 patients. They comprised six hospital patients with no anorectal symptoms, six patients with chronic constipation, and five patients with faecal incontinence. None of the patients had undergone previous anorectal surgery. All patients gave informed consent. No bowel preparation was used but patients were given the opportunity to empty their bowel before manometry, which was performed in the left lateral position. The microballoon station pull-through technique was performed first (Method 1) followed by profilometry with the microtransducer (Method 2).

Method 1

A 4 mm diameter soft rubber microballoon (HSC4, Precision Dippings Ltd, Bristol, UK) mounted onto a 6 FG ureteric catheter (Figure 1) and connected to an external transducer (4-422, Bell & Howell Ltd) was used. The entire system was water-filled and free of leakage and air bubbles. The transducer was calibrated from 0 to 200 cm H₂O pressure which was recorded on a multichannel chart recorder (Devices Ltd). The microballoon was inserted into the rectum to 7 cm from the anal verge, with 50 ml of air, and measuring the fall in resting anal canal pressure with the microballoon placed at the site of MRP. The functional sphincter length was measured as the length of the high pressure zone (HPZ) in the anal canal (zone of pressure above the resting rectal pressure).

Method 2

A catheter-mounted microtransducer (16 CT, Gaeltec Ltd, Dunvegan, Isle of Skye, UK, Figures 1 and 2) directly connected to a second channel on the chart recorder was introduced 7 cm into the rectum after calibration from 0 to 200 cm H₂O. Continuous controlled withdrawal of the catheter at 1 mm/s was performed with a profilometer (21 H05, DISA, Bristol, UK), thus obtaining a continuous pressure profile of the HPZ. This procedure was repeated three times with the transducer orientated randomly (Figure 3). The MVC and RSR amplitude were
Figure 3  Continuous pull-through sphincter profilometry with the microtransducer. (Four profiles are shown, with the patient 'squeezing' during the third pull-through). MRP, maximum resting pressure; HPZ, high pressure zone; A, area under HPZ; MVC, maximum voluntary contraction.

Figure 4  Reproducibility of maximum resting pressure with microtransducer profilometry (two plots are shown but the mean coefficient of variation has been calculated for three values). Straight line represents 100 per cent reproducibility. Mean coefficient of variation = 4.4 per cent; n = 17.

Table 1  Reproducibility of parameters measured with the microtransducer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean coefficient of variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum resting pressure</td>
<td>4.4</td>
</tr>
<tr>
<td>Maximum voluntary contraction pressure</td>
<td>4</td>
</tr>
<tr>
<td>Amplitude of rectosphincteric reflex</td>
<td>3.2</td>
</tr>
<tr>
<td>Length of high pressure zone</td>
<td>3.6</td>
</tr>
<tr>
<td>Area under high pressure zone</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Measured as in Method 1. In addition, the area under the HPZ curve was accurately measured by computer (Hewlett Packard 85 with Summagraphics attachment). The mean coefficient of variation was calculated for all parameters measured, taking all three consecutive measurements into account.

Results

Reproducibility of method 2

Figure 4 shows the reproducibility of the MRP using transducer profilometry (two values are plotted but the mean coefficient of variation was calculated for three values). All plots lie close to the 100 per cent reproducibility line with slightly higher variation at the peak values (mean coefficient of variation 4.4 per cent). Table 1 shows the mean coefficients of variation for the other parameters measured (range 3.2–5.7 per cent).

The movement of the catheter during withdrawal did not affect the magnitude of the pressures recorded; for instance the MRP value recorded was the same whether the catheter was stationary or being withdrawn. Most patients were unaware of any sensation of movement within the anal canal during profilometry.

Comparison of methods

Figure 5 shows comparison of the absolute MRP values for the two techniques. Similar results were obtained for the MVC and RSR amplitude measurements: all pressures measured with the microballoon proved to be uniformly higher than those measured with the microtransducer. However, there was a high degree of correlation between the two techniques in pressure measurements of each parameter (r = 0.96, 0.98, 0.95; MRP, MVC, RSR amplitude respectively). The HPZ length (Figure 8) was significantly greater when measured with the microtransducer (P < 0.001, paired t test).

Discussion

Pressure measurements within the anal canal are a useful and common means of assessment of sphincter function and provide...
Anorectal profilometry: J. S. Varma

References


Paper accepted 13 August 1984
The latency of the pudendo-anal reflex in man

BY A. N. SMITH and J. S. VARMA. University Department of Surgery/Urology and Wolfson Gastrointestinal Laboratory, Western General Hospital, Edinburgh EH4 2XU

Stimulation of the dorsal nerve of the penis or clitoris evokes a reflex contraction of the bulbocavernosus and external anal sphincter muscles mediated via the sacral spinal cord (Bors & Blinn, 1959). The latency of the anal sphincter response (pudendo-anal reflex) was determined in thirty-eight normal subjects (twenty-five female, thirteen male, age 23–75 years, mean 45±14.6 s.d.).

The dorsal nerve was stimulated electrically using a surface electrode (duration 0.1 ms, frequency 2 Hz, voltage 3–4 times sensation threshold, sweep 100 ms). Over 100 anal sphincter responses were detected by a bipolar surface stainless steel anal plug electrode and the digitally averaged response recorded. The procedure was repeated for each subject. All subjects gave informed consent.

Reproducible responses were confirmed in all cases. Latencies ranged from 27.2 to 46.8 ms (mean 38.5±5.8 s.d.). There was no significant difference between young and older women or between age-matched men and women (n = 10). Conduction time in the efferent limb of this response is approximately 7 ms (Marsden, Merton & Morton, 1982), the afferent conduction time being approximately similar (Haldeman, Bradley, Bhatia & Johnson, 1982), thus constituting a polysynaptic reflex. Increased latencies have been found in subjects with idiopathic (neurogenic) faecal incontinence (n = 20, range 44–66.4 ms, mean 54±6.3 s.d.; 5 absent responses). Electrophysiological recording of the evoked response by this technique is thus a convenient and reliable method of assessing the innervation of the pelvic floor.

J.S.V. was supported by a Wellcome Trust grant (no. 1219614L) and the British Digestive Foundation (Scottish Appeal).

REFERENCES

Reproducibility of the proctometrogram

J S VARMA AND A N SMITH

From the University Department of Surgery/Urology and Wolfson Gastrointestinal Laboratory, Western General Hospital, Edinburgh

SUMMARY The reproducibility of a method of measuring rectal distensibility by continuous controlled fluid inflation with a balloon has been evaluated in 15 patients. The volume at sensation threshold, constant sensation and maximal tolerance, the pressures at these volumes and rectal compliance were measured. The mean coefficients of variation of the seven variables measured ranged from 4.7%–7.9%. The expected correlation between rectal compliance and maximal tolerable volume was confirmed (r=0·85, p<0·001). The high reproducibility makes this investigation reliable for use in clinical practice and research.

In 1927 Rose described a method of recording pressure responses within the urinary bladder in response to filling.1 Since then the cystometrogram has become accepted as a useful aid in studying the bladder in health and disease. Joltra in and his colleagues proposed a method of measuring the filling pressure of the large intestine in 1919.2 They described a few observations but drew no important conclusions. White, Verlot, and Ehrentheil independently rediscovered the method in 1940.3 They noted abnormalities in patients with neurological disease by filling the entire colon with water. Their technique for undertaking the colonogram was difficult, messy, and hazardous and was therefore not accepted in clinical practice. Scott and Cantrell used a similar technique to study the effects of section of the parasympathetic nerve supply of the colon in the anaesthetised dog.4 Lipkin et al5 were probably the first to use balloon distension of the sigmoid colon to measure its pressure-volume relationships and to describe alterations with pharmacological agents. Godec et al6 and Bubrick et al7 used balloon distension of the rectal ampulla with air as an adjunct to the evaluation of bladder dysfunction and postulated its use for the study of neurogenic bowel dysfunction. Preston and coworkers described a method of evaluating rectal pressure and volume in constipation using fluid distension.8 None of these techniques, however, have been subjected to reproducibility studies.

We have used a method of continuous controlled balloon rectal distension modified from Bubrick et al7 to measure rectal sensation, volume and compliance. This study reports on its technique and reproducibility.

Methods

PATIENTS Approval for this investigation was given by the Ethical Committee of the North Lothian District, Lothian Health Board, Edinburgh, Scotland, on 16 June, 1983. Informed consent was obtained from all the subjects participating in the study.

Fifteen patients (five men, 10 women, age range 16–85 years, mean 48·4 years) were evaluated in the reproducibility study. Their details are shown in Table 1. Seven patients underwent repeat proctometrograms on the same day at an interval of two to four hours, whilst the remaining eight patients were recalled for a repeat test approximately 10 days later. All the patients were requested to fast from the night before and to empty their bowel on the morning of the study but no laxatives were used. Immediately before the proctometrogram a digital rectal examination and limited sigmoidoscopy with a

Table 1 Details of patients evaluated in reproducibility study

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients (no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ano rectal pathology</td>
<td>2</td>
</tr>
<tr>
<td>Acquired megacolon</td>
<td>3</td>
</tr>
<tr>
<td>Chronic constipation</td>
<td>3</td>
</tr>
<tr>
<td>Radiation proctitis</td>
<td>3</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Solitary rectal ulcer</td>
<td>1</td>
</tr>
<tr>
<td>Colonic sleeve anastomosis (radiation injury)</td>
<td>1</td>
</tr>
</tbody>
</table>
Reproducibility of the proctometrogram

paediatric instrument and without air insufflation were done to ensure that the rectum was empty.

The apparatus used is shown in Figure 1. The patient lies in the left lateral position. A high compliance balloon (condom type, deflated dimensions 19 cm × 5 cm) bound onto non-distensible polyvinylchloride tubing (internal diameter 5 mm, reference number 800/002/067 Portex Limited, Kent, UK) is introduced into the empty rectum. A microtransducer (type 16 CT silicone, Gaeltec Limited, Dunvegan, Isle of Skye, UK) within the rectal balloon monitors pressure continuously and is connected to a chart recorder (Devices Limited, UK). The microtransducer is precalibrated to record pressures from 0 to 100 cm H2O, the chart speed being 10 mm per minute. It is possible to use a water filled microballoon (internal diameter 4 mm, HSC4, Precision Dippings Ltd, Bristol, UK) connected via fine non-distensible tubing to an external transducer to record pressure instead of the microtransducer. It is important to exclude air from the system before inflation and to place the balloon in the rectal ampulla where the lowest rectal pressure is usually recorded (approximately 15 cm H2O). Continuous balloon inflation is done at a rate of 67 ml/min (4 litres per hour) by means of a peristaltic pump (Nouvag SP40, Plastic Pumps Limited, Middlesex, UK).

Bench testing of the system measured the pressure-volume characteristics of the distending balloon itself (Fig. 2a). Several balloons of the same make tested showed identical characteristics. On inflation the balloon adopts a cylindrical configuration. There is an initial rise in intraballoon pressure of approximately 10 cm H2O with infusion of the first approximately 50 ml water into the balloon. With further infusion there is no further rise in pressure up to a capacity of more than three litres. This system is therefore ideal for the measurement of rectal distensibility as the slope of the rectal pressure (P, cm H2O) - volume (V, ml H2O) graph after the first 50 ml infusion accurately reflects true rectal compliance (∆V/∆P, ml/cm H2O). True intrarectal pressures can also be easily calculated from the graph by subtracting the 10 cm H2O contribution from the balloon at volumes in excess of 50 ml. In the megacolon type of curve (Fig. 2d) the compliance is more easily calculated by dividing the maximal tolerable volume by the rectal pressure

![Diagram of the proctometrogram system](https://example.com/diagram.png)

**Fig. 1** Apparatus for the proctometrogram.

**Fig. 2** Diagrammatic representation of the pressure-volume characteristics of the proctometrogram balloon (a) and proctometrograms from a normal subject (b), a patient with radiation proctitis (c), and a patient with acquired megacolon (d).
increment achieved on instillation of this volume although the slope of the graph can also be measured. The patient is asked to report the first perception of rectal filling and this is recorded as the sensation threshold. This is followed by a sensation of constant rectal distension and the volume at this sensation is also recorded. In some patients these initial sensations may be indistinguishable. Inflation is continued until the patient has a strong desire to evacuate the balloon and will not tolerate further distension — this is the maximal tolerable volume. This sensation is usually not painful. The balloon is then emptied via the tubing. The parameters recorded in the reproducibility study were the volumes and pressures at the threshold, constant and maximal tolerable sensations and the rectal compliance measured on the linear portion of the graph.

Figure 2 shows some typical proctometrogram from patients in this study (Table 1). In a normal subject (Fig. 2b) there is a slow and steady rise in intrarectal pressure with distension in an approximately linear fashion. In sharp contrast to this is the proctometrogram from a patient with symptoms of urgency and frequency of defaecation following mild chronic radiation rectal injury from radiotherapy for prostatic carcinoma (Fig. 2c). The graph is shifted to the left with a relatively steep rise in pressure and there was marked reduction in sensation threshold, maximal tolerable volume and rectal compliance in this patient. In chronic idiopathic constipation and acquired megacolon the pressure volume relationship is shifted to the right (Fig. 2d) and there is a relative increase in sensation threshold, maximal tolerable volume and rectal compliance.

Results

Figure 3 shows a reproducibility plot for the maximal tolerable volume in the 15 patients studied (Table 1). The straight line represents a 100% reproducibility graph. The mean coefficient of variation for this parameter was 4.7%. Figure 4 shows a similar plot for rectal compliance. There is more variation at the higher compliance values such as those found in acquired megacolon but the mean coefficient of variation is only 6.5%. Table 2 lists the reproducibility values of the other parameters of the proctometrogram. The mean coefficients of variation ranged from 4.7% to 7.9%. No significant differences in reproducibility could be shown between the group of patients who had the investigation performed on the same day compared with the group in which it was performed on different days.

Figure 5 shows the significant correlation of the maximal tolerable volume with rectal compliance in the 15 patients comprising this study.

Discussion

An important function of the rectum is its ability to act as a dynamic reservoir for faeces. Like the urinary bladder this function is dependent on its functional capacity, perception of filling and contractile properties. The measurement of rectal volume, sensory perception and distensibility is therefore of undoubted value in the physiological investigation of anorectal function. The information obtained helps to explain the basis of many
Reproducibility of the proctometrogram

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean coefficient of variation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume at sensation threshold</td>
<td>7.9</td>
</tr>
<tr>
<td>Volume at constant sensation</td>
<td>6.7</td>
</tr>
<tr>
<td>Maximal tolerable volume</td>
<td>4.7</td>
</tr>
<tr>
<td>Pressure at sensation threshold</td>
<td>7.6</td>
</tr>
<tr>
<td>Pressure at constant sensation</td>
<td>6.2</td>
</tr>
<tr>
<td>Pressure at maximum tolerable volume</td>
<td>5.1</td>
</tr>
<tr>
<td>Rectal compliance</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Table 2: Reproducibility of the proctometrogram

Symptoms such as those described after radiation rectal injury, and may help to decide the logical course of treatment. The technique of the proctometrogram described offers a relatively simple, cheap and practical method of evaluating the physiology of rectal function in health and disease. The use of water as the distending agent eliminates the necessity of correction for pressure and temperature in calculating the distending volume when gas is used. The continuous infusion pump makes the tedious calculation involved in stepwise inflation methods unnecessary. The bench properties of the high compliance rectal balloon (Fig. 1a) were found to be consistently identical for the type used in this study. The characteristics of individual types of balloon should be ascertained, however, before use in vivo. The use of the microtransducer to measure rectal pressure avoids the drawbacks associated with fluid filled transducer systems. The calculation of intrarectal pressure and compliance is made much simpler compared with other methods because of the lack of any significant pressure contribution by the balloon. The relatively low rate of infusion (67 ml/min) was used because it corresponds to an intermediate rate (10–100 ml/min) used in medium fill cystometry and hence probably represents a more physiological rate of filling. It has also been observed that the sharp increase in pressure when the maximal tolerable volume is reached is seen less often compared to other workers, partly because of the lower infusion rate – for example, Preston et al who used a similar balloon with higher rates of infusion – and partly to the larger size and capacity of the balloon used in this study – for example compared with Bubrick et al who used a balloon of only 405 ml capacity. These factors may also explain the relatively higher maximal tolerable volumes observed in normal subjects in this study (Fig. 2b). Lipkin and Sleisenger found, not unexpectedly, that the onset of pain on distension of either the rectum or sigmoid colon was inversely proportional to the level of water pressure exerted by the balloon. Although they did not report differences in the rate of inflow, these certainly existed. There is more variation in measuring threshold sensation and pressure compared with the other parameters. This is not surprising in view of the transient and intermittent nature of this sensation which is also more difficult to explain to the patient. The reproducibility at higher volumes (Fig. 3) and compliance (Fig. 4) is also reduced although overall reproducibility remains high and the measurements therefore reliable. Such a reproducibility has not been previously shown with other methods. The functional reservoir capacity of the rectum might be expected to be dependent on its compliance. We have been able to confirm this in practice (Fig. 5) and shown a high correlation between these parameters. The compliance and accommodation properties of the rectum may also play a role in determining the characteristics of the rectosphincteric reflex as suggested by the studies of Arhan et al.

In order to obtain consistent and reliable results care must be taken to ensure that the rectum is empty, that there is no air within the system and in the placement of the balloon. Drugs can alter the pressure volume characteristics of the colon and their effects should therefore be considered.

Fig. 5 Correlation between rectal compliance and maximal tolerable volume (n=15).
JSV was supported by a Wellcome Trust Research grant no 12196 14 L.

References

1. Rose DK. Determination of bladder pressure with the cystometer. JAMA 1927; 88: 151-7.
Function of the anal sphincters after chronic radiation injury

J S V A R M A , A N S M I T H , A N D A B U S U T T I L
From the University Department of Surgery/Urology, Wolfson Gastrointestinal Laboratory and Department of Pathology, Western General Hospital, Edinburgh

SUMMARY Anorectal manometry was done in 10 men with chronic radiation proctitis and symptoms of urgency, frequency, and occasional incontinence of faeces. They were compared with 10 asymptomatic age and sex-matched controls. The maximum resting anal canal pressure and the physiological sphincter length were significantly lower (p<0.01) in the irradiated group. The rectosphincteric reflex was absent in one patient and showed abnormalities of recovery in four others, who had received radiotherapy. The squeeze pressure of the external sphincter was not significantly different. These results indicate that dysfunction of the internal anal sphincter may contribute to patients' anorectal symptoms after pelvic radiotherapy. Histological evidence suggests that damage to the myenteric plexus is mainly responsible. The manometric function of the external sphincter remains relatively unaffected.

Radiotherapy is being increasingly used for the treatment of malignancy arising in the pelvic viscera. Inevitably, the incidence of associated radiation injury to healthy surrounding tissue with its sequelae has increased, sometimes necessitating surgical intervention. The rectum is the commonest site of injury after pelvic irradiation; more than 70% of patients with radiation gastrointestinal injury have this site involved, sometimes in conjunction with other organs. The fixed anatomical position of the rectum in the pelvis makes it more susceptible to the injurious effects of radiation compared with the more 'mobile' organs such as the small bowel.

A very common symptom of radiation anorectal injury is loose bowel motions with faecal incontinence, often chronic in nature. Some of this symptomaticity may be explainable by the accompanying proctitis and changes in rectal physiology. It is conceivable that the continence function of the pelvic floor is also compromised as a result of the radiation injury, thus aggravating the severity of the faecal incontinence.

We have manometrically evaluated the function of the internal and external anal sphincters in patients with symptomatic chronic radiation rectal injury and compared it with a matched control group of asymptomatic subjects.

Methods

PATIENTS
Approval for this investigation was obtained from the ethical committee of the North Lothian District, Lothian Health Board, Edinburgh, Scotland, on 16 June 1983. Informed consent was obtained from all the subjects participating in the study. The symptomatic irradiated group comprised 10 men (age range 63–80 years, mean 74 years) who received radiotherapy for prostatic carcinoma and all had subsequently developed the symptoms of faecal incontinence, increased frequency, urgency and occasional loose bowel motions. Identical small field external beam radiotherapy (5000 Centigrays in 20 treatments over four weeks) had been given to this group of men from 2 to 5½ years before the study (mean 3½ years). The control group consisted of 10 age-matched male hospital patients who had been admitted for minor surgery not involving the gastrointestinal tract and who had no anorectal symptoms.

MANOMETRY
All subjects were requested to empty their bowel before the pressure studies. Anorectal manometry was done with the patient in the left lateral position. A water filled system consisting of microballoon
Function of the anal sphincters after chronic radiation injury

(internal diameter 4 mm HSC4, Precision Dippings Ltd, Bristol, UK) mounted onto a 6 FG ureteric catheter and connected via an external transducer (4-442, Bell & Howell Ltd, UK) to a chart recorder (Devices Ltd, UK) was used to measure anal canal pressure. The system was precalibrated and the balloon introduced into the rectum 6 cm from the anal verge and rectal pressure measured. The balloon was then withdrawn in steps of 0.5 cm and the resting pressure of each 'station' measured until a stable value was obtained. The subject was also asked to contract the external sphincter and the maximum voluntary contraction pressure recorded. The 'squeeze' pressure or the external sphincter contribution to this pressure was calculated as the difference between the maximum voluntary contraction pressure and maximum resting pressure. The rectosphinincteric reflex was elicited by placing the microballoon at the site of maximum resting pressure and quickly distending the rectum by inflating a 2x1 cm soft rubber balloon (HSC1, Precision Dippings Ltd, Bristol, UK) with 50 ml air. The rectal balloon was placed at 10 cm from the anal verge. The decrease in the resting anal canal pressure on rectal distension was recorded as the amplitude of the rectosphinincteric reflex.

All the data were analysed by means of the Wilcoxon's test for pair differences.

HISTOPATHOLOGICAL MATERIAL
Histological material was obtained from eight other patients who had undergone excisional surgery for complications of radiation rectal injury. Six of these patients had been treated for bladder cancer and two for prostatic cancer (mean 2.2 years before surgery). The total radiation dosage that these patients had received (3000 to 5000 Centigrays) was similar to that used in the study group of symptomatic but unoperated patients (5000 Centigrays). Formalin-treated tissue from the lower rectum was examined by conventional haematoxylin and eosin staining and light microscopy after paraffin embedding. Special stains were not used. At least three sections were examined from each patient.

Results

MANOMETRY AND SYMPTOMS
Figure 1 shows a comparison of the maximum resting anal canal pressures between the two groups. There is a significant reduction in this pressure in the radiation group (p<0.01). Figure 2 compares the length of the manometrically determined high-pressure zone in the two groups as measured with the station pull through technique. This is also significantly reduced in the radiation group (p<0.01). The Table shows the values for the other parameters measured and their statistical significance. The presence and recovery of the rectosphinincteric reflex was affected by radiation. The amplitude was significantly reduced after radiation and in one patient the reflex was absent. All control subjects showed restoration of the maximum resting pressure to baseline levels within 30 seconds on inflation of the rectal balloon and immediately on deflation of the balloon. In contrast, four patients in the radiation group showed no recovery of this
reflex as long as the balloon remained inflated, and time to recovery of resting pressure was prolonged to more than 60 seconds on deflation of the balloon.

### Table Comparison of the five sphincter parameters in the two groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group (n=10)</th>
<th>Radiation group (n=10)</th>
<th>Significance (Wilcoxon's signed rank sum test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum resting pressure</td>
<td>± 99</td>
<td>± 66</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>(cm. H₂O, mean±SEM)</td>
<td>± 6-7</td>
<td>± 7-6</td>
<td></td>
</tr>
<tr>
<td>Functional sphincter length</td>
<td>± 4-25</td>
<td>± 2-65</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>(cm. H₂O, mean±SEM)</td>
<td>± 0-2</td>
<td>± 0-2</td>
<td></td>
</tr>
<tr>
<td>Amplitude of rectosphincteric reflex</td>
<td>± 46</td>
<td>± 25</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>(cm. H₂O, mean±SEM)</td>
<td>± 2-7</td>
<td>± 4-8</td>
<td></td>
</tr>
<tr>
<td>Maximum voluntary contraction pressure</td>
<td>± 219</td>
<td>± 131</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>(cm. H₂O, mean±SEM)</td>
<td>± 10-5</td>
<td>± 16-9</td>
<td></td>
</tr>
<tr>
<td>Maximum squeeze pressure</td>
<td>± 120</td>
<td>± 86</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>(cm. H₂O, mean±SEM)</td>
<td>± 10-9</td>
<td>± 27-0</td>
<td>(NS)</td>
</tr>
</tbody>
</table>

The remaining five patients showed normal recovery of the reflex. Maximum voluntary contraction pressure was reduced in the radiated group but this is probably attributable to the reduced maximum resting pressure because no difference in the 'squeeze' pressure - that is, maximum voluntary contraction pressure minus maximum resting pressure, could be demonstrated (p>0.05). All the patients had identical symptoms of urgency and frequency of defeacation with occasional faecal incontinence.

### HISTOPATHOLOGY

Microscopic examination of the sections taken from all the eight resected specimens showed identical histopathological changes. Figures 3, 4, and 5 are sections taken from the lower rectums of patients who had undergone anterior resection of the rectum with coloanal sleeve anastomosis for severe radiation injury. They show the histopathological effects of irradiation on the neuronal plexuses and smooth muscle. There is hypertrophy of the muscle of both the *muscularis mucosae* and *muscularis propria* with some enlargement of the myocytic nuclei (Figs 3 and 4). In the submucosal nerve plexus (Meissner’s)

![Fig. 3 Lower rectum. Hypertrophy of the muscularis layers and prominence of Auerbach’s plexus (H&E×40 orig. mag.).](image-url)
ganglion cells are sparse but hypertrophy of the nerve fibres is not present. The few ganglion cells are degenerate and their nuclei pyknotic. In the muscular plexus (Auerbach's) there is marked hypertrophy of the nerve fibres with vacuolation of the nerve sheaths giving the plexus a laciform pattern (Figs 3 and 4). The ganglion cells are diminished in number and show cytoplasmic vacuolation and degranulation (Fig. 5). Their nuclei are eccentrically placed. The chromatin pattern is altered with increase in density, loss of outline of the nuclear membrane and diminution of nucleolar prominence.

Discussion

Urgency, increased frequency of defaecation and incontinence of faeces are common symptoms in patients with chronic radiation anorectal injury. There is evidence that reduction in rectal compliance and volume is partly responsible for these symptoms. The pelvic floor – in particular the anal canal and sphincters – is also susceptible to the effects of radiation directed at the primary pelvic pathology. Damage to the sphincteric mechanisms may therefore further compromise continence. The purpose of this study was to determine whether anal sphincter function is affected in patients with the symptoms of chronic radiation rectal injury. All the irradiated patients had identical symptoms of faecal incontinence with urgency and frequency of defaecation. Male patients were chosen for the study to eliminate the effects of parturition and chronic straining at stool predominantly found in women with resultant effects on sphincter function. None of the patients had anorectal symptoms before radiotherapy. Digital rectal examination of the prostate had been carried out only at six monthly intervals after radiotherapy and was therefore not presumed to have had any adverse effects on anal sphincter function. Although the histological preparations were taken from different patients to those studied manometrically, the total therapeutic dosage of pelvic irradiation delivered to the two groups and the time since radiation was identical.

The internal anal sphincter is responsible for up to 85% of the maximum resting pressure in the anal canal and therefore also for the length of its manometric high pressure zone. The significant reduction in the maximum resting pressure and physiological sphincter length in the irradiated group suggests dysfunction of this muscle. Relaxation of the internal anal sphincter on distension of the rectum is a smooth muscle reflex partly mediated via the myenteric plexus, although receptors in the pelvic floor may share in this. The abnormalities in the elicitation, amplitude, and recovery of this reflex after pelvic radiotherapy point to a possible functional abnormality of the autonomic ganglion cells or axons constituting this neuronal network. The reduction in the amplitude of the rectosphincteric reflex in the irradiated group is partly because of the lower resting anal canal pressures but can also be influenced by other variables – for example, the radius of the rectal lumen and compressibility of the air filling the rectal balloon. Nevertheless, it has been used as an index of internal sphincter function by other workers and complements the results obtained from measurement of the other parameters in this study. Furthermore, there is some evidence that the presence and amplitude of the rectosphincteric reflex is inversely related to the compliance and accommodation properties of the rectum. The observation that this reflex is reduced after radiation injury – that is, in the presence of severe...
reduction in rectal compliance, is therefore good evidence of internal anal sphincter malfunction in this disorder. It is relevant that similar abnormalities of the rectosphincteric reflex may be seen in Hirschprung's disease where the significant pathology is an absence of the ganglion cells and in other forms of neuronal intestinal dysplasia. The hypertrophy of the smooth muscle seen in the histological preparations is further evidence of damage to the myenteric plexus as there is some evidence that denervated smooth muscle hypertrophies.

The function of the striated external sphincter as evaluated manometrically appears relatively less prone to the effects of pelvic irradiation. This is perhaps not surprising as somatic nerve axons and muscle are considered relatively resistant to radiation with resultant 'sparing' of the manometric function of this sphincter. It remains possible, however, that late effects occur with microvascular involvement. Modern electrophysiological methods may be able to provide further information on the effects of radiation on the function of the striated musculature of the pelvic floor. With higher doses of local irradiation such as that used for the treatment of cervical cancer, dysfunction of the external sphincter may become more apparent.

This study shows physiological dysfunction of the internal anal sphincter in symptomatic radiation anorectal injury. This may contribute to and therefore aggravate symptoms caused by abnormalities of rectal function. The manometric and histopathological evidence suggests that radiation damage to the relatively radiosensitive myenteric plexus is an important factor in the pathophysiology of this disorder, although a degree of direct damage to smooth muscle may also occur.

Awareness of the pathophysiological effects of radiation on pelvic floor function may lead radiation oncologists to study the feasibility of less injurious techniques and gastroenterologists to search for better therapeutic measures.

J S V was supported by a Wellcome Trust Research grant no 12196 14 L. We are most grateful to Professor G D Chisholm and Mr L L Beynon for enabling us to study patients under their care.
References

Correlation of clinical and manometric abnormalities of rectal function following chronic radiation injury

Radiotherapy is being used increasingly for the treatment of malignancy arising in the pelvic viscera. The incidence of associated radiation injury to healthy surrounding tissue with its sequelae has increased, sometimes necessitating surgical intervention. The rectum is the commonest site of injury after pelvic irradiation with more than 70 per cent of patients with radiation-induced gastrointestinal injury suffering from rectal involvement, sometimes in conjunction with other organs. The fixed anatomical position of the rectum in the pelvis makes it more susceptible to the injurious effects of radiation compared to the more 'mobile' organs such as the small bowel.

A very common symptom of radiation rectal injury is urgency and increased frequency of defaecation with occasional faecal incontinence, often chronic in nature. Some of these symptoms are explainable by the accompanying dysfunction of the internal anal sphincter. However, it is conceivable that the reservoir function of the rectum is also compromised as a result of the radiation injury, thus aggravating the severity of the faecal incontinence.

In an attempt to elucidate these observations, the function of the rectum was evaluated manometrically in patients with symptomatic chronic radiation injury of the rectum and compared with a matched control group of asymptomatic subjects. The manometric results were correlated to the patients' symptoms and sigmoidoscopic findings. Specimens from a further group of patients who had undergone excisional rectal surgery for radiation injury were also examined histologically.

**Patients and methods**

Approval for this investigation was obtained from the Ethical Committee of the North Lothian District, Lothian Health Board, Edinburgh, and informed consent was obtained from all the subjects participating in the study. The symptomatic irradiated group comprised 10 men (age range 63-80 years, mean 74 years) who received radiotherapy for prostatic carcinoma and had subsequently developed chronic symptoms of faecal incontinence, increased frequency, urgency and occasional loose bowel motions. Identical small field external beam (4000 cGy in 20 treatments over four weeks) had been given to this group of men from 2 to 5.5 years before the study (mean 3.5 years). The control group consisted of ten age-matched male hospital patients who had been admitted for minor surgery not involving the gastrointestinal tract and who had no anorectal symptoms. All the patients in the radiation group had double contrast barium enema performed during the course of investigation of their symptoms.

These were reviewed by one person (J.S.V.) before manometry to assess rectal capacity which was graded as normal or diminished.

**Manometry**

Patients were fasted from the night before the study and requested to empty their bowel on the morning of the study. This was assisted by means of a saline washout if necessary but no laxatives were used. Immediately before the proctometrogram a digital rectal examination and limited sigmoidoscopy using a paediatric instrument but without air insufflation were performed to ensure that the rectum was empty. Proctometrograms were obtained with the patient in the left lateral position. A high-compliance balloon (10 cm in diameter) bound onto nondistensible polyvinylchloride tubing (internal diameter 5 mm) was introduced into the empty rectum. A microtransducer (type 16 CT silicone, Gaeltec Limited, Dunvegan, Isle of Skye, UK) within the rectal balloon monitored pressure continuously and was connected to a chart recorder (Devices Limited, UK). The microtransducer was calibrated to record pressures from 0 to 100 cmH₂O. Air was excluded from the system before inflation. Continuous balloon inflation was performed at a rate of 67 ml min⁻¹ (4 litres/h) by means of a peristaltic pump (Novouga SP40, Plastic Pumps Limited, Middlesex, UK). This enabled accurate calculation of rectal volumes. Bench testing of the system revealed that the pressure contribution of the distending balloon itself was only 10 cmH₂O over a volume of 3 litres. The slope of the rectal pressure (P, cmH₂O) - volume (V, mlH₂O) graph therefore accurately reflected true rectal compliance (ΔP/ΔV, mlH₂O cmH₂O⁻¹). The true intrarectal pressures at any volume can also be easily calculated from the graph by subtracting the 10 cmH₂O contribution of the balloon from the recorded pressure.

The patient was asked to report the first perception of rectal filling and this was recorded as the secondary threshold. This was followed by a sensation of constant rectal distension and the volume at this sensation was also recorded. In some patients these initial sensations were indistinguishable. Inflation was continued until the patient had a strong desire to evacuate the balloon and could not tolerate further distension — the maximal tolerable volume. The balloon was then emptied via the tubing. The manometric parameters measured were the volumes and pressures at the threshold, constant and maximal tolerable sensations and rectal compliance.

**Scoring of symptomatic and sigmoidoscopic findings**

Table 1 lists the symptoms and sigmoidoscopic appearances in the irradiation group that were considered important correlates to the physiological measurements with the proctometrogram. A scoring system was utilized in which one point was allocated to each positive finding. The respective scores were added and correlated to the proctometrogramic measurements. Sigmoidoscopic scoring was performed several days before proctometrography by one observer. An
adult instrument with a distal light source was used to a distance of 15 cm from the anal verge.

Histology

Histological material was obtained from eight patients who had undergone anterior resection of the rectum with colo-anal sleeve anastomosis for complications of radiation injury. Two of these patients had been treated for prostatic cancer and six for bladder tumours. The total radiation dosage that these patients had received (3000-5000cGy) was similar to that used in the study group of symptomatic but unoperated patients (5000 cGy). Following fixation with formalin, paraffin embedded sections were examined by conventional techniques using light microscopy and haematoyxl and eosin (H and E) staining.

Statistics

The manometric measurements between the two matched groups were analysed by the Wilcoxon signed rank sum test for paired differences. Correlation between manometric and clinical findings were performed by Pearson’s correlation coefficient and a regression line thus computed.

Results

Manometry, clinical and radiological findings

Table 2 lists the values for all the manometric parameters measured. There is marked and significant reduction in the maximal tolerable volume after radiotherapy (P < 0.01). Rectal compliance is also severely reduced following irradiation (P < 0.01). A significant correlation exists between these two parameters (r = 0.77, P < 0.01; Figure 1). The volumes at threshold and constant perception of rectal distension are also significantly reduced after irradiation. Comparison of rectal pressures at the three volumes do not show significant differences.

Figure 2 demonstrates the high correlation between rectal compliance and the added scores from sigmoidoscopic and symptomatic evaluation (r = -0.89, P < 0.001). Table 3 lists the correlation coefficients and their significance between rectal compliance and the other parameters.

Double-contrast barium enemas failed to demonstrate any abnormalities of function or capacity in eight patients. In two patients rectal capacity appeared reduced and in three patients mucosal abnormalities consistent with proctitis were identified.

Histopathology

Microscopic examination of the sections taken from all the eight resected specimens showed identical histopathological changes. An excess of round cells with no evidence of active inflammation was present in the lamina propria; no glandular abnormalities were noted. Hypertrophy of the muscle of both the muscularis mucosae and muscularis propria (Figure 3) with some enlargement of the myocytes nuclei (Figure 4) were prominent features. In the submucosal nerve plexus (Meissner’s) ganglion cells were sparse but hypertrophy of the nerve fibres was not present. The residual ganglion cells were degenerate and their nuclei pyknotic. In the muscular plexus (Auerbakh’s) there was marked hypertrophy of the nerve fibres with vacuolation of the nerve sheaths giving the plexus a laciform pattern (Figure 3). The ganglion cells were diminished in number and showed cytoplasmic vacuolation and degranulation. Their nuclei were eccentrically placed. The chromatim pattern was altered with increase in density, loss of outline of the nuclear membrane and diminution of nucleolar prominence (Figure 4).

Discussion

The rectum has the ability to act as a dynamic reservoir for faeces. Like the urinary bladder, the role is dependent on its functional capacity, perception of filling and contractile properties. The measurement of rectal volume, sensory perception and distensibility is therefore of value in the physiological investigation of anorectal function.7,9,10.

---

**Table 1** Parameters used for the scoring system

<table>
<thead>
<tr>
<th>Symptomatic</th>
<th>Sigmoidoscopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Mucosal pallor/atrophy</td>
</tr>
<tr>
<td>Urgency</td>
<td>Telangiectasia</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Contact bleeding</td>
</tr>
<tr>
<td>Loose bowel movements</td>
<td>Ulceration</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>Loss of distensibility</td>
</tr>
</tbody>
</table>

**Table 2** Comparison of manometric measurements and their significance

<table>
<thead>
<tr>
<th></th>
<th>Sensory threshold</th>
<th>Constant sensation</th>
<th>Maximal tolerable volume</th>
<th>Rectal compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P=Pressure (cmH2O)</td>
<td>V=Volume (mlH2O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group (n=10)</td>
<td>31 ± 3.5</td>
<td>224 ± 31.4</td>
<td>38 ± 3.7</td>
<td>303 ± 22.6</td>
</tr>
<tr>
<td>Radiation group (n=10)</td>
<td>31 ± 4.4</td>
<td>99 ± 25.3</td>
<td>36 ± 4</td>
<td>122 ± 26.5</td>
</tr>
<tr>
<td>Significance (P)</td>
<td>n.s.</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>9 ± 0.5</td>
</tr>
</tbody>
</table>

P=Pressure (cmH2O); V=Volume (mlH2O). All values mean ± s.e.m.
Abnormalities of rectal function after radiation: J. S. Varma et al.

Urgency, increased frequency of defaecation and incontinence of faeces are common symptoms in patients with chronic radiation-induced anorectal injury. There is evidence that dysfunction of the internal anal sphincter is partly responsible for these symptoms. The rectum is particularly susceptible to the effects of radiation directed at the primary pelvic pathology due to its fixed anatomical position. Damage to the rectum may therefore further compromise the continence of faeces. The purpose of this study was to define alterations in the motor function of the rectum in patients with the symptoms of chronic radiation rectal injury and to attempt to correlate these with clinical parameters. Male patients were chosen for the study to eliminate the effects of pelvic floor abnormalities predominantly found in women with their possible resultant effects on rectal function. None of the patients had anorectal symptoms before radiotherapy. Patients with severe symptoms often refuse permission to be studied because of the discomfort of rectal examination. The patients in this study, therefore, may represent lesser degrees of symptomatic radiation injury. Digital rectal examination of the prostate had been performed at 6 monthly intervals following radiotherapy and was not presumed to have any adverse effects on rectal function.

The maximal tolerable volume and hence the reservoir capacity of the rectum appears to be dependent on its compliance (Figure 1). On distension of the rectum, intrarectal pressures appear to play an important part in its proprioceptive ability (Table 2) probably mediated by sensory receptors in the levator ani muscles or perirectal tissues. The highly significant correlations between the manometric and clinical parameters (Table 3) suggest that the reduction in rectal volumes and compliance are responsible for the frequency, urgency and urge type of faecal incontinence that are common symptoms in this group. Similar symptoms are encountered in other forms of inflammatory bowel disease. Farthing and Lennard-Jones were able to demonstrate changes in rectal volumes in ulcerative colitis and correlate them to clinical features. Similar observations were confirmed by other workers. Keighley et al. demonstrated abnormalities of rectal volume in Crohn’s disease and used it as a prognostic indicator for the results of anterior resection and ileorectal anastomosis in this group. A maximum rectal capacity of less than 150 ml before surgery was associated with poor postoperative anorectal function. The correlation of manometric and sigmoidoscopic parameters in this study may be taken to implicate mucosal damage as the direct cause of the patients’ symptoms. However, the sigmoidoscopic scoring system takes into account the distensibility of the rectum, a feature that is also related to smooth muscle function. The sigmoidoscopic scores, therefore, may also reflect chronic damage to the underlying muscle and neuronal plexuses, although alteration of the sensory modalities in inflamed mucosa may influence symptoms as suggested in the colitis study. Myenteric plexus or smooth muscle damage are not histological features of ulcerative colitis and therefore mucosal changes alone correlate well with the severity of symptoms and experimental findings. Not surprisingly, the best correlation to manometric evaluation after radiotherapy was obtained with the added symptomatic and sigmoidoscopic scores.

Although the histological preparations were taken from different patients to those studied manometrically, the total therapeutic pelvic radiation dosage delivered to the two groups was identical. The marked damage to the myenteric plexus seen histologically may be responsible for the abnormalities of distensibility or non-relaxation as suggested by the absence or reduction in amplitude of the rectal distension reflex in such patients. The hypertrophy of the smooth muscle seen in the histological preparations is further evidence of damage to the myenteric plexus; there is some evidence that denervated smooth muscle hypoplastrophies.

We were unable to demonstrate radiological changes in rectal capacity or function in most patients but this may be because the patients chosen for this study represented milder degrees of radiation injury. We also did not evaluate rectal capacity on true lateral pelvic radiographs which appear to be more accurate. Keighley et al., using standard radiographs to assess rectal capacity, found poor correlation between this and the maximal tolerable volume. This study demonstrates and helps to explain the physiological abnormalities of rectal function in symptomatic radiation anorectal injury. The manometric and histopathological evidence suggests that radiation damage to the relatively radiosensitive myenteric plexus and hypertrophy of smooth muscle may be important factors in the pathophysiology of this disorder, although mucosal damage is contributory. The treatment of mucosal inflammation in chronic radiation injury is hence important but resolution of symptoms may be disappointing due to the underlying myenteric plexus and muscle abnormalities. These also contribute to dysfunction of the internal anal sphincter.
Abnormalities of rectal function after radiation: J. S. Varma et al.

Longitudinal studies of rectal function in patients with radiation injury would further help to clarify the pathophysiology and clinical course of this disorder and assist in their management.

Acknowledgements
J. S. V. was supported by a Wellcome Trust Research Grant No. 1219614L. We are most grateful to Professor G. D. Chisholm and Mr L. L. Beynon for enabling us to study patients under their care.

References

Paper accepted 22 May 1985
Anorectal function following colo-anal sleeve anastomosis for chronic radiation injury to the rectum

Anorectal manometry and electrophysiological studies of the pelvic floor were performed in eight patients who had undergone anterior resection of the rectum with mucosal proctectomy and colo-anal sleeve anastomosis for radiation rectal injury. There is a severe reduction in the compliance of the neorectum and in the maximal tolerable volume. Maximum basal anal canal pressure and physiological sphincter length are also significantly reduced although the 'squeeze' pressure of the external anal sphincter and the latency of the pudendo-anal reflex were unaffected. Four patients had an absent rectosphincteric reflex, four patients involuntarily expelled the test balloon at the maximal tolerable volume during a proctometrogram and four patients demonstrated increased EMG activity of the pelvic floor on straining and on rectal distension. These abnormalities help to explain many of the patients' symptoms. Histological abnormalities of the myenteric plexus were a prominent feature in all the excised specimens and may be responsible for some of the functional abnormalities.

Keywords: Radiation rectal injury, anorectal manometry, rectal compliance, colo-anal anastomosis

With greater use of radiotherapy for the treatment of pelvic malignancy the incidence of chronic radiation intestinal injury, particularly to the rectum, has also increased and the organic complications such as haemorrhagic proctitis may be life-threatening, sometimes necessitating surgical intervention. Parks' operation of anterior resection of the rectum with mucosal proctectomy of the rectal stump and an endo-anal pullthrough anastomosis has been used to treat these complications. However, urgency and frequency of defecation, occasionally accompanied by anorectal incontinence, often persist following these measures and can be most troublesome for the patient. To explain the physiological basis of these symptoms, the function of the neorectum and anal sphincter was evaluated by manometric and electrophysiological techniques. In addition, the excised rectal specimens were examined histologically.

Patients and methods

Informed consent was obtained from all the subjects participating in the study (Ethical Committee approval June 1983). The symptomatic operated group comprised six women and two men (age range 35-71 years, mean 71 years). Six patients had received external beam radiotherapy for carcinoma of the urinary bladder and two for carcinoma of the cervix. The bladder carcinoma patients had received small fields (10 x 10 cm) external beam radiotherapy (5500 cGy in 20 treatments over 4 weeks); the cervical cancer patients had been given whole pelvic, external beam radiotherapy supplemented by a single intravesical implant (cumulative dosage of 9500 cGy) to the vaginal vault, equivalent to 7500 cGy to point A. The interval from radiotherapy to the study ranged from 2.8 to 5.5 years (mean 3.5 years). All patients had subsequently developed chronic haemorrhagic proctitis, with a rectal stricture, and were treated by a Parks' colo-anal procedure after exclusion of recurrent malignancy. There were no further complications. All patients had been followed up for more than 2 years since operation. There was no evidence of proctitis, haemorrhage or stricture at the time of the study but all had varying degrees of troublesome urgency and frequency of defecation by day and night; three patients had to wear an incontinence pad for occasional faecal leakage. Table I lists some of the important clinical features. The control group consisted of eight sex-matched and approximately age-matched hospital patients who had been admitted for minor surgery not involving the gastrointestinal tract and who had no anorectal symptoms.

Manometry

Fasted patients were requested to empty their bowel on the morning of the study, assisted by means of saline washout if necessary but laxatives were not used. Digital rectal examination and limited sigmoidoscopy using a paediatric instrument were performed to ensure that the rectum was empty and for tube placement in the left lateral position. Basal and squeeze sphincter pressures, sphincter length and rectosphincteric reflex were measured with a conventional water-filled microballoon and external transducer using a 0.5 cm station-pullthrough technique. The larger soft rubber balloon was inflated slowly with air to obtain a value for the sensory threshold of rectal distension and an average of three measurements calculated. Proctometrograms were performed to measure rectal compliance and the maximal tolerable volume. The manometric parameters measured with this technique were the volumes and pressures at the maximal tolerable volume and rectal compliance.

Electrophysiology

A standard concentric needle EMG electrode (type 13L49 DISA, Copenhagen) was inserted into the external anal sphincter without anaesthetic via a puncture site 1 cm posterior to the anal orifice to a depth of approximately 2.5 cm. This was connected via preamplifiers to an oscilloscope (Medelec MS92a, Woking, Surrey, UK). Electrical activity of the sphincter was continuously monitored using a time base of 100 ms/cm with the gain at 100 μV/cm and filter settings of 20 Hz-10 kHz. Permanent recordings were obtained of electrical activity at rest, on voluntary contraction, on defaecation straining and on distension of the rectal balloon with 50 and 200 ml of air (Figure 1). The tip of the needle was moved to at least three different sites to ensure reproducibility of the recordings. The electrical activity was also heard as amplified sound via a loudspeaker incorporated in the equipment. The pudendo-anal reflex was elicited by electrical stimulation of the dorsal nerve of the penis or clitoris with a felt bipolar surface stimulating electrode (type LBS 53051, Medelec, UK) and recording the
Anorectal function: J. S. Varma and A. N. Smith

Table I

<table>
<thead>
<tr>
<th>Continence grade</th>
<th>Pad</th>
<th>Day</th>
<th>Night</th>
<th>Urgency</th>
<th>Recto-sphincteric reflex</th>
<th>Rectal compliance (mL/cmH₂O)</th>
<th>Expulsion of balloon</th>
<th>50 ml distension</th>
<th>200 ml distension</th>
<th>Straining</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A. Fully continent; B. Incontinent of flatus only; C. Incontinent of liquid stool + flatus; D. Incontinent of solid and liquid stool

Figure 1

Diagrammatic representation of the pressure-volume characteristics of the rectoanastomosis balloon, a, and typical proctograms obtained from a normal subject, b, and a patient with colonic sleeve anastomosis for radiation injury, c.

reflex contraction of the external anal sphincter with a bipolar surface stainless-steel anal plug electrode (type 13K78, DISA, Copenhagen) using the Medelec MS92a evoked response unit. Over 100 square-wave stimuli (duration 0.1 ms, frequency 2 Hz) were applied and the digitally averaged response displayed on the oscilloscope at a sweep speed of 10 ms/cm with a gain at 10 or 20 μV/cm and filter settings of 2 Hz 10 kHz. The stimulation voltage was approximately three times the voltage at sensation threshold, typical threshold and stimulation voltages being 25 and 80 V respectively. In no case was the stimulation repeated in each subject to ensure reproducibility. The latency of the pudendo-anal reflex was measured from the onset of the sweep (triggered by the stimulus) to the onset of the clearly defined evoked response.

Histopathology

Histological material was obtained from the eight patients who had undergone a colo-anal procedure. Following fixation with formalin, paraffin-embedded sections of the rectum were examined by conventional techniques. Sections were taken from various sites in each specimen.

Statistics

The manometric and electrophysiological measurements between the two matched groups were analysed by the Wilcoxon signed rank sum test for paired differences.

Results

Manometry

Table 2 compares the manometric parameters measured in the two groups. There is a significant reduction in the physiological sphincter length, maximum resting pressure and the amplitude of the rectoanastomotic reflex in the colo-anal group. The squeeze pressure of the external anal sphincter appears to be reduced in the colo-anal group but this difference does not reach statistical significance. In four patients the rectoanastomotic reflex could not be elicited despite several attempts, its amplitude being reduced in the remainder. Figure 1 illustrates typical proctograms from a colo-anal patient and a control subject. In the control subject there is a slow and steady rise in rectal pressure with inflation until no further distension can be tolerated to the maximal tolerable volume of approximately 450 ml of water. In contrast to this the patient with colo-anal sleeve anastomosis shows a rapid and steep rise in rectal pressure with infusion of only 250 ml of water, prominent rectal contractions occurring during this distension. There is a severe and significant reduction in the rectal compliance in the colo-anal group (Figure 2). The volumes at the sensory threshold of rectal distension and at maximal tolerance are also significantly reduced (Table 2). Comparison of rectal pressures at the maximal tolerable volume did not show a significant difference. In addition to these abnormalities, in four patients in the colo-anal group the proctogram balloon was expelled involuntarily at the maximal tolerable volume, although the phenomenon was not seen in any of the control subjects. Table II lists some of the clinical, manometric and electromyographic findings in the colo-anal group.

Electrophysiology

There appeared to be no difference in the resting and 'squeeze' external sphincter electrical activity between the two groups. However, on defaecation straining, four patients demonstrated paradoxical increase in EMG activity of the external sphincter whereas all the control subjects showed a reduction in activity. In addition, on balloon distension of the rectum with 200 ml of air, another four patients had increased electrical activity of the external sphincter in contrast to the control subjects all of whom showed a reflex reduction in the EMG activity of the sphincter (Table I). The latency of the pudendo-anal reflex appeared to be prolonged in the operated group although the difference was not statistically significant (Figure 3).

Histopathology

Proximal sections taken from the eight resected specimens showed identical histopathological changes. Mild non-specific chronic inflammatory changes were present in the lamina propria; the glandular epithelium appeared normal. The muscle of both the muscularis propria and muscularis mucosa was hypertrophied and showed some enlargement of the nuclei of the muscle cells. In the submucosal nerve plexus (Meissner's) the ganglion cells were sparse but the nerve fibres were hypertrophied. The residual ganglion cells demonstrated degenerative changes with pyknosis of their nuclei. In the muscularis propria (Auerbach's) the nerve fibres were hypertrophied and the nerve sheaths vacuolated, producing a lace-like appearance. There were few ganglion cells and these showed cytoplasmatic vacuolation and degeneration. The chromatin pattern of their nuclei showed an increase in density.

286

Br. J. Surg., Vol. 73, No. 4, April 1986
Table 2  Comparison of manometric anorectal parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=8)</th>
<th>Colo-anal sleeve anastomosis (n=8)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum resting anal pressure (cmH₂O, mean ± s.e.m.)</td>
<td>104 ± 5.3</td>
<td>54 ± 7.7</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Maximum anal squeeze pressure (cmH₂O, mean ± s.e.m.)</td>
<td>159 ± 15.9</td>
<td>120 ± 17.9</td>
<td>P &gt; 0.01</td>
</tr>
<tr>
<td>Sphincter length (cm, mean ± s.e.m.)</td>
<td>5.5 ± 0.25</td>
<td>24 ± 0.21</td>
<td>P &lt; 0.02</td>
</tr>
<tr>
<td>Amplitude of rectosphincteric reflex (cmH₂O, mean ± s.e.m.)</td>
<td>47.5 ± 3.1</td>
<td>12.5 ± 5.6</td>
<td>P &lt; 0.02</td>
</tr>
<tr>
<td>Rectal sensory threshold (ml H₂O, mean ± s.e.m.)</td>
<td>58 ± 10.2</td>
<td>29 ± 18</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Maximal tolerable rectal volume (ml H₂O, mean ± s.e.m.)</td>
<td>504 ± 29</td>
<td>120 ± 25</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Rectal pressure at maximal tolerable volume (cmH₂O, mean ± s.e.m.)</td>
<td>73 ± 28</td>
<td>86 ± 6.5</td>
<td>P &gt; 0.01</td>
</tr>
</tbody>
</table>

Compliance

![Graph showing compliance values](image)

Figure 2  Scattergram of rectal compliance values (with mean ± s.e.m.)

Figure 4  Photomicrograph of myenteric plexus from excised, radiation-injured rectum (haematoxylin and eosin, × 150). The ganglion cells show marked degenerative changes with cytoplasmic shrinkage and pyknosis of nuclei. There is proliferation of perineural tissue with vacuolation.

Figure 5  Photomicrograph of normal Auerbach’s plexus (haematoxylin and eosin, × 250) showing typical ganglion cells with scanty perineural connective tissue and there is a loss of outline of the nuclear membrane and absence of the nucleolar detail (Figure 4). These striking abnormalities are in contrast to the histological appearances of the myenteric plexus from normal rectum illustrated in Figure 5. Sections from the proximal resection line showed similar normal appearances.

Discussion

Park’s operation of colo-anal sleeve anastomosis after anterior resection of the rectum with mucosal proctectomy of the stump appears to deal with the organic complications of severe radiation injury to the rectum, at the same time restoring intestinal continuity with preservation of the anal sphincters. The long-term functional results after colo-anal...
Anorectal function: J. S. Varma and A. N. Smith

sleeve anastomosis for the treatment of low rectal cancer appear to be satisfactory. However, following this operation for radiation rectal injury many patients experience some degree of troublesome urgency and frequency of defaecation which may be associated with occasional incontinence. In this study, mucosal appearances were normal although rectal distensibility on sigmoidoscopy could be decreased. No previous physiological studies have been reported on patients treated by this operation for radiation injury. The reduction in the maximum resting sphincter pressure, physiological sphincter length and the abnormalities of the rectosphincteric reflex suggest a dysfunction of the internal anal sphincter. It has been shown that a similar dysfunction of the internal sphincter may occur in patients with chronic radiation proctitis who have not had surgery performed. The anal stretch necessary for the mucosal proctectomy and colo-anal anastomosis may contribute to the decrease in anal canal pressure. The more extreme anal dilatation involved in Lord’s operation for haemorrhoids can produce a similar permanent decrease in resting anal canal pressure. Mucosal proctectomy includes excision of the lower rectal mucosa and submucosa along with the submucosal plexus of Meissner which may already have been compromised by radiation effects. The presence and function of normal intramural ganglion cells and nerve fibres is of paramount importance to the dynamic functional properties of the internal anal sphincter. The abnormalities of the rectosphincteric reflex seen in the patients in this study may therefore at least in part, be explained by the excision of the submucosal plexus. Decrease in anal canal pressure and loss of inhibition of the internal sphincter has been noted in other studies of patients after sphincter-saving excision of the rectum without pre-operative radiotherapy. The radiation-induced damage to the myenteric plexus must further compromise the function of the internal sphincter. This is supported by the manometric evidence. Although the histological sections were taken from the lower rectum, it is likely that similar abnormalities are present at the sphincteric level.

The external anal sphincter appears to be relatively ‘spared’ as assessed by its squeeze pressure and the electrophysiological latency of the pudendo-rectal reflex. Although both these parameters appear to be altered in the colon-anal group suggesting some weakness of the external sphincter, the differences do not achieve statistical significance. It is possible, however, that more sensitive techniques such as single fibre electromyography could detect subtle abnormalities in the sphincter following radiation. The increase in activity of the external sphincter on distension of the rectum with 50 ml air is a normal reflex and was present in all the patients and controls. The paradoxical increase in external sphincter EMG activity on distension of the rectum with 200 ml air is abnormal and may be due to involuntary sphincter contraction by the patient. Rectal distension with this volume of air tended to be a painful procedure, in contrast to patients with a normal rectum. This is probably due to higher rectal pressures being produced with smaller rectal volumes compared to controls. There is therefore some contribution by the internal sphincter in maintaining continence. This phenomenon has been observed by earlier workers. The physiological interpretation of the paradoxical increase in external sphincter activity on defaecation straining is difficult. It may be due to inadvertent voluntary activity by the patient who is under constant threat of incontinence from rectal and internal sphincter dysfunction. A similar phenomenon has been observed in some patients with the solitary rectal ulcer syndrome which have anatomical and functional abnormalities at the anorectal angle. An abnormality of the sampling response developing in the lower rectum and anal canal following mucosal proctectomy could also be responsible.

This study confirms the findings of other workers of intact rectal proprioception after low sphincter-saving surgery. On distension of the rectum, intrarectal pressure appears to play an important part in its proprioceptive ability; the intrarectal pressures attained at the maximal tolerable volume in both groups do not differ. It appears that intrarectal pressure may also determine its sensory thresholds, thus explaining the lower threshold values seen with loss of rectal compliance. There is now evidence that this function is mediated by sensory receptors in the levator ani muscles or extrarectal tissues rather than in the rectal wall as suggested by earlier workers. The very severe reduction in rectal compliance and volumes following colo-anal sleeve anastomosis for radiation injury is somewhat surprising because relatively healthy, compliant sigmoid or lower descending colon was anastomosed to form the neorectum. Rectal compliance is markedly reduced before operation in these patients and would be expected to be improved, even if not to normal values, following surgery. These findings suggest that the neorectum is unable to expand in the pelvis. This may be due to ‘internal’ fibrosis between the layers of the neorectum or extramural fibrosis in the pelvis and/or loss of compliance in the ‘sleeve’ of remaining rectal stump. Minor degrees of anastomotic dehiscence and ‘cuff’ sepsis may be contributory. Other factors may be implicated in the motility disturbances involved. Brown, for example, demonstrated hypermotility of the mobilized sigmoid colon following colo-anal anastomosis in some patients.

The marked damage to the myenteric plexus seen histologically may also contribute to the abnormalities of distensibility or non-relaxation as suggested by the absence of reduction in amplitude of the rectal distension reflex in such patients. The hypertrophy of the smooth muscle seen in the histological preparations is further evidence of damage to the myenteric plexus as there is some evidence that denervated smooth muscle hypertrophies. The loss of compliance of the neorectum together with internal sphincter dysfunction further explains the expulsion of the proctometrogram balloon at the maximal tolerable volumes in four patients. A clear correlation between clinical and physiological features is difficult to demonstrate due to the relatively small number of patients in this study, and the complex interaction of rectal and pelvic floor function is determining symptomatology. However, involuntary balloon expulsion appears to occur in those patients with the poorest continence and the need to wear a pad occasionally. Frequency of defaecation appeared to be more related to internal sphincter dysfunction; abnormalities of external sphincter relaxation occurred more often in patients with severe reduction in rectal compliance. This study helps to explain the physiological basis of the abnormalities of anorectal function which follow colo-sleeve anastomosis for severe radiation rectal injury. Increased knowledge of the pathophysiology of this disorder may help achieve better functional results. For example, it may be possible to improve anorectal function by leaving a very short rectal stump and/or performing a full-thickness myotomy of the stump before the sleeved anastomosis. Dilatation of the neorectum might increase its compliance and capacity and improve functional results although conclusive results with this technique are not yet available. Repair operations of the pelvic floor musculature have been unlikely to confer much symptomatic benefit in view of the normal function of the external sphincter. The development of radiotherapeutic techniques to reduce injurious effects to the anorectum is also of paramount importance.

Acknowledgements

J.S.V. was supported by a Wellcome Trust Research Grant No. 21081 L. and the British Digestive Foundation (Scottish Appeal). We are grateful to the Consultants in the Gastrointestinal Unit and the University Department of Radiation Oncology, Western General Hospital, Edinburgh, for enabling us to study patients under their care. We wish to thank Dr A. Busuttil, Department of Pathology, Western General Hospital, for assistance with the photomicrographs.
References

A Unit for the Physiological Assessment of Colonic and Ano-Rectal Disorders—Its Activities over a Two-Year Period

AN Smith
Reader in Surgery
University Department of Surgery/Urology
Western General Hospital
Crewe Road
Edinburgh EH4 2XU
J S Varma
Wellcome Trust Surgical Research Fellow
University Department of Surgery/Urology and Wolfson Laboratories
Gastro-intestinal Unit
Western General Hospital

Introduction
The number of patients attending hospital with ano-rectal problems has grown in recent years. A main contributing factor is the increased longevity which is a feature of the end of the twentieth century. The range of the procedures available for disorders of the distal bowel has also increased and this in turn leads to investigation into their problems. A factor increasing the range of available investigative measures is the ‘simplification’ and refinement of the apparatus used and the understanding of their applicability. For example, the use of stapling devices in surgery has enabled patients who until recently might have needed a permanent colostomy to have restorative operations. Such operations done at very low levels of excision need assessment before and after operation to assess the function of the residual rectum and the competence of the anal sphincters. Increased co-operation between various disciplines also brings patients into contact with other specialists. Patients in the care of geriatricians, urologists, radiation oncologists and gynaecologists may, for example, require joint management of faecal incontinence, constipation or radiation injury to the intestine for seemingly intractable bowel problems.

The purpose of this contribution is to give an account of the tests available and their application in the first two years of the working of a unit created for the physiological assessment of colonic and ano-rectal disease.

We also suggest some of the clinical situations to which this type of manometric and electrophysiological investigation may contribute.

Patients
The unit functioned as part of the investigative facilities offered by the Gastro-intestinal (GI) Unit, Western General Hospital, Edinburgh. The work reviewed was done from 22 April 1983 to 30 April 1985, during the tenure of a Wellcome Research Fellowship by one of us (JSV) in the Department of Surgery, Western General Hospital and University of Edinburgh. Three hundred and thirty-three patients underwent tests of colonic and ano-rectal function together with 42 control subjects. All agreed to the preferred tests in terms of ethical permission granted in June 1983. The total number of investigations performed was 763.
Ano-rectal problems were vastly more common in female patients. Thus 279 females were examined compared with 54 males. The control subjects were, however, chosen in an approximately equal sex ratio (20 males:22 females).

The patients investigated came from within Edinburgh predominantly; 147 were patients of the GI Unit, 91 from the General Surgical Unit, 19 from the Department of Surgical Urology and seven others (mainly Radiation Oncology and Gynaecology) all from within the Western General Hospital. Of the patients from the GI Unit approximately one-third had been referred from other hospitals in Edinburgh and outwith. Nineteen patients were studied from the University Department of Geriatric Medicine at the City Hospital, five from the Spinal Injuries Unit at Edenhall Hospital, 12 from the Royal Infirmary, mainly from the Gastro-intestinal Service of that hospital; seven patients were from Leith Hospital and three from Deaconess Hospital. Twenty-one patients were referred directly from other parts of Scotland; 13 from the Greater Glasgow area, four from Dumfriesshire, three from Fife and one from Ayrshire.

**Indications**

The conditions investigated are shown in Table I. The need for colonic motility measurements in diverticular disease has diminished in the era of bran and high-fibre diets. It

<table>
<thead>
<tr>
<th>Condition</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faecal incontinence</td>
<td>5</td>
<td>63</td>
</tr>
<tr>
<td>Chronic constipation</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>Irritable bowel</td>
<td>9</td>
<td>45</td>
</tr>
<tr>
<td>Radiation rectal injury</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Post-operative assessment</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>Rectal prolapse</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>*Other</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>Diverticular disease</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Controls</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>74</td>
<td>301</td>
</tr>
</tbody>
</table>

*Disseminated sclerosis, diabetes, paraplegia, solitary rectal ulcer, descending perineum syndrome, etc.

Inflammatory bowel disease pressure studies have been performed only to explain features such as faecal incontinence and urgency of defaecation. The majority of tests were done to assess the reason for abdominal pain in the irritable bowel syndrome, for the assessment of the integrity of the pelvic floor in prolapse and faecal incontinence or for the post-operative assessment of sphincter competence mainly in relationship to low anastomoses ( stapled low or mid-rectal cancer surgery; colo-anal sleeve anastomosis; or ileo-anal anastomosis after colectomy with mucosal proctectomy (ileal pouch reservoir) done for ulcerative colitis). Another common reason for tests was the elucidation of the cause of chronic intractable constipation with or without megacolon or redundant colon detected by barium enema.
Methods
The investigations performed are listed in Table II and described below.

Table II: Investigations Performed

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sphincter manometry (including recto-anal reflex tests)</td>
<td>190</td>
<td>41</td>
<td>231</td>
</tr>
<tr>
<td>Colonic motility</td>
<td>36</td>
<td>8</td>
<td>44</td>
</tr>
<tr>
<td>Proctometrogram</td>
<td>136</td>
<td>35</td>
<td>171</td>
</tr>
<tr>
<td>Sacral-evoked response</td>
<td>135</td>
<td>60</td>
<td>195</td>
</tr>
<tr>
<td>Motor unit potential duration</td>
<td>56</td>
<td>31</td>
<td>87</td>
</tr>
<tr>
<td>*Others</td>
<td>21</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Total</td>
<td>574</td>
<td>189</td>
<td>763</td>
</tr>
</tbody>
</table>

*Transcutaneous spinal stimulation, cerebral motor cortex, stimulation, straining and rectal distension EMGs, etc.

(a) Sphincter Manometry
A pressure profile of the sphincter is obtained by pulling a small balloon mounted on a fine catheter and connected to an external pressure transducer outwards through the lower rectum and anal canal. This is usually done 1 cm at a time till the anal verge is reached just proximal to which there is a sharp rise in the intraluminal pressure which reflects the activity of the internal sphincter. Voluntary 'squeeze' pressures are also recorded to measure the action of the external sphincter.

This test was most often needed pre-operatively and post-operatively to assess the effectiveness of repair operations performed on the pelvic floor. It was also found prudent to assess the reactions of the sphincters before and after low rectal or colo-anal anastomosis and was considered mandatory in the latter. Many patients of advanced years who had come from geriatric units had faecal incontinence with poor sphincter tone as their particular problem. Sphincter pressure profiles have also been used to assess trauma to the sphincters post-episiotomy, after manual dilatation of the anus (in Lord's treatment for haemorrhoids) and in the radical excision of fistulae. Tests were also needed to assess sphincter problems occurring as a result of autonomic neuropathy in patients treated by radiotherapy for pelvic malignancies.

The recto-sphincteric reflex is elicited by measuring the relaxation of the internal sphincter in response to rectal distension performed using a larger balloon placed in the rectal ampulla. This reflex is absent in Hirschsprung's disease. This deficit is also found in problems affecting the spinal cord and in Chaga's disease which, however, is almost unknown in this country.

(b) Proctometrograms
This test was done to obtain information on the compliance of the bowel wall but also to give information on any sensory change arising in neurological disease, e.g. diabetes or sacral spinal cord abnormalities. Rectal compliance is measured by assessing the pressure change developing after instillation of known volumes of fluid pumped slowly into a high compliance balloon. Compliance is increased in megacolon but reduced in the irritable bowel syndrome and in some instances of inflammatory bowel disease. This test can also be used to estimate the 'sensory awareness' as the rectal balloon is filled with increasing volumes of fluid in addition to the pressure/volume changes.
(c) The Sacral-Evoked Response or Pudendo-Anal Reflex Test\textsuperscript{10} This test gives an estimate of conduction via the sacral spinal cord after a stimulus is applied to the perineal skin in the sacral S2, 3, 4 dermatomes. The evoked contraction of the external anal sphincter which is produced by this reflex is detected after a measurable latency, which reflects the conduction time of the impulse via a reflex arc to the external anal sphincter. This reflex may be absent or delayed in patients with faecal incontinence due to a sacral spinal cord anomaly or pudendal nerve damage. It may also be abnormal in patients with constipation related to obvious or occult lesions of the spinal cord or in systemic neurological disease.

(d) Motor Unit Potential Duration (MUPD) This is measured using standard EMG equipment by inserting a concentric needle electrode into the external sphincter and monitoring the action potential from individual motor units. At least 20 action potentials are recorded from each sphincter site and the mean and standard deviation calculated. After denervation MUPD is significantly prolonged due to attempted re-innervation of the muscle fibres. This test is therefore an index of pelvic floor or external sphincter neuropathy\textsuperscript{11}.

(e) Concentric EMG and Mapping of the External Anal Sphincter Traumatic damage to the pelvic floor can disrupt part of the ano-rectal sphincter ring, resulting in retraction of the divided ends and in incontinence. Insertion of a concentric EMG needle into the external sphincter and pubo-rectalis muscle identifies the electrical activity of the muscle. When repeated measurements are made around the circumference of the sphincter this can greatly assist in ‘mapping’ the ‘silent’ area of divided and retracted muscle. This test will therefore assist the surgeon in finding and repairing the tear in the sphincter accurately and hence achieving continence. This assessment can be supplemented by manometry of the sphincters, especially important for comparison post-operatively.

(f) Colonic Motility A triple lumen, open-ended, perfused catheter is placed at sigmoidocolcopy so that its orifices lie 5 cm apart in the sigmoid colon, recto-sigmoid and rectum. The various channels are connected to a pressure measuring transducer. The recordings which are made in the basal state and after stimulation by food and cholinergic stimulation are measured over half-an-hour. The average wave height and the percentage time of activity are calculated from which a motility index is derived. Colonic motility is raised in stimuli in diverticular disease and in the irritable colon and is diminished in megacolon.

(g) These physiological tests are always supplemented by radiological assessment of the lower gastro-intestinal tract, e.g. by barium enema and during this examination measurement of the ano-rectal angle may be undertaken. This is increased in incontinence and is corrected by surgical post-anal repair\textsuperscript{2}.

Treatment
The types of operation performed as a result of these studies are listed in Table III. In general the operations reflect the proctological trends in recent years, e.g. the surgical management of faecal incontinence by post-anal repair and the treatment of intractable constipation due to colon inertia by colectomy; stapled low rectal and anal anastomoses sphincter repair for trauma and the surgery of prolapse and solitary rectal ulcer, as well as the increasing use of surgery as a form of salvage for radiation injury, etc. by sleeve procedures such as colo-anal anastomosis; with similar ileo-anal procedures in conjunction with reservoirs and mucosal protectomy for ulcerative colitis.

Manometry of the anal sphincters in incontinence is important in determining the relative function of the internal and external anal sphincter\textsuperscript{1}. There is no satisfactory operative
Table III: Operations Performed and Assessed Post-Operatively for Various Colonic and Ano-Rectal Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Operation/Procedure</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ano-rectal incontinence</td>
<td>Post-anal repair</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Primary sphincter repair</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>Radiation rectal injury</td>
<td>Colo-anal sleeve anastomosis</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Chronic constipation</td>
<td>Colectomy and ileo-rectal anastomosis</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Hirschsprung's disease</td>
<td>Duhamel or sub-total colectomy</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Solitary rectal ulcer</td>
<td>Ivalon sponge repair</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>York-Mason excision</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Rectal prolapse</td>
<td>Ivalon sponge repair</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>Proctocolectomy</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Mucosal protectomy + pouch</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diverticular disease</td>
<td>Resection of pelvic colon</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Paraplegia</td>
<td>Anterior sacral root stimulator implant assessment</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>24</strong></td>
<td><strong>74</strong></td>
</tr>
</tbody>
</table>

Treatment for internal sphincter disruption and hence in these patients surgical intervention can be avoided by appropriate pre-operative assessment. Anal pressures also have a predictive value inasmuch as these patients with low voluntary squeeze pressures have a greater incidence of post-operative incontinence.

It is also important to distinguish between traumatic disruption of the sphincter ring and functional (neuropathic) disturbance as the former is treated by primary sphincter repair and the latter by post-anal repair. In these cases manometry should be supplemented by radiological assessment of the ano-rectal angle and sphincter mapping to locate precisely the retracted ends of the divided sphincter. The four patients treated by 1° sphincter repair achieved full continence and post-operative manometry in this group revealed improvement of sphincter pressures to normal values in correlation to their clinical function. The results of post-anal repair in our series appear to be similar to those repaired by other workers, achieving satisfactory continence in approximately 70% of patients. In these patients in whom rectal prolapse is associated with incontinence, it is important to assess sphincter function because a small percentage of these patients require post-anal repair in addition to rectopexy to achieve satisfactory continence.

In the surgical treatment of severe radiation injury of the rectum, post-operative physiological assessment of the ano-rectum can greatly assist the surgeon in estimating the extent of sphincter and rectal abnormalities. These measurements have implications in the selection of operation and the post-operative management, e.g. anal stretch, closure of incontinence, etc.

Physiological assessment in constipation is important in several ways. The proctogram is a useful way of confirming the manometric abnormality of the irritable bowel syndrome and excluding these patients from surgical intervention. It also provides a method of evaluating response to treatment in these patients (ongoing project). Anal sphincter manometry is important and useful in the diagnosis of Hirschsprung's disease and hence its operative treatment which is different from other forms of constipation. Other aspects of constipation can be elucidated by measurement of the latency of the pudendo-
anal reflex\textsuperscript{10}, prolongation of this suggesting a functional abnormality\textsuperscript{19}. These patients are best treated by sub-total colectomy with ileo-rectal anastomosis. A very small proportion of women develop intractable constipation following pelvic surgery. In these there appears to be an abnormality of motility of the sigmoid colon, probably due to denervation\textsuperscript{20}. Such patients can be treated by excision of the segment of inert large bowel. It is therefore important to define the motility abnormalities in these patients pre-operatively by procto-\textsuperscript{\textsuperscript{-}}metrogram and measurement of colonic motility. If surgery is contemplated, sphincter manometry should also be performed to ensure post-operative continence.

Sphincter manometry is also recommended prior to excisional surgery for Crohn’s disease or mucosal proctectomy and Parks’ pouch procedures for ulcerative colitis to assess the integrity of the pelvic floor and hence predict post-operative function.

Conclusion
The success of operations performed in this speciality is dependent in almost every instance on a rational understanding of the underlying dysfunction. The outcome of such operations can nowadays be almost always predicted in quantitative as well as qualitative terms. This helps to ensure that such surgery as is performed is done to exacting standards. Many more clinical problems in this area can now be solved, which is a tribute to the physiological studies which elucidated what the abnormalities were\textsuperscript{1} and made possible the advances which are now part of the contemporary surgical scene\textsuperscript{2}.

Acknowledgements
We express our thanks to the many clinicians who referred the patients for investigation and to the Wellcome Trust for support during the tenure of a Fellowship by JSV (Grant No. 121964 L). We are grateful to the British Digestive Foundation (Scottish Appeal) for their assistance with EMG equipment.

References
Differential effects of sacral anterior root stimulation on colorectal motility in spinal man

By N. Binnie, G. Creasey, P. Edmond, A. N. Smith and J. S. Varma. University Department of Surgery, Western General Hospital, Edinburgh and Spinal Injuries Unit, Edenhall Hospital, Musselburgh

Electromicturition by neuroprosthetic stimulation of the sacral anterior roots (S2-S4) has proved effective in facilitating micturition and urinary continence in paraplegia (Cardozo, Kirshnan, Polkey, Rushton & Brindley, 1984). However, faecal stasis with colonic dilatation remains a distressing problem in these patients. This study evaluates the motility responses of the sigmoid colon, rectum and pelvic floor to such stimulation in five men (Ethical Committee approval June 1983).

The integrity of the conus medullaris was ascertained by confirmation of normal pudendo-anal reflex latencies in all the patients. Colonic and rectal motility and anal sphincter pressures were monitored by conventional manometric techniques. This was supplemented by concentric needle e.m.g. of the striated pelvic-floor musculature.

Identical and reproducible results were obtained in all five studies. S4 stimulation increased colonic and rectal tone. S3 stimulation initiated high-pressure colorectal motor activity which appeared peristaltic and was enhanced with repetitive train stimuli. This response was frequency-dependent. Stimulation of the S2 roots provoked isolated low-pressure colorectal contractions. Pelvic-floor activity was stimulated in increasing order from S2 to S4.

This study examines directly the central control of colonic, rectal and pelvic floor activity in man and has implications in the treatment of the intractable constipation and megacolon which follow spinal injury.

REFERENCE


This work was supported by the Wellcome Trust (Grant No. 12196 14L) and the Scottish Hospital Endowment Research Trust (Grant No. 720).
Electrophysiological observations on the human pudendo-anal reflex

JS Varma, AN Smith, AMcInnes
From the University Department of Surgery/Urology, Wolfson Gastrointestinal Laboratories and Department of Clinical Neurophysiology, Western General Hospital, Edinburgh, UK

SUMMARY A reproducible electrophysiological technique is described to determine the latency of reflex contraction of the external anal sphincter in response to stimulation of the dorsal genital nerve: the pudendo-anal reflex. This was studied in 38 asymptomatic control subjects and 20 women with neurogenic faecal incontinence, supplemented by determination of the mean motor unit potential duration (MUPD) of the external anal sphincter and anorectal manometry. The reflex latency in the control group was 38.5 ± 5.8 (SD) ms and appeared to be independent of age or sex. Three patients with faecal incontinence had absent reflexes; the remainder showed significant prolongation of latency (56 ± 12.2 SD ms) and diminution of amplitude. MUPD was prolonged in incontinence and showed significant correlation with the corresponding reflex latency determination (r = 0.56, p < 0.001). The latency of this polysynaptic spinal reflex hence provides a reliable index of neuropathy of the external anal sphincter.

There has recently been much interest and controversy about the electrically evoked reflex activity of the external anal sphincter, particularly in relation to faecal incontinence of neurogenic origin.1-7 Swash et al suggested that the latency of the classical anal reflex measured electrophysiologically was significantly increased in idiopathic faecal incontinence.2-3 However, studies by other workers did not confirm the usefulness of the latency of this reflex as an index of pelvic floor neuropathy,6-7 and raised doubts about the interpretation of the earlier latency measurements. It has since become clear that electrical stimulation of the perianal skin results in direct stimulation of the terminal innervation of the external anal sphincter. This produces the “early” or short-latency responses4-9 that had previously been erroneously interpreted as spinal cord reflexes.2-3-8-9 These inconsistencies have limited the usefulness of the classical anal reflex for studying the clinical neurophysiology of the pelvic floor. Electrical stimulation of the dorsal nerve of the glans penis or clitoris evokes a reflex contraction of the external anal sphincter mediated via the sacral spinal cord segments 2, 3, and 4, a modification of the bulbocavernosus reflex described by Bors and Blinn in 195910 (fig 1). The availability of modern electrophysiological equipment has enabled more precise studies on the latency of the pudendo-anal reflex.11 We describe a reproducible method of measuring the latency of this reflex and investigate its variation with age and sex, and in neurogenic faecal incontinence.

Patients and methods

Approval for this investigation was obtained from the Ethical Committee of the North Lothian District, Lothian Health Board, Scotland, in June 1983. Informed consent was obtained from all subjects participating in the study. The control group consisted of 25 female and 13 male subjects (age range 23–75 years, mean 45 years). They were hospital patients who had been admitted for minor surgery outwith the alimentary tract and none had any anorectal symptoms. The group with neurogenic faecal incontinence comprised 20 women (age range 37–79 years, mean 59.9 years). The duration of anal incontinence ranged from 6 months to 10 years (mean 1.9 years). All subjects underwent anorectal manometry and measurement of the latency of the pudendo-anal reflex. Determination of the mean motor unit potential duration of the external anal sphincter was performed in all the incontinent patients and in 15 control subjects.

Manometry

Patients were requested to empty their bowel on the morning
Suprasegmental influence

Sacral cord segments 2-4

Stimulator

Pudendoanal reflex

Bulbocavernosus reflex

Fig 1  Diagrammatic representation of the anatomical basis of the bulbocavernosus and pudendo-anal reflexes (modified from Ertekin and Reel).16

of the study. The investigations were performed with the patient in the left lateral position. Basal and squeeze sphincter pressures and sphincter length were measured with a conventional water-filled microballoon and external transducer using a 0.5 cm station-pullthrough method.12

Latency of the pudendo-anal reflex

Figure 1 illustrates the anatomical basis of the pudendo-anal reflex.11 It was elicited by electrical stimulation of the dorsal nerve of the glans or clitoris with a felt bipolar surface stimulating electrode (type LBS 53051, Medelec, UK). The reflex contraction of the external anal sphincter was recorded with a bipolar surface stainless-steel anal plug electrode (type 13K78, DISA, Copenhagen) using the Medelec MS92a evoked response unit. Electrode jelly was used to improve electrical contact between the plug electrode and the sphincter. A saline-soaked felt strip wrapped around the right thigh was used as the ground electrode. More than 100 square-wave stimuli (duration 0.1 ms, frequency 2 Hz) were applied and the digitally averaged response displayed on the oscilloscope at a sweep speed of 10 ms/cm with the gain at 100 μV/cm and filter settings of 20 Hz–10 kHz. The stimulation voltage was approximately three times the voltage at sensation threshold; typical threshold and stimulation voltages being 30 V and 90 V respectively. In no case was the stimulation reported by the patient to be painful. The procedure was repeated in each subject to ensure reproducibility. The latency of the pudendo-anal reflex was measured from the onset of the sweep (triggered by the stimulus) to the onset of the clearly defined reflex response at the external anal sphincter (fig 2).

Determination of the mean motor unit potential duration (MUPD) of the external anal sphincter

A modification of the method described by Bartolo et al13 was used. A standard concentric needle EMG electrode (surface area 0.07 mm², type 13L49 DISA, Copenhagen) was inserted into the external anal sphincter without anaesthetic via a puncture site 1 cm lateral to the anal orifice to a depth of approximately 250 mm. This was connected via preamplifiers to an oscilloscope (Medelec MS92a, Woking, Surrey, UK). The tonic electrical activity of the sphincter was monitored using a time base of 10 ms/cm with the gain at 100 μV/cm and filter settings of 20 Hz–10 kHz. Single motor units firing at a steady rate were identified using the delay and trigger facilities incorporated in the apparatus. A


determination from Ertekin and Reel16).

Varma, Smith, McInnes

Fig 2  Typical traces of the pudendo-anal reflex.
Electrophysiological observations on the human pudendo-anal reflex

Table 1: Anorectal manometry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n = 25)</th>
<th>Faecal incontinence (n = 20)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum resting pressure (cm H₂O)</td>
<td>100 ± 28</td>
<td>60 ± 24.6</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Squeeze pressure (cm H₂O)</td>
<td>167 ± 35</td>
<td>86 ± 32.6</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Physiological sphincter length (cm)</td>
<td>3.2 ± 0.5</td>
<td>2.2 ± 0.9</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

All measurements Mean ± SD.

Table 2: Normal range and variations with sex and age of the pudendo-anal reflex latency

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age (Range, mean ± SD, yr)</th>
<th>Latency of pudendo-anal reflex (Range, mean ± SD, ms)</th>
<th>Statistical significance of differences in latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>23-75 (45 ± 14.6)</td>
<td>27-2-46.8 (38.5 ± 5.8)</td>
<td>p &gt; 0.1</td>
</tr>
<tr>
<td>Female (age-matched)</td>
<td>28-57 (46 ± 12.6)</td>
<td>33-46 (40.7 ± 4.4)</td>
<td>p &gt; 0.1</td>
</tr>
<tr>
<td>Female (&quot;young&quot;)</td>
<td>23-49 (33 ± 9.2)</td>
<td>33-44.8 (39.6 ± 4.3)</td>
<td>p &gt; 0.1</td>
</tr>
<tr>
<td>Female (&quot;old&quot;)</td>
<td>55-75 (62 ± 6)</td>
<td>29-2-46 (36.6 ± 6.6)</td>
<td>p &gt; 0.1</td>
</tr>
</tbody>
</table>

Statistics
Non-parametric methods were used. Differences in the manometric and electrophysiological measurements between the various groups were analysed by the Wilcoxon rank sum test. Correlation between the latency of the pudendo-anal reflex and mean motor unit potential duration of the external sphincter was performed by Kendall's rank correlation.

Results

Manometry
Table 1 compares the manometric parameters measured in the two groups. There was a significant reduction in the physiological sphincter length, maximum resting pressure and the squeeze pressure of the external anal sphincter in the incontinent group.

Electrophysiology
Reproducible reflex responses were confirmed in all subjects. Reversal of the polarity of the stimulating electrode simply resulted in reversal of the stimulus artefact without altering the shape or latency of the evoked response. “Bifid” responses were observed in some patients and controls, that is, responses with late components. In these cases the latency of the pudendo-anal reflex was taken from the onset of the first response because this represents the shortest measurement. Table 2 lists the latencies of the pudendo-anal reflex in the control group of 38 subjects. These were further subdivided into age-matched male and female groups (n = 10) and “young” and “old” female groups (n = 10). No differences in the latency of the reflex were demonstrable with either sex or age. Table 3 compares the electrophysiological data between the control and incontinent groups. There were no differences in the voltage at sensation threshold and that used for maximal stimulation. However, the latency of the pudendo-anal reflex was significantly prolonged and its amplitude reduced in the incontinent group. In three of these patients the reflex could not be elicited despite several attempts. No differences were apparent in the duration of the reflexly evoked anal sphincter response between the

saline-soaked felt strap wrapped around the right thigh was used as the ground electrode. Approximately 100 consecutive action potentials of the same motor unit were digitally averaged on one channel of the oscilloscope and the process repeated on the second channel. When two identical traces were obtained on both channels, the action potential duration for that motor unit was measured from the first deflection from the baseline to the return of the action potential to the baseline. Stable late components were thus easily identified. Permanent recordings were obtained of at least 20 action potentials from the external anal sphincter spreading approximately ten recordings from each side of the sphincter. This was made possible by minor movements of the tip of the needle electrode in the sphincter. The arithmetic mean of the 20 recorded potential durations was calculated and represented the mean motor unit potential duration for that sphincter. This was used as an index of neuropathy.14

Non-parametric methods were used. Differences in the manometric and electrophysiological measurements between the various groups were analysed by the Wilcoxon rank sum test. Correlation between the latency of the pudendo-anal reflex and mean motor unit potential duration of the external sphincter was performed by Kendall's rank correlation.

Table 3: Electrophysiological anal sphincter data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n = 25)</th>
<th>Faecal incontinence (n = 20)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensation threshold (Volts)</td>
<td>35.2 ± 14.5</td>
<td>31 ± 8.9</td>
<td>p &gt; 0.1</td>
</tr>
<tr>
<td>Stimulating voltage (Volts)</td>
<td>112 ± 33</td>
<td>96.8 ± 20.1</td>
<td>p &gt; 0.05</td>
</tr>
<tr>
<td>Amplitude of pudendo-anal reflex (µV)</td>
<td>39 ± 5.8</td>
<td>56 ± 12.2 (3 absent)</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Latency of pudendo-anal reflex (ms)</td>
<td>4.5 ± 3.4</td>
<td>1.95 ± 1.9</td>
<td>p &lt; 0.1</td>
</tr>
<tr>
<td>Amplitude of pudendo-anal reflex (µV)</td>
<td>16.9 ± 7</td>
<td>15.4 ± 5.4</td>
<td>p &gt; 0.1</td>
</tr>
<tr>
<td>Latency of pudendo-anal reflex (ms)</td>
<td>(n = 15)</td>
<td>(n = 20)</td>
<td></td>
</tr>
<tr>
<td>Mean motor unit potential duration of external sphincter (ms)</td>
<td>8.66 ± 1.39</td>
<td>12.23 ± 1.83</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

All measurements Mean ± SD.
Discussion

Patients, r = 0-4, p < 0-02 (for linear correlation, r = 0-56, p < 0-001; for linear correlation between the latency of the pudendo-anal reflex and the mean MUPD of the external anal sphincter was significantly increased in the incontinent patients. Figure 3 illustrates the high correlation of the corresponding latency of the pudendo-anal reflex.

![Absence of reflexes](image)

Fig 3 Scattergram showing correlation between the mean motor unit potential duration of the external anal sphincter and the corresponding latency of the pudendo-anal reflex.

two groups. The mean MUPD of the external anal sphincter was significantly increased in the incontinent patients. Figure 3 illustrates the high correlation between the latency of the pudendo-anal reflex and the mean MUPD of the respective external anal sphincter (τ = 0.56, p < 0.001; for linear correlation r = 0.69, p < 0.001). Taking only the incontinent patients, τ = 0.4, p < 0.02 (for linear correlation, r = 0.5, p < 0.05).

Discussion

Reflexes involving the perineal muscles have stimulated much interest in the neurological evaluation of the conus medullaris and its afferent and efferent connections. These studies are considered to be of particular value in disorders of the genito-urinary system and the pelvic floor muscle activity. Since the description of the classical anal reflex by Rossolimo in 1891 using mechanical stimulation of the perianal skin, the reflex has been extensively investigated by more sophisticated electrophysiological methods. Henry and Swash described a latency for this reflex of 8.3 ± 1.7 (SD) ms in 13 normal subjects and suggested that it was prolonged in faecal incontinence and rectal relapse. The presence of these short-latency responses has been observed by other workers who also noted later responses of longer duration. The early reactions have a uniform electrical pattern and show no signs of fatigue. They are not abolished by spinal anaesthesia and their latencies are too short for a spinal reflex. They have therefore been attributed to direct activation of the terminal innervation of the anal sphincter. Some of the intermediate responses may be due to antidromic stimulation via interaction between neighbouring α-motoneurons to the Onuf's nucleus hence resulting in "oligosynaptic latencies." The "classical" polysynaptic anal reflex now recognised to have a latency of 50 ± 10.5 (SD) ms. These variable factors have made the precise determination of the latency of the anal reflex difficult and its interpretation controversial.

Reflex reaction of the external anal sphincter can also be provoked by stimulating the glans penis, clitoris, the mucosa, the rectum, urethra and bladder and even the posterior tibial nerve. Stimulation of the dorsal nerve of the penis or clitoris evokes a reflex contraction of the bulbocavernous muscle: the classical bulbocavernous reflex and pudendal sex reflex. However, at a recent meeting of the Physiological Society the more accurate terminology "pudendo-anal reflex" was adopted.

The latency of this response appears to depend on the intensity of stimulation and shows little or no signs of habituation. Hence, the most appropriate electrophysiological method for investigating this reflex is to use a train of high voltage stimulus impulses and to average digitally the analysed sphincter response as described in this study. The averaging technique helps to obtain a clearly defined response by reducing background activity. The relatively greater distance between recording and stimulating electrodes diminishes the stimulus artefact and, more importantly, eliminates the "direct" short-latency responses such as those observed in the elicitation of the classical anal reflex. The use of a surface anal plug electrode is preferred to concentric needle electrodes because a much larger area of muscle is sampled thus giving a more accurate indication of its function. Voltage was used to measure sensory threshold and stimulation parameters in this study as have many other previous reports, although current probably constitutes a better measurement.

Haldeman et al. were able to demonstrate a conduction time of approximately 8 ms in the afferent limb of the pudendo-anal reflex by recording evoked potentials over the sacral conus. Marsden et al. using percutaneous spinal cord stimulation, measured a latency of approximately 8 ms in the afferent limb of the reflex in normal subjects. This observation was confirmed by Snooks et al. who also showed prolongation of this latency in neurogenic incontinence, thus demonstrating a lesion in the afferent
Electrophysiological observations on the human pudendo-anal reflex

...nal cord in the absence of neuropathic changes in the external anal sphincter. Hence, it has been used in the investigation of patients with neurogenic disorders of the urinary bladder and of sexual function. Many of these patients often have radiological evidence of lumbo-sacral spinal dysraphism. Similar observations have been made in some patients with intractable constipation of idiopathic origin.

Electrophysiological measurement of the pudendo-anal reflex latency provides a simple and reliable method of evaluating pelvic floor neuropathy. It also provides information of the neurogenic function of the sacral conus. Its diagnostic value is increased when supplemented by other functional investigations. These include anorectal manometry, EMG (duration of motor units, number of polyphasic potentials, fibre density) and measurement of conduction velocity in the motor innervation of the pelvic floor.

This work was supported by grants from the Wellcome Trust research (No. 12196 14L) and the British Digestive Foundation (Scottish Appeal) held by JSV. We thank Dr JA Jarratt, Department of Clinical Neurophysiology, University of Sheffield for technical advice in determination of the mean motor unit potential duration, and Dr M Swash, Sir Alan Parks Physiology Unit, St Mark's Hospital, London, for helpful comments. Professor CD Marsden, University Department of Neurology, London, suggested the nomenclature for the pudendo-anal reflex.

References

Differential effects of sacral anterior root stimulation on anal sphincter and colorectal motility in spinally injured man

The motility responses of the sigmoid colon, rectum and external anal sphincter to sequential electrical stimulation of the anterior sacral roots (S₂, S₃ and S₄) were studied in five patients with traumatic spinal cord injury. Identical and reproducible results were obtained. S₂ stimulation provoked isolated low-pressure colorectal contractions. S₃ stimulation initiated high-pressure colorectal motor activity which appeared peristaltic and was enhanced with repetitive stimuli. This response appeared to be frequency-dependent. S₄ stimulation increased colonic and rectal tone. External sphincter activity was stimulated in increasing order from S₂ to S₄. These observations directly elucidate the central control of colorectal motility and may have implications in the treatment of severe constipation following spinal injury.

**Keywords**: Paraplegia, constipation, colorectal motility, conus medullaris, sacral roots, implant, stimulator

**Patients and methods**

**Patients**

Informed consent was obtained from the patients participating in the study. Five men were studied (Table I), their mean age being 38 ± 2 years. All had traumatic cord lesions resulting in complete spinal cord injury in tar and incomplete tetraplegia in one. Sacral anterior root stimulators had been implanted for recurrent or persistent urinary tract infections and had proved effective in emptying the bladder.

**Table I**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Segmental level of cord injury</th>
<th>Duration of injury (years)</th>
<th>Duration of implant (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>M</td>
<td>T₂, complete</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>M</td>
<td>C₄, incomplete</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>M</td>
<td>C₄, complete</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>M</td>
<td>C₄, complete</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>M</td>
<td>C₄, complete</td>
<td>15</td>
<td>6</td>
</tr>
</tbody>
</table>

All patients had experienced digital evacuation of the rectum approximately every third day. In addition, some needed the aid of suppositories. At the time of the study most of the patients were observed to be faecally impacted. It was apparent that these patients had abnormal perineal descent and anal mucosal prolapse. None of the patients had observed any significant improvement in bowel function with use of the stimulator for faecal control. However, three of them admitted improvement in the anal mucosal prolapse since implant surgery.

**Implants, surgery and stimulation technique**

A type of stimulator and surgical procedure to implant it was similar to that described by Brindley et al. 

**Results**

The electromyographic responses of the external anal sphincter to sacral stimulation were performed twice to ensure reproducibility. The latency of the pudendo-anal reflex was measured to ensure the neurogenic integrity of the conus medullaris and its afferent and efferent pathways. This reflex was elicited by electrical stimulation of the dorsal nerve of the penis with a bipolar stainless-steel stimulator electrode (type LBS 5205, Medelec, UK) and recording the reflex contraction of the external anal sphincter with a bipolar stainless-steel anal plug electrode (type LBS 5205, Medelec, UK) using the Medelec MS92a evoked response unit. Over 100 square-wave stimuli (duration 0.1 ms, frequency 2 Hz) were applied and the digitally averaged response displayed on the oscilloscope at a sweep speed of 10 ms/cm with the gain at 10 or 20 μV/cm and filter settings of 2 Hz-10 kHz. A stimulation voltage of 150 V was used. In no case was the stimulation reported to be uncomfortable by the patient. The procedure was repeated in each subject to ensure reproducibility. The latency of the pudendo-anal reflex was measured from the onset of the sweep (triggered by the stimulus) to the onset of the clearly defined reflex response.

**External sphincter EMG**

The electromyographic response of the external anal sphincter to sacral stimulation was monitored by a standard concentric needle EMG electrode (type 13149 DISA, Copenhagen) inserted into it at a site 1 cm posterior to the anal orifice to a depth of approximately 2.5 cm. This was connected via preamplifiers to an oscilloscope (Medelec MS92a, Woking, Surrey, UK). Electrical activity of the sphincter was continuously monitored using a time base of 100 ms/cm with the gain at 100 μV/cm and filter settings of 20 Hz-10 kHz. Permanent recordings were obtained of electrical activity at rest and on root stimulation.
electrical activity was also heard as amplified sound via a loudspeaker incorporated in the equipment.

Manometry

Fasted patients were assisted in emptying their bowel on the morning of the study by digital evacuation and a saline rectal washout if necessary but laxatives were not used. Digital rectal examination and limited sigmoidoscopy using a paediatric instrument were performed to ensure that the rectum was reasonably empty and for tube placement in the left lateral position.

Maximum basal anal canal pressure and the response to root stimulation was recorded by a conventional technique using a waterfilled microballoon connected to an external transducer via fine tubing. This was held in place by adhesive tape.

Proctogrammetry was performed to determine the volumes at maximal distension, and rectal compliance. Thereafter the large proctogrammetric balloon was emptied and refilled with 200 mL of water and the pressure responses of the rectum to root stimulation recorded. Motility of the sigmoid colon was monitored in the basal state and following root stimulation by three waterfilled balloons made of soft rubber (HSCI, Precision Dippings Ltd, UK) connected to external transducers by fine tubing. The balloons were placed sigmoidoscopically at distances of 15, 20, and 25 cm from the anal verge (Figure 1). Following completion of the colonic motility responses all three balloons were withdrawn into the rectum (to lie at 5, 10, and 15 cm from the anal verge) and its motility assessed by this method also.

Results

Pudendo-anal reflex

The reproducible latencies of this electrophysiological reflex in the five patients are shown in Table 2. These were considered to be within the normal range.

Anal sphincter responses

Figure 2 illustrates typical anal canal pressure tracings obtained during stimulation of sacral anterior roots S2, S3, and S4. There is a successive increment in pressures with stimulation of the more caudal roots. S4 stimulation also produces a more sustained contraction of the external anal sphincter. Figure 3 shows the sequential pressure increments in all five patients. These manometric responses were confirmed electromyographically by simultaneous EMG traces from the external anal sphincter. The resting 'tonic' electrical activity of this muscle appeared to be diminished in most patients.

Rectal responses

None of the patients had any perception of rectal distension during the proctogrammetry. Rectal compliance and the maximal volumes and pressures recorded are shown in Table 2.

Table 2 Electrophysiological and manometric data in five patients with spinal cord injury and in control subjects

<table>
<thead>
<tr>
<th>No.</th>
<th>Pudendo-anal reflex latency (ms)</th>
<th>Rectal compliance (ml/cm H2O)</th>
<th>Maximum rectal volume (ml H2O)</th>
<th>Balloon expulsion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>9.5</td>
<td>5.5</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>5.5</td>
<td>355</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>39.2</td>
<td>18.5</td>
<td>&gt;800</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>32.4</td>
<td>10.4</td>
<td>409</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>6.4</td>
<td>355</td>
<td>Yes</td>
</tr>
<tr>
<td>Control (mean ± s.d.)</td>
<td>38.5 ± 5.8</td>
<td>9 ± 1.6</td>
<td>493 ± 80</td>
<td>None</td>
</tr>
</tbody>
</table>

---

Figure 1 Diagrammatic illustration of the technique for monitoring colorectal and anal sphincter motility responses to sacral root stimulation

Figure 2 Anal canal pressure tracings (redrawn). Note the sustained high-pressure response to S4 stimulation

Figure 3 Graphical representation of maximum anal canal pressure increments in response to sequential root stimulation in five patients. Each point represents the mean of two experiments
Anal sphincter and colorectal motility: J. S. Varma et al.

**Figure 4** Rectal pressure tracings illustrating the various motility responses to low and high frequency sacral anterior root stimulation. Pressures recorded in a proctometrogram balloon containing 200 ml water.

Two patients (1 and 4) had normal compliance, two had reduced compliance (2 and 5) and patient 3 had markedly increased compliance. Three patients (patients 1, 2 and 5) expelled the proctometrogram balloon at the maximal volume. This phenomenon is not seen in normal subjects.

**Figure 5** Graph depicting maximum rectal pressures following sequential root stimulation in five patients. (Each point represents the mean of two experiments)

### Discussion

Experimental studies in animals have suggested that the motility of the gastrointestinal tract can be altered by lesions of the spinal cord. Evidence also exists for changes in colonic motility in man following spinal cord injury. White, Verlot and Ehrentheil recorded the pressure curve of the colon during slow filling with water. They found a hypertonic response in those patients with 'high' lesions of the spinal cord, and a hypotonic response in patients with lesions involving the sacral spinal cord or cauda equina. Connell et al. found that the resting, unstimulated motility of the pelvic colon was diminished in patients with high cord transection but was significantly increased in those with low cord lesions. Weber et al. provided evidence for the pons as a possible supraspinal level of control of colonic and anorectal motility. Meshkinpour et al. demonstrated poor colonic compliance in patients with thoracic spinal cord injury. These patients also failed to demonstrate the normal increase in qualitatively similar to those of the rectum but more exaggerated. In particular, S4 root stimulation produced complex high-pressure phasic contractions reminiscent of peristaltic activity. This response appeared to be facilitated and increased in amplitude by successive stimuli and continued for some time following their cessation. Furthermore, stimulation at the higher frequencies produced more prominent contractions. The quantitative sequential pressure increments in all five patients are shown in Figure 7.

**Reproducibility of data**

The latency of the pudendo-anal reflex was completely reproducible. The data obtained from the proctometrogram were very reliably reproducible (mean coefficient of variation < 8 per cent). Pressure recordings in the anal canal, rectum and sigmoid colon in response to stimulation (Figures 3, 5, 7) had a mean coefficient of variation of < 7 per cent. Between patients, the qualitative type of response obtained (Figures 2, 4, 6) was always the same.

Br. J. Surg., Vol. 73, No. 6, June 1986
Anal sphincter and colorectal motility: J. S. Varma et al.

These and other studies have suggested that the mechanisms controlling defaecation are mediated through the sacral segments of the spinal cord and its peripheral ramifications. It is now recognized that the sacral anterior roots carry the parasympathetic outflow to the left colon, rectum and internal anal sphincter. In addition they convey the somatic innervation to the striated anal sphincter muscle which is intimately involved in the control of continence and defaecation.

Brindley et al. utilized this knowledge to promote bladder emptying and urinary continence following spinal cord injury by controlled electrical stimulation of the sacral anterior roots with satisfactory long-term results. Patients with such implants hence present a unique physiological opportunity to study directly the neurogenic influence on the anal sphincter and colorectal motility. Furthermore, this information could prove beneficial in the treatment of disorders of colorectal motility. These points are addressed in the present study.

The manometric and electrophysiological observations on the external anal sphincter simply confirm its innervation from these sacral roots. Our evidence suggests that the S4 roots supply the principal part of this innervation. Although the puborectalis is now thought to receive a nerve supply separate from the external anal sphincter, their root innervation is similar.

Brindley et al. did not observe any response in the anal sphincter musculature during S2 stimulation. However, their observations did not include manometric or EMG data. Tonic basal electrical activity was present in all the patients in this study although it was thought to be diminished in comparison to that found in normal subjects. This resting activity is mediated through reflexes via the conus medullaris and further confirms its integrity. Although most of the pressure increase in the anal canal on sacral root stimulation is attributable to contraction of the striated anal sphincter muscle, some contraction of the internal anal sphincter must also occur as is suggested by the smooth muscle responses of the rectum and sigmoid colon. However, it is difficult to quantify the differential activity of the internal sphincter alone.

Postprandial motor and myoelectrical activity of the colon were investigated by Menard et al., using transit studies. They showed that the following spinal transection the left colon and rectum were the main sites of stasis. Haldeman et al. showed abnormal colonograms in patients with multiple sclerosis affecting the supra-sacral segments. These abnormalities in colorectal motility following injury to the spinal cord often result in troublesome constipation which is usually treated empirically.

Figure 6 Sigmoid colon pressure tracings at 15, 20 and 25 cm from the anal verge illustrating the differential motility responses to low and high frequency stimulation of: a, S2; b, S3; and c, S4 sacral anterior roots.

Figure 7 Graphical representation of maximal pressure responses in the sigmoid colon (25 cm from anal verge) to sequential sacral anterior root stimulation. (Each point represents the mean of two experiments.)
The effects of S₃ stimulation on the sigmoid colon and rectum are similar to those on the detrusor smooth muscle described by Brindley et al.1,2. In a larger number of patients they found only slight variation in the motor innervation of this organ. However, it appeared to be more responsive to S₃ than S₂ stimulation. In the colon and rectum there is little difference in the quantitative pressure responses obtained on stimulation of these two roots but the type of responses are quite different. The S₃ root simply increases the tone of the muscle during the stimulation phase. It is possible that this 'tonic' pressure response is due to the contraction of the pelvic floor; however, these effects would not be expected to be observed at 25 cm from the anus. Furthermore, no such effects were observed on S₃ stimulation which also causes contraction of the pelvic floor. As in the urinary bladder, facilitation and enhancement of the colorectal contractions seems to occur after repeated stimuli, resulting in complex, periodic trains of waves (Figure 6b). This is hence the site of stimulation that may benefit patients with faecal stasis. Nevertheless, it must be realised that the stimulation parameters used in this study were limited to those used for detrusor contraction1. Further studies are needed to clarify the optimum stimulation parameters to achieve the most effective motility responses. For example, simultaneous stimulation of S₂ and S₃ may prove more effective than S₃ alone in increasing colonic motility. Supplementary data by recording myoelectric activity of the distal bowel would further help to elucidate this.

The decrease in rectal compliance seen in some of our patients is in keeping with the findings of Meshkinpour et al.3-5. One patient, however, appeared to have an 'atonic' rectum, its aetiology being uncertain. Balloon expulsion seems to occur more easily in those patients with rectal compliance. Other factors such as loss of rectal propoception and the amount of resting activity in the external sphincter must also contribute to this phenomenon which is of practical importance in the context of automatic evacuation5-3. It is observable that sacral root stimulation might be utilized to facilitate contraction of the colonic colon and rectum resulting in movement of faeces caudally into the anal canal. This would further initiate the complex reflex relaxation of the pelvic floor muscles to allow unresisted evacuation of the rectum. Although anorectal incontinence is usually not a major problem following spinal cord injury, continuous weak sacral root stimulation could also be used to improve anal continence in the same way as that demonstrated for nocturnal control of injury continence6. We have already observed beneficial effects of sphincter stimulation on rectal mucosal prolapse in some of these patients.

Further studies are in progress to determine the long-term effects of sacral anterior root stimulation on colorectal function in spinally injured patients.

Acknowledgements

JS Varma was supported by a Wellcome Trust Research Grant No. 11596/4. L and the British Digestive Foundation (Scottish Appeal). NS Varma was supported by a grant from the Scottish Health Endowment Research Trust (No. 720). We are indebted to Professor G.B. Brindley, Neurological Prosthesis Unit, the Maidstone Hospital, London, and Mr P. Harris, University Department of Surgical Neurology, Western General Hospital, Edinburgh, for their expert help with the implant operations.

References

Late results of mucosal proctectomy and colo-anal sleeve anastomosis for chronic irradiation rectal injury

Ten patients with severe chronic irradiation injury to the rectum were treated by mucosal proctectomy and colo-anal sleeve anastomosis. The indications were: recurrent rectal bleeding (five), stricture (three), fistula (one) and intractable pain (one). Overall follow-up has ranged from 8 to 77 months (mean 40 months). In the present survivors (n = 7) the follow-up ranges from 18 to 77 months (mean 52 months). Six patients have been followed up for more than 3 years and four for more than 5 years. There was no operative mortality. Three anastomotic strictures occurred but the protecting stoma could be closed in all but one patient. Continence was acceptable although urgency and frequency of defaecation were troublesome symptoms. The operation is recommended for life-threatening, haemorrhagic chronic irradiation injury to the rectum.

Keywords: Irradiation rectal injury, haemorrhagic proctitis, colo-anal sleeve anastomosis, anorectal function

Radiotherapy makes an important contribution to the treatment of malignant disease arising in the pelvis. Some irradiation of adjacent healthy tissue inevitably occurs, the rectum being most commonly involved.1-6 The symptomatic disturbances from chronic irradiation rectal injury are distressing,7 the organic complications such as haemorrhage and perforation can be life-threatening and may necessitate urgent surgical intervention.2-6 Surgical excision of the irradiation-injured rectum may be extremely hazardous and its risks have been repeatedly emphasized. Anterior resection, Hartmann's procedure and abdomino-perineal excision of the rectum are all associated with an unacceptably high incidence of anastomatic dehiscence, poor tissue healing and chronic pelvic sepsis.8-11 The late Sir Alan Parks described a technique of anastomosis between healthy proximal colon and the anal canal within a sleeve of rectal muscle demucosalised of mucosa.8 This procedure avoids extensive pelvic dissection and preserves the anal sphincter muscle and its innervation. It has been applied successfully to the treatment of a number of different conditions including irradiation-induced rectovaginal fistulae.8,9 However, the long-term results of the operation when performed for more extensive irradiation rectal injury have received little attention. We describe the clinical progress and long-term results in ten patients treated by this method for severe chronic irradiation injury to the rectum. Based on previous experience8,9 and these results, a protocol is suggested for the management of delayed irradiation injury to the rectum requiring surgical intervention.

Patients and methods

Table 1 lists details of the ten patients treated between 1979 and 1985. Their mean age was 65 years; eight patients were over the age of 60 years. Before radiotherapy, two patients had a Hartmann's procedure for complications of diverticular disease. Seven patients had been treated for carcinoma of the urinary bladder. Five of these had received small field (10 x 10 cm) external beam radiotherapy (5500 cGy in 20 treatments over 4 weeks), and two had received neutron therapy using the small-field (0.8 x 1 cm) technique (mean dose to the bladder 300 cGy for ten treatments over 4 weeks; mean dose to the whole pelvis 1300 cGy for ten treatments over 4 weeks). The three patients with cervical cancer had received whole pelvis, external beam radiotherapy supplemented by a single caesium implant (cumulative dosage of 9500 cGy to the vaginal vault, equivalent to 7500 cGy to point A).

Five patients had experienced recurrent life-threatening rectal bleeding requiring several hospital admissions and repeated blood transfusions (Figure 1). All the irradiation patients had undergone courses of intensive medical therapy in an attempt to control their rectal symptoms. The patients were assessed jointly by a senior surgeon and radiation oncologist to exclude recurrent malignant disease; radiological investigations were also performed to assess the site, extent and severity of damaged bowel. Before they could be considered for rectal excision, six patients required a preliminary laparotomy and transverse colostomy to defunction severely diseased distal bowel. At this procedure a full assessment of the abdomen and pelvis was also made to exclude recurrent malignancy.

Anal sphincter function was assessed clinically and manometrically in most of the patients.12

Operative technique

The bowel was prepared as for a major colonic resection.11 In those patients with a loop colostomy the distal colon was additionally cleansed by saline washouts on the day before operation. Prophylactic antibiotics were used and continued for 5 days postoperatively. With the patient in the modified Trendelenburg lithotomy position a careful laparotomy was performed to assess the extent of inflammation and confirm the absence of metastatic disease. Excision of the rectum was then performed to mid-rectal level, sparing approximately 6-7 cm of distal rectum. The site of section proximally was determined by the extent of the macroscopic irradiation damage and the presence and extent of diverticular disease. Sufficient healthy proximal colon was mobilized to reach the anal canal, ensuring adequate vascularity. The anastomosis was performed peranally using a Park's self-retaining retractor to expose the anorectal mucosa. After infiltration of the submucosa with saline containing adrenaline (1:300 000) the rectal mucosa was excised in strips from the underlying circular muscle, preserving a 1 cm cuff of mucosa above the dentate line. The proximal colon was then pulled through the denuded rectal muscle tube to lie without tension in the sacral concavity. The anastomosis was fashioned approximately 1 cm above the dentate line. Using interrupted polyglycolic acid sutures, full-thickness bites were taken of both the colon and the upper part of the internal anal sphincter (Figure 2). A soft rubber drain was placed in the pre-sacral space behind the transposed colon. In the absence of a proximal stoma, a loop transverse colostomy13 was fashioned in the right upper quadrant; one patient did not have a protecting stoma. Stomas were closed when the anastomosis was clinically healed and any stoma present had been dilated. Tests of anorectal continence were performed in several patients.
Irradiation rectal injury: G. G. P. Browning et al.

Table 1  Clinical details of ten irradiated patients showing treatment and complications

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Carcinoma</th>
<th>Treatment</th>
<th>Onset of symptoms following radiotherapy (months)</th>
<th>Complications</th>
<th>Time from presentation to resection (months)</th>
<th>Duration of treatment (months)</th>
<th>Time to closure of colostomy (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>F</td>
<td>Bladder</td>
<td>XRT</td>
<td>12</td>
<td>Proctitis</td>
<td>17</td>
<td>16 (Medical)</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>F</td>
<td>Bladder</td>
<td>XRT</td>
<td>9</td>
<td>Stricture (8 cm)</td>
<td>21</td>
<td>8 (Medical)</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>F</td>
<td>Bladder</td>
<td>XRT</td>
<td>15</td>
<td>Proctitis</td>
<td>24</td>
<td>13 (Loop colostomy)</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>M</td>
<td>Bladder</td>
<td>Neutron XRT</td>
<td>9</td>
<td>Haemorrhage Proctitis Stricture Obstruction</td>
<td>4</td>
<td>4 (Medical)</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>M</td>
<td>Bladder</td>
<td>Neutron XRT</td>
<td>6</td>
<td>Proctitis Stricture (10 cm) Haemorrhage Proctitis</td>
<td>28 (Medical)</td>
<td>2 (Loop colostomy)</td>
<td>4 (Loop colostomy)</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>F</td>
<td>Cervix</td>
<td>Hartmann’s XRT</td>
<td>6</td>
<td>Proctitis Haemorrhage Proctitis</td>
<td>2 (Medical)</td>
<td>3 (Loop colostomy)</td>
<td>No colostomy</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>F</td>
<td>Cervix</td>
<td>Hartmann’s XRT</td>
<td>7</td>
<td>Proctitis Haemorrhage Proctitis Pain</td>
<td>2 (Medical)</td>
<td>3 (Loop colostomy)</td>
<td>No colostomy</td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>F</td>
<td>Bladder</td>
<td>XRT</td>
<td>1</td>
<td>Proctitis Stricture (15 cm) Ileitis Fistula (5 cm) Proctitis Stricture (2 cm)</td>
<td>17 (Medical)</td>
<td>1 (Loop colostomy)</td>
<td>7 (Loop colostomy)</td>
</tr>
</tbody>
</table>

XRT, X-ray therapy

Follow-up and assessment
Follow-up has ranged from 8 to 77 months (n=10, mean 40 months) in the whole group and from 18 to 77 months in the present survivors (n=7, mean 32 months). Six patients have been followed up for more than 3 years, and four patients for more than 5 years.

At each clinic visit continence and bowel function were assessed objectively according to a predefined protocol. Continence was graded A (fully continent), B (continent for solid stool only), or C (incontinent for both solid and liquid stool). Continence for flatus was not taken into consideration. Frequency and urgency of defaecation were also noted, and discrimination between stool and flatus was assessed.

Results
Complications
There was no operative mortality. The early complications (three perianastomotic abscesses, three anastomotic strictures, one stomal haemorrhage) were managed successfully by conservative measures. The late complications are of more interest. In the irradiation group, there were three anastomotic strictures, two in neutron irradiated patients. All were treated by repeated dilatation but in one patient (patient 5, Table 1) the protecting colostomy could not be closed owing to the severity of the stricture. One patient (patient 1, Table 1) developed a fistula 5 years postoperatively and required re-establishment of a colostomy. A second patient (patient 10, Table 1) developed a vesicovaginal fistula 3 months after closure of the colostomy and is awaiting repair.

Stomas
The mean time to closure of the protecting stoma was 11 weeks.
It is a sad commentary on our surgical skills that such patients admitted to very poor discrimination between flatus and faeces. Intense villous adenomas of the rectum, rectovaginal fistulae, ischaemia contributed to their aetiology. Nevertheless, one of these patients managed successfully without a colostomy for 5 years. A similar factor was probably also responsible for the late development of a vesicovaginal fistula in one patient.

Despite the advanced age of the patients, no operative mortality was sustained. The early postoperative complications were as expected with any low pelvic anastomosis and did not present problems in management. Two of the three chronic anastomotic strictures occurred in patients who had received neutron therapy and developed particularly severe irradiation injuries, suggesting that progressive irradiation-induced ischaemia contributed to their aetiology. Nevertheless, one of these patients managed successfully without a colostomy for 5 years. A similar factor was probably also responsible for the late development of a vesicovaginal fistula in one patient.

Continent has been acceptable overall. The most troublesome and distressing symptoms have been urgency and frequency of defaecation by day and night. These symptoms often occur after low anterior resection of the rectum in the early postoperative period but in most patients tend to resolve later as rectal capacity and compliance improve. This symptomatic improvement did not occur with the irradiation patients. There is evidence that rectal compliance is severely and permanently compromised in irradiation injury to the rectum. The diarrhea can be partly due to myenteric plexus injury. Minor degrees of postoperative 'cuff' sepsis may also be contributory. Internal sphincter dysfunction is also present and may be exacerbated by stretching of this muscle during the peranal anastomosis. All these factors may have contributed to the functional disturbances observed in these patients. It is conceivable that rectal function may be less compromised by leaving a shorter 'cuff' and performing a routine posterior proctotomy, especially in the presence of rectal narrowing. Furthermore, there is evidence that the reduction of the diameter of the rectum at a later time can improve its function. A 1 cm cuff of mucosa was left above the dentate line to retain anorectal discriminatory function and therefore help maintain continence. However, some patients admitted to very poor discrimination between flatus and faeces. This may be due to accompanying abnormalities of internal sphincter function and loss of rectal compliance. There is also evidence that transposition of the transverse colon to the pelvis can itself result in motility disturbances.

Figure 3 illustrates a protocol for the surgical management of the severely irradiation-injured rectum. It is important that recurrence of malignancy be excluded before a colo-anal procedure is considered. This should be done by an examination under anaesthesia pre-operatively in conjunction with the radiation oncologist and at laparotomy. A proximal loop colostomy was beneficial in the presence of stricture or fistula, it did not relieve tenesmus, discharge and haemorrhagic complications.

In contrast, delayed abnormalities appear after a latent interval of 6 months to 30 years and are due to progressive ischaemia from irradiation induced changes affecting the intestinal vasculature. Only 2–5 per cent of patients are affected but the pathological changes are severe and irreversible. Conservative treatment is of little benefit, although every effort was made in our patients to relieve symptoms by this approach. Although a proximal colostomy was beneficial in the presence of stricture or fistula, it did not relieve tenesmus, discharge and haemorrhagic complications.

Irradiation rectal injury: G. G. P. Browning et al.

Discussion

Colo-anal sleeve anastomosis has been used for a variety of rectal conditions including large rectal haemangiomata, extensive villous adenomas of the rectum, rectovaginal fistulae, low pelvic colostomies and severe irradiation injury to the rectum. Because a sleeve anastomosis avoids the hazards of deep dissection in an inflamed and fibrosed pelvis, it has been regarded as an advance in the surgical management of the radiation injured rectum. This is exemplified by the results in our patients with recurrent severe rectal haemorrhage which only ceased following operation (Table 1); in these patients the procedure was life-saving. Preservation of the anal sphincter is an added attraction and important consideration as many of the patients are elderly. It can be important in such patients to avoid a perineal wound and permanent colostomy associated with complete rectal excision. Our experience with this operation over a 6 year period with careful follow-up has permitted an accurate assessment of its immediate and long-term functional results. Previous clinical and pathological studies have distinguished two types of irradiation intestinal injury. Early symptoms occur during treatment and are due to a reversible dose injury to the intestinal mucosa. Up to 75 per cent of patients may be affected, usually by transient mild proctocolitis which subsides following cessation of radiotherapy. In contrast, delayed abnormalities appear after a latent interval of 6 months to 30 years and are due to progressive ischaemia from irradiation induced changes affecting the intestinal vasculature. Only 2–5 per cent of patients are affected but the pathological changes are severe and irreversible. Conservative treatment is of little benefit, although every effort was made in our patients to relieve symptoms by this approach. Although a proximal colostomy was beneficial in the presence of stricture or fistula, it did not relieve tenesmus, discharge and haemorrhagic complications.

Despite the advanced age of the patients, no operative mortality was sustained. The early postoperative complications were as expected with any low pelvic anastomosis and did not present problems in management. Two of the three chronic anastomotic strictures occurred in patients who had received neutron therapy and developed particularly severe irradiation injuries, suggesting that progressive irradiation-induced ischaemia contributed to their aetiology. Nevertheless, one of these patients managed successfully without a colostomy for 5 years. A similar factor was probably also responsible for the late development of a vesicovaginal fistula in one patient.

Continent has been acceptable overall. The most troublesome and distressing symptoms have been urgency and frequency of defaecation by day and night. These symptoms often occur after low anterior resection of the rectum in the early postoperative period but in most patients tend to resolve later as rectal capacity and compliance improve. This symptomatic improvement did not occur with the irradiation patients. There is evidence that rectal compliance is severely and permanently compromised in irradiation injury to the rectum. The diarrhea can be partly due to myenteric plexus injury. Minor degrees of postoperative 'cuff' sepsis may also be contributory. Internal sphincter dysfunction is also present and may be exacerbated by stretching of this muscle during the peranal anastomosis. All these factors may have contributed to the functional disturbances observed in these patients. It is conceivable that rectal function may be less compromised by leaving a shorter 'cuff' and performing a routine posterior proctotomy, especially in the presence of rectal narrowing. Furthermore, there is evidence that the reduction of the diameter of the rectum at a later time can improve its function. A 1 cm cuff of mucosa was left above the dentate line to retain anorectal discriminatory function and therefore help maintain continence. However, some patients admitted to very poor discrimination between flatus and faeces. This may be due to accompanying abnormalities of internal sphincter function and loss of rectal compliance. There is also evidence that transposition of the transverse colon to the pelvis can itself result in motility disturbances.

Figure 3 illustrates a protocol for the surgical management of the severely irradiation-injured rectum. It is important that recurrence of malignancy be excluded before a colo-anal procedure is considered. This should be done by an examination under anaesthesia pre-operatively in conjunction with the radiation oncologist and at laparotomy. A proximal loop colostomy was beneficial in the presence of stricture or fistula, it did not relieve tenesmus, discharge and haemorrhagic complications. It is, however recommended as a protecting stoma at the time of the definitive operation. Clinical and laboratory tests of anorectal function are useful before closure of the protecting stoma. Severe loss of rectal compliance and/or anal sphincter dysfunction would be contra-indications to colostomy closure. This long-term study suggests that colo-anal sleeve anastomosis is an acceptable and preferred operation for the surgical treatment of the severely irradiation-injured rectum, especially in the haemorrhagic, life-threatening situation.

Acknowledgements

J. S. V. was supported by a Wellcome Trust Research Grant No. 12196. 14 L and the British Digestive Foundation (Scottish Appeal).
Figure 3 Suggested protocol for the surgical management of chronic irradiation injury to the rectum. Life-threatening haemorrhage may necessitate primary excision and colo-rectal sleeve anastomosis. Other complications may require laparotomy and transverse colostomy.

(Abbreviations: BE, barium enema; LIF, left iliac fossa; LAP, laparotomy; TV, transverse; 2/12, 3/12 and 6/12, 2, 3 and 6 months)

References


Paper accepted 2 September 1986
Constipation in the Elderly
A Physiologic Study

J.S. VARMA, F.R.C.S.E.,* J. BRADNOCK, M.R.C.P.,† R.G. SMITH, F.R.C.P.E.,† A.N. SMITH, M.D.*

Colorectal motility was studied in 25 elderly patients with chronic constipation and compared with an asymptomatic control group (N = 11). Proctocleograms were performed to measure rectal volumes at sensation threshold and maximal tolerance, and rectal compliance. Anal and/or pudendal pressures and reflexes were measured by conventional techniques. Indices of colonic motility were also assessed. Significant impairment of rectal sensory threshold was apparent in constipation. Six patients presenting with impaction demonstrated functional megaesophagus. The remaining 19 showed a significant reduction in maximal rectal volume and rectal compliance and 14 extruded the balloon. There were no differences in sphincter length or presence of the rectosigmoidic reflex. Four patients had an absent pudendal reflex and the remainder significant prolongation. Total gastrointestinal transit times were prolonged in the constipation group, mainly distally due to rectal stasis. In two patients bisacodyl failed to elicit a sigmoid motor response. Constipation in the elderly is not merely due to delayed transit. Neuropathic deficits of sacral spinal cord function may be responsible for abnormalities in rectal motor and sensory function.

Keywords: Elderly; Anorectal function; Constipation; Colonic motility; Conus medullaris

Although constipation is a recognized problem in elderly patients,1,2 its pathophysiology is poorly understood. It is particularly distressing when associated with fecal impaction and incontinence.3-5 Some patients may respond to empiric measures such as change of diet, mobilization, and colonic stimulants.1,5,7,8 In others, however, the condition becomes intractable and difficult to treat and may be related to basic abnormalities of colorectal physiology.5,9 The aim of this study was to attempt to evaluate the various underlying physiologic abnormalities of colorectal motor function in elderly patients that may result in chronic constipation.

Materials and Methods

Ethical permission for this study was obtained from the Ethical Committee of the North Lothian District, Lothian Health Board, Scotland, in June 1983 as part of a Wellcome Trust Research project. Fifteen female and ten male elderly patients (age, 68 to 95 years; mean, 78.2 years) were studied. All had long-standing constipation (range, 8 months to 32 years; mean duration, four years). The frequency of bowel motions ranged from once every four days to once every ten days with the aid of laxatives and enemas (mean, once per week). This proved difficult to treat despite dietary and drug adjustments; eight patients were on lactulose, four on Dorbanex, three on Dulcolax and two on laxobetal; nine patients required enemas regularly. Associated anorectal incontinence was present in three male and four female patients. Occasional urinary incontinence was present in six male and five female patients.
patients; in one female patient chronic urinary retention necessitated an indwelling catheter. Six patients (four male, two female) were fecally impacted on admission. Male) with no anorectal symptoms were studied to compare data. The age range of this group was 35 to 85 years (mean, 52.4 years). Six patients in the control group were over 60 years of age. Although the patients and controls were not age-matched, this was not considered essential as it has been demonstrated that anorectal manometry is not significantly affected by age. This premise was further tested by dividing the control group into young (age range, 26 to 45 years; mean, 36 years) and old (age range, 52 to 85 years; mean, 67 years) groups to compare various parameters of anorectal manometry between them. The latency of the pudendoanal reflex and intestinal transit have also been shown to be unaffected by age.

**Manometry:** This was performed in the morning after patients had fasted. Bowel preparation was achieved by saline washouts if necessary on the day before. All except the most essential medications were withdrawn 72 hours prior to the motility investigations.

The tests were performed in the left lateral position using conventional techniques. Basal anal sphincter pressure and length and the presence of the rectosphincteric reflex (relaxation of the internal anal sphincter in response to rectal distention) were determined in 25 of the patients and all controls. Squeeze pressures were not measured as they tend to be unreliable due to poor patient cooperation. Sensory threshold of the rectum to distention was estimated by the amount of air necessary to inflate the rectal balloon for the patient to declare the first sensation of rectal distention.

**TABLE 1. Variations in Anorectal Manometry with Age in Control Subjects**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age 26-45 Years (Mean 36 ± 6.9)</th>
<th>Age 52-85 Years (Mean 67 ± 11.3)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRP (cm H2O)</td>
<td>129 ± 6.4</td>
<td>162 ± 6.8</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>HPZ (cm)</td>
<td>3.4 ± 0.18</td>
<td>3.3 ± 0.14</td>
<td>&gt; .1</td>
</tr>
<tr>
<td>STV (ml air)</td>
<td>51 ± 15</td>
<td>58 ± 11</td>
<td>&gt; .1</td>
</tr>
<tr>
<td>MTV (ml H2O)</td>
<td>519 ± 24</td>
<td>500 ± 31</td>
<td>&gt; .1</td>
</tr>
<tr>
<td>RC (ml/cm H2O)</td>
<td>8.9 ± 0.6</td>
<td>8.6 ± 0.6</td>
<td>&gt; .1</td>
</tr>
</tbody>
</table>

All measurements are mean ± SEM.

MRP: maximum sphincter resting pressure; HPZ: length of sphincteric high pressure zone; STV: rectal sensation threshold volume; MTV: rectal maximal tolerable volume; RC: rectal compliance. Rectosphincteric reflex present in all subjects.

Proctometrograms were performed by continuous fluid distention of a soft-rubber, highly compliant rectal balloon. This produced a pressure-volume graph to measure rectal compliance and the volumes and pressures at maximal distention.

Motility of the sigmoid colon was recorded as intraluminal pressure events in 15 constipated and ten control subjects. Three 2 x 1 cm water-filled, soft-rubber balloons (HSCI, Precision Drippings Ltd., Bristol, UK) were placed sigmoidoscopically at 15, 20, and 25 cm from the anal verge and connected by fine tubes to external transducers. After a 5-minute basal period, bisacodyl solution (3 ml, 2.74 mg/ml, Boehringer Ingelheim Ltd.) was instilled intraluminally through a fourth channel with its opening adjacent to the 25-cm balloon. The motility response of the sigmoid colon was then monitored over a further 15 minutes.

**Intestinal Transit:** Total gastrointestinal transit time was measured by the method of Kirwan and Smith; monitoring the progress of an isotope capsule through the colon with a scintillation counter. Fifteen constipated elderly patients and ten control subjects underwent this investigation.

**Electrophysiology:** The neurogenic integrity of the sacral spinal cord was examined by measuring the latency of the pudendoanal reflex. This was performed in 15 patients and 15 controls.

**Radiology:** All patients had a plain supine abdominal x-ray to assess the extent of fecal loading.

**Statistics:** All statistical analyses were performed by the Wilcoxon rank sum test for unpaired data.

**Results**

Table 1 examines the effect of age on anorectal manometry. Table 2 lists the manometric, electrophysiological, and transit data in the two groups.

**Effect of Age on Anorectal Manometry in the Control Group:** The difference in age between the young and old control groups was statistically significant (P < .01). However, the only parameter of anorectal manometry measured in this study that was significantly affected by age was the basal sphincter pressure (Table 1).

**Sphincter Manometry:** Basal anal sphincter pressures were significantly reduced in the constipated group. No differences were apparent in the length of the physiologic sphincter or in the demonstration of the manometric rectosphincteric reflex between the constipated and control groups.

**Rectal Sensation:** Rectal sensory threshold to distention with air was significantly increased in the constipated patients as compared with the control group. Six constipated patients but none of the controls had a sensory threshold in excess of 200 ml of air (Fig. 1).
### Table 2. Manometric, Electrophysiological, and Transit Data in Elderly Constipated Patients Compared with Controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Constipation</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRP (cm H₂O)</td>
<td>79 ± 5.6</td>
<td>115 ± 5.6</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>(n = 23)</td>
<td>(n = 17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPZ (cm)</td>
<td>3.1 ± 0.18</td>
<td>3.4 ± 0.12</td>
<td>&gt; .1</td>
</tr>
<tr>
<td>(n = 23)</td>
<td>(n = 17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STV (ml air)</td>
<td>135 ± 16</td>
<td>34 ± 7</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>(n = 25)</td>
<td>(n = 17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTV (ml H₂O)</td>
<td>358 ± 28</td>
<td>509 ± 19</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>(n = 19)</td>
<td>(n = 17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RC (ml/cm H₂O)</td>
<td>5.5 ± 0.5</td>
<td>8.7 ± 0.4</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>(n = 19)</td>
<td>(n = 17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAR latency (ms)</td>
<td>43.2 ± 3.6</td>
<td>39.4 ± 1.1</td>
<td>&lt; .02</td>
</tr>
<tr>
<td>(n = 15, absent)</td>
<td>(n = 16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total transit time (days)</td>
<td>4.3 ± 0.7</td>
<td>1.7 ± 0.5</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>(n = 15)</td>
<td>(n = 10)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All measurements are mean ± SEM.

MR = megarectum; MRP = maximum sphincter resting pressure; HPZ = length of sphincteric high pressure zone; STV = rectal sensation threshold volume; MTV = rectal maximal tolerable volume; RC = rectal compliance; PAR = pudendoanal reflex.

Rectosphincteric reflex present in all patients and controls.

**FIG. 1. Rectal sensory deficit in constipation. Six patients had a severely impaired threshold in excess of 200 ml air. Bars represent mean ± SEM values.**

**Discussion**

Exton-Smith emphasized the prevalence of constipation and difficulties in management of it in the elderly. Geboes and Bossaert recorded constipation as a common condition in elderly patients admitted to the hospital. Forty-nine percent of their patients were taking laxatives before hospitalization. Brocklehurst and Khan and Gurll and Steer have emphasized the need for prevention of colonic stasis, impaction, and incontinence in the elderly. Others have stressed the possible serious complications of fecal impaction. Read et al. were able to describe some of the abnormalities of anorectal physiology in elderly patients that may be responsible for fecal impaction and leakage. Newman and Freeman reported a progressive rise with age in defecatory sensation, especially in those patients who were constipated. The functional abnormalities leading to constipation in the elderly, however, have remained poorly understood. The
Fig. 2. Electrophysiologic latency of the pudendoanal reflex in the two groups. Note the “absent” responses (latency > 100 ms). Bars represent mean ± SEM values.

The diminution in basal anal sphincter pressures in constipation is probably a manifestation of both internal and external anal sphincter weakness that is recognized in this age group\(^\text{20}\) and is present in both elderly patients and controls (Tables 1 and 2). It is likely to be a reflection of multiparity but is exacerbated by chronic straining at stool.\(^\text{21}\) However, it is significant that functional sphincter length is unaffected and the rectosphincteric reflex was demonstrable in all the constipated patients. Weakness of the anal sphincters, although present, is therefore unlikely to result in the constipation observed in these patients.

Both groups of patients appear to suffer from defects of rectal proprioception (Fig. 1), which is probably mediated by receptors in the striated pelvic floor muscles or pararectal tissues.\(^\text{22}\) This sensory deficit is more severe in megarectum\(^\text{23-25}\) and probably contributes to the rectal dyschezia and impaction observed in such patients as suggested by Read et al.,\(^\text{3,4}\) with resultant leakage of mucus and feces. Rectal proprioception is important in initiating the complex cycle of events that result in defecation, involving interaction of rectum and anal sphincters.\(^\text{26,27}\) Many of these patients also have anal and perianal sensory deficits\(^\text{3,4}\) further compromising the “sampling” reflex involved in defecation.\(^\text{28}\) This sensory deficit may be partly reflected in the electrophysiologic abnormalities of the pudendoanal reflex (Fig. 2).

This study defines two main groups of elderly patients with chronic constipation—those with a functional megarectum (and possibly megacolon) and those with a hypertonic or “irritable” type of distal bowel. The abnormalities of rectal distensibility in the group with reduced rectal compliance are similar to those observed in the irritable bowel syndrome in younger patients.\(^\text{29}\) The inadvertent expulsion of the proctometrogram balloon by many of these patients is probably a consequence of bowel hypertonicity, with the rectal sensory deficit and anal sphincter weakness also being factors. Their constipation takes the form of difficult passage of hard, pellety feces. The precise cause of this hypertonicity remains unknown, but there are apparent implications in the treatment of these patients as opposed to those with the megarectum syndrome. When treating those patients identified by the proctometrogram to have a megarectum, it is important to prevent fecal impaction and incontinence by regular emptying of the rectum, e.g., by means of suppositories or enemas. It is noteworthy that a somewhat similar grouping has been observed in younger patients with chronic idiopathic constipation.\(^\text{30,31}\) The isotope transit studies performed suggest that in many patients the delay in colonic transit follows from stasis in the rectum. In a few patients, however, abnormalities of colonic motility may also contribute, as is suggested by the absence of stimulation with intraluminal bisacodyl, a surface-acting colonic stimulant.\(^\text{16}\) This abnormality may reflect either a primary disorder of the myenteric plexus or a secondary, possibly laxative-induced abnormality.\(^\text{32,33}\) The same abnormality may be responsible for the colonic hypertonicity observed in these patients.\(^\text{34}\) Abnormalities of colonic motility may also exist in megacolon.\(^\text{35}\) The transit differences are not simply due to the aging process as other studies have demonstrated no difference in transit in the elderly.\(^\text{11,36}\) The abnormalities of the pudendoanal reflex demonstrated in this study reflect a neurologic
deficit in these patients. This deficit presumably com-
prises a combination of sensory, central, and motor
abnormalities of the pathways involved in defecation and
continence. They may be related to the observed
anatomic abnormalities. There is some evidence for a
central or peripheral neurogenic etiology in megarectum
and fecal impaction and for colonic hypertonic-
centra l or peripheral neurogenic etiology in megarectum
problems in many of these patients are in keeping with a
generalized or central neurogenic disorder as the common
cause. In this age group, concomitant diseases such
as diabetes mellitus may further impair bowel function
by secondary neurogenic effects.

Acknowledgments

The authors thank Professor J. Williamson, University Department
of Geriatric Medicine, Edinburgh, for permission to study patients
under his care. JSV was supported by a Wellcome Trust Research
Grant (No. 12916 H L) and the British Digestive Foundation (Scottish
Appel). The University Department of Geriatric Medicine contrib-
uted generously to ward the electrophysiologic apparatus.

References

1. Exton-Smith AN. Constipation in geriatrics. In: Avery Jones F,
Golding E W . eds. Management of constipation. Oxford:
2. Geboes K, Bossaert H. Gastrointestinal disorders in old age. Age
3. Read NW, Abouzekri L, Read MG, et al. Anorectal function in
elderly patients with fecal impaction. Gastroenterology 1985;
90:59-56.
4. Read NW, Abouzekri L. Why do patients with fecal impaction
5. Tobin GW, Brocklehurst JC. Fecal incontinence in residential
homes for the elderly: prevalence, aetiology and management.
6. Young RW. The problem of fecal impaction in the aged. J Am
7. Brocklehurst JC, Khan Y. A study of fecal stasis in old age and use
8. Irvine RE. Fecal incontinence is not inevitable. Br Med J 1986;292:
181-8.
10. Loevening-Bauche V, Amuras S. Effect of age and sex on ano-
11. Varma JS, Smith AN, McInnes A. Electrophysiological observa-
tions on the human pudendo-anal reflex. J Neurosurg Psychiatry
12. Eastwood H D. Bowel transit studies in the elderly: radiopaque
markers in the investigation of constipation. Gerontol Clin
13. Varma JS, Smith AN. Anorectal profilemetry with the microtrans-
effects of rectal anterior root stimulation on anal sphincter
and colorectal motility in spinally injured man. Br J Surg
intraluminal bisacodyl in slow-transit constipation. Dig Dis Sci
17. Kirkman WD, Smith AN. Gastrointestinal transit time measured by
18. Gurli N, Steer M. Diagnostic and therapeutic considerations for
19. Sutton R, Blake JR. Massive rectal bleeding following fecal
20. Percy JP, Neil ME, Kardelik TF, Swash M. A neurogenic factor in
21. Henry MM, Swash M. Fecal incontinence—pathogenesis and
features. In: Coloproctology and the pelvic floor. London: But-
terworths, 1985:222-7.
22. Lane RH, Parks AG. Function of the anal sphincters following
1974;67:467-77.
24. Callaghan RH, Nixon HH. Megarectum: physiological observa-
25. Meunier P, Mollard P, Marechal JM. Physiology of megarectum:
the association of megarectum with encopresis. Gut 1976:17:
224-7.
26. Parks AG, Porter NH, Melza J. Experimental studies of the reflex
mechanism controlling the muscles of the pelvic floor. Dis
27. Denny-Brown D, Robertson EG. An investigation of the nervous
1975;4:467-77.
29. Varma JS, Smith AN. Abnormalities of rectal distensibility in the
Different patterns of intestinal transit time and ano-rectal
motility in painful and painless chronic constipation. Gut 1981;
31. Meunier P. Physiologic study of the terminal digestive tract in
32. Smith B. The myenteric plexus in drug-induced neuropathy. J
33. Smith B. Effect of irritant purgatives on the myenteric plexus in
34. Alvarez WC. A simple explanation of cardiopasm in Hirsch-
Variation of bowel habit in two population samples. Br Med J
37. Adamson WA, Aird L. Megacolon: evidence in favour of a neuro-
38. White JC, Verlot MG, Ehrenheil O. Neurogenic disturbances of
the colon and their investigation by the colonometrogram. Am
39. Scott WH, Cantrell JR. Colonometrical studies of the effects of
section of the parasym pathetic nerves of the colon. Bull Johns
40. Abdel-Rahman M, Topper C, Duguy C, et al. Ureterodynamics
colonic inertia: A manifestation of systemic disease? Dig Dis Sci
42. Lawrence WT, Bannister JJ. Urodynamic assessment of young
women with chronic constipation. Proc 15th Ann Meet Int Cont
43. Schiller LR, Santa Ana CA, Schmelen AC, Hendler RS, Hartford
LV, Fordtran JS. Pathogenesis of fecal incontinence in diabetes
44. Wald A, Tununguntaka AN. Anorectal sensation dysfunction in
The Action of Cisapride on the Chronic Constipation of Paraplegia

N. R. Binnie, FRCSE, G. H. Creasey, FRCSE, P. Edmond, CBE, TD, FRSE, A. N. Smith, MD, FRCSE, FRSE

1Spinal Injuries Unit, Edenhall Hospital, Musselburgh, UK. 2Department of Surgery/Urology, Western General Hospital, Edinburgh, UK.

Summary

Paraplegic patients have intractable constipation associated with prolonged colonic transit time. The agent Cisapride significantly reduced the colonic transit time from 7.7 days to 5.1 days. It also improved the intraluminal tone in the rectum, resulting in a significant reduction in maximal rectal capacity from 305.8 ml to 224.3 ml. There was a reduction in residual urine volume from 51.5 ml to 27.7 ml. The increased number of stools containing transit markers showed that intraluminal mixing was increased by cisapride. Faecal water remained unchanged. A side effect was retention of urine in one subject after sudden withdrawal of the drug but this was avoided by its gradual reduction over 2 days.

Key words: Paraplegia; Constipation; Colonic transit time; Cisapride.

Severe Spinal cord injury results in motor paralysis which is later complicated by bladder and bowel problems (Denny-Brown 1935; Connell 1963). The commonest bowel problem in the later phase is intractable constipation (Glick 1984). The release of acetylcholine (ACh) at the myenteric plexus by pharmacological means could be expected to stimulate colonic activity. The agent cisapride (Janssen Pharmaceutical Ltd) acts to stimulate gastrointestinal activity by releasing ACh at the myenteric plexus (Smout 1985). The present study investigates the effect of cisapride on colonic transit time and on rectal capacity in spinal injured subjects. The study was part of a wider project for which ethical permission was granted by the Lothian Health Board, Scotland in July 1985.

Patients

Ten patients with complete, traumatic spinal cord injury were studied. There were 9 males and 1 female with a mean age of 34.1 years (range 20–45 years). The level of cord injury varied from C4 to T10. The mean time since injury was 8.1 years (range 1–20 years). All subjects gave informed consent and were investigated while in the spinal injuries unit. During the study each patient acted as his/her own control.
Methods

When patients entered the trial, the extent of their constipation was determined by first establishing their intestinal transit times. The 10 subjects were fasted for a control period of at least 8 hours before being given an intravenous injection of 10 mg cisapride. Rectal capacity and pressure studies done in the control period were now repeated. After an interval of at least 48 hours the subject was commenced on oral cisapride 10 mg 8 hourly. This was taken for 48 hours before the transit times were repeated. The cisapride was continued until each transit time estimation was complete. At this time blood tests and residual urine volumes were repeated.

Gastrointestinal transit time

The Oro-Caecal Transit Time (OCT) was estimated using the oral lactulose and expired breath hydrogen method (Bond 1975). A sample of end expiratory breath is taken as a baseline level of breath hydrogen. The subject swallows 10g of lactulose with a standard breakfast of 500 cal, having fasted for 8 hours. Thereafter the breath is sampled every 15 minutes until the rise in hydrogen due to the lactulose reaching the caecum is observed. The Oro-Anal Transit Time (OAT) is estimated using radio-opaque polythene markers and X-raying of the stools (Hinton 1969). This allows a reasonable measure of transit time and avoids unnecessary exposure of the subject to X-rays. The Colonic-Transit Time (CTT) was calculated by subtracting the OCT from the OAT.

The method of stool collection was by manual rectal evacuation with the occasional spontaneous evacuation. A digital rectal examination was performed each morning after breakfast and any rectal contents were evacuated into the collection bag. The patients were divided into two groups of five subjects. The group with spinal lesions C4 to C7 had the rectal examination and evacuation performed by an attendant while the second group with lesions T3 to T10 were able to perform the examinations and evacuations themselves.

Anal sphincter studies

The functional Sphincter Length (SL) of the combined internal and external anal sphincter was recorded in increments of 1 cm together with the maximum resting pressure (MRP) (Varma 1984). The Recto-Anal Sphincteric Inhibitory Reflex (RSR) (Gowers 1877, Henry 1985) records the reflex induced fall in pressure due to the internal anal sphincter relaxing on rapid distention of the rectum with 50 ml of air.

Electrophysiological studies

The integrity and latency of the Pudendo-Anal Reflex (PAR) (Smith 1984) involves a minor electrical stimulus over the dorsal genital nerve while recording from an anal plug electrode. Using this same anal plug electrode as a stimulating electrode, the integrity and latency of conduction in the spinal cord can be determined...
assessed by recording Somatosensory Cerebral Evoked Potentials (SSEP) with scalp electrodes (Lehmkull 1986).

**Proctometrogram**

The rectal capacity (MAXV) and rise in intraluminal pressure (MAXP) as changes in rectal volume are achieved is derived by this technique (Varma 1986). A large compliant rectal balloon is distended at a rate of 67 ml/min while the pressure in the balloon is recorded by a second device. The point of spontaneous expulsion of the rectal balloon or the detection of autonomic dysreflexia is taken as being at maximal rectal capacity. The ratio of MAXV to MAXP (RATIO V/P) gives an indication of the distensibility of the rectum.

**Pulse rate and blood pressure**

These were recorded when intravenous cisapride was given and continued every 5 minutes for up to 30 minutes afterwards. The recordings were taken from the tracheal pulse just proximal to the antecubital fossa with a Dynamap automatic pneumatic cuff recording device.

**Blood count, urea electrolytes and liver function**

These tests were carried out in the hospital laboratories in the normal way.

**Residual urine volume**

This was carried out in the subjects who did not have an indwelling catheter, both before and during administration of oral cisapride (RUV).

**Fecal water content**

The percentage water content (% H₂O) of the faeces was derived by weighing the samples before and after a freeze drying technique (Eastwood 1984).

**Transit marker dispersion**

The number of separate stools containing transit marker pellets (STM) was recorded for each subject, giving an indication of intraluminal mixing.

**Statistical analysis**

Statistical significance was determined by a t test after logarithmic conversion of the data.

**Results**

The results are given in the Table. Figures 1, 2 and 3 show the results for colonic transit time, maximum rectal volume and the ratio of rectal volume to
Table  Results of investigations. Those measured before cisapride was taken orally are in the column termed ‘Control’ while those recorded with the effect of cisapride are in the column headed ‘Cisapride’

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Cisapride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transit times</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCT</td>
<td>3.4 ± 1.4 hr</td>
<td>2.6 ± 0.58 hr</td>
</tr>
<tr>
<td>OAT</td>
<td>187.3 ± 87.6 hr</td>
<td>125.0 ± 77.0 hr</td>
</tr>
<tr>
<td>CTT</td>
<td>185.0 ± 86.3 hr</td>
<td>123.0 ± 77.0 hr</td>
</tr>
<tr>
<td>Pressure and volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SL</td>
<td>3 cm</td>
<td>3 cm</td>
</tr>
<tr>
<td>MRP</td>
<td>116 ± 33. cmH2O</td>
<td>125 ± 28.8 cmH2O</td>
</tr>
<tr>
<td>RSR</td>
<td>65 ± 19.5 cmH2O</td>
<td>72.5 ± 25.1 cmH2O</td>
</tr>
<tr>
<td>MAXV</td>
<td>305.8 ± 93.6 ml</td>
<td>224.3 ± 55.4 ml</td>
</tr>
<tr>
<td>MAXP</td>
<td>72.5 ± 18.8 cmH2O</td>
<td>76 ± 21.2 cmH2O</td>
</tr>
<tr>
<td>Ratio V/P</td>
<td>4.3 ± 1.4</td>
<td>3.1 ± 1.1</td>
</tr>
<tr>
<td>RUUV</td>
<td>51.5 ± 16.7 ml</td>
<td>27.7 ± 8.4 ml</td>
</tr>
<tr>
<td>Electrophysiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAR</td>
<td>37.1 ± 4.6 ms</td>
<td>Absent</td>
</tr>
<tr>
<td>SSEP</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Faecees</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2O</td>
<td>63.8 ± 4.8</td>
<td>64.3 ± 63</td>
</tr>
<tr>
<td>STM</td>
<td>1.9 ± 0.6</td>
<td>3.1 ± 1.6</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYST</td>
<td>112.5 ± 15.7 mmHg</td>
<td>112 ± 12.2 mmHg</td>
</tr>
<tr>
<td>DYST</td>
<td>64.5 ± 19 mmHg</td>
<td>59 ± 16.4 mmHg</td>
</tr>
<tr>
<td>HR</td>
<td>77.2 ± 9.7/min</td>
<td>76.3 ± 10.1/min</td>
</tr>
</tbody>
</table>


rectal pressure. All three achieved statistical significance with \( p < 0.001 \), \( p < 0.005 \) and \( p < 0.005 \) respectively. The colonic transit time was reduced from 185 hours to 123 hours, the maximum rectal volume was reduced from 305 ml to 224 ml and the ratio of maximum rectal volume to maximum rectal pressure was reduced from 4.3 to 3.1. The faecal water remained unchanged. Stool mixing of markers was increased from 1.9 to 3.1 stools.

**Discussion**

The colon has an intrinsic myenteric nerve plexus which has a degree of spontaneous activity and causes autonomous colonic muscle activity (Christensen 1981). This myenteric plexus can also be stimulated by the extrinsic nerve supply of the colon (Bayliss 1900; Wood 1981). The constipation in spinal injury subjects may be due to interruption, at the spinal level, of the extrinsic nerve supply to the distal colon. The extrinsic parasympathetic nerve supply to
The distal colon emerges from the central nervous system with the anterior sacral roots S 2, 3 and 4. Direct electrical stimulation of these sacral nerve roots has been shown to affect the pelvic colon and ano-rectal function (Varma and Binnie et al., 1986). As neuroprosthetic stimulation to increase the activity of the colon is not yet as appropriate as its use for bladder stimulation, a suitable pharmacological preparation capable of stimulating intestinal motility would have more immediate application. The agent cisapride is a synthetic substituted benzimidazoles which has been shown to have a potent stimulation effect on isolated rabbit colonic smooth muscle, probably through a muscarinic receptor (Snape et al., 1985). There is a similar effect on guinea pig ileum. Using binding studies for dopamine receptors on rat striatum and when tested against apomorphine...
induced vomiting in dogs, there was no anti-dopaminergic properties (Van-Nueten 1985). The effect on motor activity may be mediated in part by blocking type 2 serotonin receptors (Moriarty 1985) and the possible release of other gastrointestinal hormones (Koop 1986). The action of this agent has been studied in humans, on oesophageal motility (Wienbeck 1984; Corazziari 1985; Smout 1985). These authors have shown that this agent reduces gastro-oesophageal reflux by increasing the pressure in the region of the gastro-oesophageal junction. In gastric motility (Jian 1985; Thomforde 1985; Edwards 1987) cisapride stimulates gastric emptying. As a consequence of jejunal activity (Stacher 1986) and stimulation of colonic motility (Miller-Lissner 1985; Lee 1984; Lederer 1985) it is said to reduce transit time.

The present study shows that in spinal injured subjects cisapride significantly reduces both colonic transit time and the maximum rectal capacity. The intraluminal mixing of contents is increased, as detected by the increased dispersion of markers in stool collections. The faecal water content is little changed. The internal anal sphincter reflex relaxation caused by rectal distention is not inhibited by cisapride. There appeared to be no adverse effects on heart rate or blood pressure although there was a slight reduction in diastolic pressure. No side effects on parameters of full blood count, urea, electrolytes and liver function tests were noted. In the first patient, who normally emptied his bladder by suprapubic tapping, the unwanted side effect of acute retention of urine was noted on the morning after abrupt cessation of oral cisapride. This resolved after 1 day of intermittent catheterisation. In subsequent subjects the cisapride was tailed off at 10 mg twice and 10 mg once per day for 1 day each before stopping the drug completely. A reduction in residual volume while taking cisapride was noted in 7 of the remaining subjects but a more formal study would be required to determine the significance, if any, of this finding.

Regarding the long-term effects of cisapride, there are to date several subjects, including 2 from this study, who have taken the drug for periods in excess of 1
year. The beneficial effects on colonic function are maintained and will be formally reported at a later date. We have not detected any deleterious long term effects of oral cisapride 10 mg thrice daily on modalities of blood pressure or heart rate, full blood count, urea, electrolytes and liver function tests. We did however record 1 case of retention of urine after abrupt cessation of the drug and we have subsequently recorded increased frequency of micturition in 3 subjects with incomplete spinal lesions being treated with cisapride for colonic transit problems. This increased frequency was troublesome in 1 female subject and was corrected by reducing the dosage of cisapride to 10 mg twice per day.

Acknowledgements

Mr N. R. Binnie was supported by the Scottish Hospital Endowment Research Trust, Grant number 720 and an attachment to the Wolfson G.I. Research Laboratories, Western General Hospital, Edinburgh, EH4 2XU.

References


CONNELL AM, FRANKEL HL, GUTTMANN L 1963 The motility of the pelvic colon following complete lesions of the spinal cord. Paraplegia 1:93-115.


LIPPELL LD, DIMITRIJEVIC MR, ZIDAR J 1986 Lumbar spinal evoked potentials (SEP) and cortical somatosensory evoked potentials (SEP) in patients with a cauda equina lesion. Paraplegia 24:46.

MILLER-LISSNER SA 1985 Cisapride in chronic constipation and laxative abuse. Gastroenterology 98:1510.


Neurophysiological abnormalities in genuine female stress urinary incontinence

J.S. VARMA, A. FIDAS, A. McINNES, A. N. SMITH, G. D. CHISHOLM

Summary. Perineal sensory and motor function was investigated in 28 women with genuine stress incontinence of urine and compared with a matched control group. Electrosensitivity of the dorsal nerve of the clitoris and of the urethral mucosa was significantly diminished in these patients (eight measurements ‘insensitive’). Three different reflex latency measurements (dorsal nerve to external anal sphincter, dorsal nerve to urethral sphincter, urethral mucosa to external anal sphincter) were prolonged in incontinence (14 absent reflexes). Mean motor unit potential duration of the external anal sphincter was also prolonged, reflecting an early neuropathy. Anorectal manometry detected significantly weaker squeeze pressures in stress incontinence although other variables were unaffected.

Stress incontinence of urine in women is a relatively common and distressing condition. As there are often no overt neurological signs, the condition had for long been attributed to ‘pelvic floor weakness’, its precise aetiology remaining poorly defined. There is now some evidence for an abnormality of motor innervation of the urethral sphincter musculature in this disorder (Snooks et al. 1985), similar to that seen in neurogenic faecal incontinence (Henry & Swash 1985). It is conceivable that sensory abnormalities of the perineum also exist and exacerbate the urodynamic and clinical disturbances in stress urinary incontinence. These various factors may influence the results of conservative or surgical treatment of this condition. The aim of this study was to further investigate perineal sensory and motor abnormalities in such patients using new electrophysiological techniques (Abrams et al. 1986).

Patients and methods

Permission for this study was obtained from the ethics committee, North Lothian District, Edinburgh on 16 June 1983, as part of a larger pelvic floor physiology project. Twenty-eight women with urodynamically proven genuine stress incontinence of urine were entered into the study. Their age range was 24–63 years (mean 41 years). Duration of symptoms ranged from 6 weeks to 23 months. Twenty-four were parous and four were nulliparous. Four dated their incontinence to a simple abdominal hysterectomy, a total of seven patients having had this operation. Three patients had previously had an anterior colporrhaphy. For purposes of comparison, 28 patients matched approximately for age and parity (age range 18–75 years, mean 44 years) with no urological symptoms were also studied. They were patients who were being
investigated for minor colorectal and urological conditions such as polyps, bleeding, etc., and had given informed consent for this study. None of these control patients had previous pelvic floor surgery and they did not undergo urodynamic investigations. It was difficult to obtain informed consent from large numbers of continent and control subjects because of the 'invasive' nature of this study which included urethral catheterization, perineal electrical stimulation and the insertion of needle electrodes in the external anal sphincter. For the same reasons and due to occasional technical faults, we were not able to perform all the measurements on every subject, necessitating variation in sample sizes. However, it was ensured that the data remained comparable in terms of age and parity matching.

Urodynamics

All 28 symptomatic patients had undergone clinical examination and conventional video-cystometry to ascertain the diagnosis of genuine stress urinary incontinence (Bates et al. 1976; Godec et al. 1980).

Anorectal manometry

This was performed in 11 patients using a conventional microballoon technique (Varma & Smith 1984a) to determine basal and (sustained) squeeze anal sphincter pressures, the functional sphincter length and the presence and amplitude of therectosphincteric reflex. The rectal sensory threshold to distension was also measured (ml air) by slow inflation of the rectal balloon. It was defined as the amount of air necessary for the patient to perceive the first sensation ofrectal distension and used as a measure of pelvic floor 'propriocceptive' function.

Electrophysiology

The sixth report of the International Continence Society has standardized the terminology of procedures related to neurophysiological investigation of the lower urinary tract (Abrams et al. 1986). The procedures used in this study are described below.

Reflex responses

The electrophysiological latency of the reflex contraction of the external anal and urethral sphincters in response to stimulation of the dor- nal nerve of the clitoris was determined by a digitally averaging method. The dorsal nerve was stimulated by a felt surface electrode and the reflex responses recorded by surface ring electrodes, those within the urethra being mounted on a urinary catheter. This urethral electrode was also used as a stimulating electrode to record the urethra to anal sphincter reflex latency. The details of the methodology are as described by Smith & Varma (1984), Galloway et al. (1984), Fidas et al. (1985), and Varma et al. (1986). The dorsal nerve to anal sphincter reflex latency was measured (sweep 100 ms) in all the patients and controls. The dorsal nerve to urethral sphincter latency was measured (sweep 100 ms) in 15 patients and 19 controls. The urethral mucosa to anal sphincter latency was measured (sweep 200 ms) in 15 patients and 16 controls.

Electrosensitivity

Electrosensitivity of the dorsal nerve and the urethral mucosa was determined by use of the same stimulating electrodes as used for the reflex responses. The principle is based on the method described by Kieswetter (1977) and Powell & Feneley (1980). Sensory threshold was recorded in milliamperes (maximum 70 mA) and was defined as the first sensation of 'tapping' (threshold) perceived by the patient on increasing the stimulating current via the constant-current generator (DISA, Copenhagen). The dorsal nerve electrosensitivity was measured in 15 patients and 22 controls. The electrosensitivity of the urethral mucosa was determined in 16 patients and 17 control subjects.

Mean motor unit potential duration

Mean motor unit potential duration of the external anal sphincter was measured by the technique described by Varma et al. (1986) being a modification of the method described by Bartolo et al. (1983). A total of 20 motor units (10 from each side of the sphincter) were studied using a concentric needle electrode, and their mean calculated. This was used as an index of neuropathy of the external anal sphincter (Buchtel & Pinelli 1953). This investigation was per-
formed in 13 patients and 15 controls. The technique was used instead of the more sensitive single fibre electromyography because of our better acquaintance with it.

Statistics

Comparisons between control and incontinent were made by Wilcoxon’s test for unpaired data.

Results

Table 1 summarizes the electrophysiological and manometric data in patients with stress incontinence and enables comparison with control patients.

Reflex response latencies

Reproducible results were obtained for all latency measurements. The three reflex response latencies were increased compared with the control group. Many of the reflexes from incontinent patients were noted to be of low amplitude (Varma et al. 1986). In addition, a total of 14 reflexes out of 58 were ‘absent’.

Table 1. Electrophysiological and manometric data in stress urinary incontinence compared with controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stress incontinence</th>
<th>Control</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>DN-EAS latency (ms)</td>
<td>49.6 (29-70)</td>
<td>39 (27.5-49)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(3 absent, ( n = 28 ))</td>
<td>(( n = 28 ))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DN-US latency (ms)</td>
<td>60 (42-67)</td>
<td>40.5 (30-50)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(4 absent, ( n = 15 ))</td>
<td>(( n = 19 ))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UM-EAS latency (ms)</td>
<td>83 (65-120)</td>
<td>69.6 (54.5-80.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(7 absent, ( n = 15 ))</td>
<td>(( n = 16 ))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DN electrostimuity (mA)</td>
<td>8.8 (6-14)</td>
<td>6.1 (4.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(2 insensitive, ( n = 15 ))</td>
<td>(( n = 22 ))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UM electrostimuity (mA)</td>
<td>13.8 (9-30)</td>
<td>8.3 (6-12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(6 insensitive, ( n = 15 ))</td>
<td>(( n = 18 ))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EAS MUPD (ms)</td>
<td>11.3 (8.9-15.5)</td>
<td>8.7 (6-11.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(( n = 13 ))</td>
<td>(( n = 15 ))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPZ (cm)</td>
<td>3.4 (3-4)</td>
<td>3.3 (3-4)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>MRP (cm H(_2)O)</td>
<td>93 (55-140)</td>
<td>108 (80-140)</td>
<td>&gt;0.01</td>
</tr>
<tr>
<td>SP (cm H(_2)O)</td>
<td>46 (20-140)</td>
<td>75 (30-180)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>STV (ml air)</td>
<td>44 (15-140)</td>
<td>52 (30-100)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Amplitude RSR (ml H(_2)O)</td>
<td>48 (20-90)</td>
<td>42 (20-60)</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

All measurements show mean and range.

DN, Dorsal nerve; UM, urethral mucosa; EAS, external anal sphincter; MUPD, mean motor unit potential duration; HPZ, functional anal sphincter length; MRP, maximum basal anal sphincter pressure; SP, squeeze anal sphincter pressure; STV, rectal sensory threshold volume; RSR, rectosphincteric reflex.

Dorsal nerve and urethral mucosal electrosensitivity

Reproducible measurements were confirmed at both sites. Dorsal nerve and urethral mucosal electrosensitivity was diminished in incontinent patients (Table 1). Nine out of 31 women investigated had thresholds in excess of the maximum obtainable output (>70 mA). They were described as 'insensitive'.

External anal sphincter motor unit potential duration (MUPD)

Patients with stress urinary incontinence (\( n = 13 \)) had prolonged MUPD of the external anal sphincter compared to control patients (\( n = 15 \); Table 1). This difference was significant (\( P < 0.01 \)).

Anorectal manometry

The only significant difference that could be detected between control and stress incontinent patients by conventional anorectal manometry was a reduction in voluntary sphincter contraction pressures in the latter (Table 1).
Discussion

Genuine stress incontinence of urine is defined as the involuntary loss of urine when intra-abdominal pressure exceeds maximum urethral pressure due to an elevation of intra-abdominal pressure and in the absence of detrusor contraction (Bates et al. 1976). Urethral continence at rest is dependent primarily on the bladder neck and intramural striated sphincter (external sphincter) composed of slow twitch muscle fibres which exhibit 'tonic' activity at rest (Gosling et al. 1981). These are supplied directly by the pelvic nerves from the sacral segments S2–S4 (Gil Vernet 1968). The periurethral striated muscle sphincter functions reflexly to augment urethral closure during 'stress' events which elevate intra-abdominal pressure such as coughing, laughing, straining, etc. This muscle receives its motor innervation from the perineal branch of the pudendal nerve (Gosling et al. 1981; Gosling 1985). The reflex activation of the peri-urethral musculature is mediated via excitation of its innervating α-motoneurones in the conus medullaris (S2–S4) by sensory afferents in the bladder, urethra and pelvic floor. The sensory innervation of the urethral mucosa derives predominantly from the perineal branch of the pudendal nerve (Warwick & Williams 1980). A direct branch from the motor roots of S3 and S4 reaching the pelvic floor via its visceral surface also carries sensory fibres from the posterior urethra and anal canal (Lawson 1974). The inferior rectal nerve, a direct branch of the pudendal nerve, supplies the external anal sphincter, the lining of the lower part of the anal canal and skin around the anus (Warwick & Williams 1980). Anatomical or functional deficits in the sensory, central or motor pathways of reflexes involving the urethral sphincter may, therefore, compromise urinary continence. ‘Idiopathic’ faecal incontinence is now recognized to be of neurogenic origin secondary to traumatic or chronic stretch injury to the innervation of the puborectalis and/or the external anal sphincter muscles. With the sophistication of electrophysiological techniques there has been accumulating evidence in favour of similar damage to the motor innervation of the striated urethral and peri-urethral muscles in stress urinary incontinence (Godec et al. 1980; Snooks et al. 1985). It is, however, conceivable that the dysfunction in such patients is further compounded by sensory deficits of the perineum.

Indeed, such an abnormality has been demonstrated in some patients with idiopathic faecal incontinence (Roe et al. 1986). Isolated electromyographic abnormalities of the external anal and urethral sphincters and of their motor innervation have been previously described in urinary incontinence (Fowler et al. 1984; Anderson 1984; Snooks et al. 1985). This comprehensive study has examined the perineum by a combination of electrophysiological methods to evaluate sensory impairment at two sites and reflex sphincter contraction by three different methods at both the anal and urethral sphincters. This was supplemented by direct needle EMG of the external anal sphincter and by manometric data. Reflex sphincter function is considered functionally more informative than the isolated electrophysiological abnormalities demonstrated by other methods because it mimics the ‘physiological’ stress response. The methods of measuring reflex response latencies used test the integrity of the entire reflex pathway and therefore have obvious advantages over other methods that measure motor latencies only or the integrity of the sphincters by needle electromyography. These other methods when used in conjunction with ‘cumulative’ reflex latency measurements are of value in the differential analysis of neurogenic incontinence. The additional investigation of electrosensitivity helps to examine further the nature and extent of neurological deficit. It is not possible from these results alone to incriminate ‘central’ neurogenic defects in Onuf’s nucleus (Onuf 1901) for at least some of these abnormalities. Other studies, however, suggest that this may sometimes be the case in functional bowel and bladder disturbances (Galloway & Tainsh 1985; Vereecken et al. 1982; Varma & Smith 1984b; Kondo et al. 1986). A manometric abnormality of the external anal sphincter was demonstrable in stress urinary incontinence, although these patients had no ano-rectal symptoms. This is not surprising because of the larger muscle bulk of the anal sphincter, its differential innervation, and the supplementation to the maintenance of faecal continence by the substantial puborectalis muscle with its different innervation directly from the pelvic nerves (Percy et al. 1981). Other studies have not found a reduction in anal sphincter pressures, although they certainly exist in double incontinence (Henry & Swan 1985). These differences may simply represent the degree of neuropathy in the patient group.
studied. Pelvic floor ' proprioceptive ' function as determined by rectal sensory threshold appears also to be unaltered in stress incontinence. The possible adverse effects of hysterectomy on vesico-urethral dysfunction (Farghaly et al. 1986; Hanley 1969) may have been responsible for precipitating stress urinary incontinence in at least four patients.

This study establishes a neurogenic basis for stress urinary female incontinence. The electrophysiological methods described and their results should be of value in the management of such patients. For example, our early experience with supervised pelvic floor physiotherapy for such patients. For example, our early experience with supervised pelvic floor physiotherapy for stress incontinence suggests that those patients with severe neurological deficit do not respond to this treatment.

Acknowledgments

J.S.V. was supported by a Wellcome Trust Research Grant (No. 12196 14L) and the British Digestive Foundation (Scottish Appeal). We are indebted to the surgeons in the Joint Incontinence Clinic for enabling us to study patients under their care.

This paper was read in part at the 65th Meeting of the Surgical Research Society, U.K., at the University of Surrey on 9 January 1987.

References


Powell, P. H. & Feneley, R. C. L. (1980) The role of...


Received 5 May 1987
Accepted 21 November 1987
Neurophysiological dysfunction in young women with intractable constipation

J S VARMA AND A N SMITH

From the University Department of Surgery/Urology and Wolfson Gastrointestinal Laboratories, Western General Hospital, Edinburgh

SUMMARY Fifteen women with intractable chronic idiopathic constipation dating from adolescence were investigated by anorectal manometry, neurophysiological evaluation of the conus medullaris and external anal sphincter. Comparison was made with 25 asymptomatic female control subjects. Urological disturbances were common amongst the constipated, in five of whom incidental lumbosacral spinal dysraphism was found. No differences in sphincter pressures or the recto-sphincteric reflex were demonstrable between the two groups. Rectal defecatory sensation was blunted and the compliance was increased in the constipated group. The latency of the pudendo-anal reflex was significantly prolonged in idiopathic constipation, two women having an absent reflex (>100 ms). Mean motor unit potential duration of the external anal sphincter was not significantly prolonged in the eight constipated women tested. A central neurogenic deficit is postulated in some women with this disorder.

Methods

PATIENTS

Formal approval for the study was obtained from the Ethical Committee of the Lothian Health Board, Edinburgh, Scotland and informed consent was obtained from all the participants who comprised 15 women with intractable idiopathic constipation (age range 19–54 years, mean 32). All gave a history of severe constipation starting in adolescence with a duration ranging from five to 45 years (mean 19.8). Almost all patients described difficult rectal evacuation. None had had previous abdominal or pelvic surgery. Full clinical investigation including biochemical and haematological screening, sigmoidoscopy, and barium enema had failed to define a cause for the constipation. Their symptoms were inconsistent with the irritable bowel syndrome. Hirschsprung's disease had been excluded by anorectal manometry in all the patients and by full thickness rectal biopsy in six. At the time of this study the frequency of the bowel movements of the constipated patients ranged from once per week to once every five weeks (mean, once every 19 days). Dietary and drug adjustments had been of little benefit. Three
patients had to have regular enemas to encourage defecation. All the patients were on some form of laxative. Urological symptoms were elicited in 12 of the 15 patients. Frequency, urgency, urge, and stress incontinence were the commonest. Two patients had recurrent urinary tract infections and three nocturnal enuresis. The pattern of voiding was urgent but some had difficulty in voiding by volition. Twenty five female controls consented to manometric and electrophysiological investigations. Their ages ranged from 23–60 years (mean 40). These patients had been admitted to hospital for investigations or surgery outwith the alimentary tract and had no bowel symptoms.

**Radiology**

All the patients had a standard double contrast barium enema performed to exclude an obvious organic cause for the constipation.

**Manometry**

All the patients and subjects were requested to refrain from all but the most essential medication for 48 hours before the manometric and electrophysiological investigations.

Anal sphincter manometry was done using a conventional microballoon technique to measure physiological sphincter length, basal, and squeeze pressures. The presence of the rectosphincteric reflex (reflex relaxation of internal anal sphincter in response to rectal distension) was confirmed in all patients and controls. Proctometrograms were done in 10 patients and a similar number of approximately age matched controls. Rectal volumes at sensation threshold, constant (defecatory) sensation and maximal tolerance were measured and rectal compliance calculated.

**Electrophysiology**

Measurement of the electrophysiological latency of the pudendo-anal reflex (PAR) was carried out by the averaging method described by Varma et al. It was elicited by electrical stimulation of the dorsal genital nerve with a felt bipolar surface electrode (type LBS 53051, Medelec, UK). The reflex contraction of the external anal sphincter was recorded with a bipolar surface stainless-steel anal plug electrode (type 13K78, DISA, Copenhagen) using the Medelec MS92a evoked-response unit. More than 100 square wave stimuli (duration 0–1 ms, frequency 2 Hz) were applied and the digitally averaged response displayed on the oscilloscope at a sweep speed of 10 ms/cm with the gain at 100 μV/cm and filter settings of 20 Hz–10 kHz. The stimulation voltage was approximately three times the voltage at sensation threshold. In no case was the stimulation reported to be painful. The procedure was repeated in each subject to ensure reproducibility. The latency of the PAR was measured from the onset of the sweep (triggered by the stimulus) to the onset of the clearly defined reflex response at the external anal sphincter. The sensory threshold and stimulation voltages, amplitude, and duration of the reflex contraction of the external anal sphincter as determined by this method were also noted. Mean motor unit potential duration of the external anal sphincter was able to be carried out in eight patients and compared with data gathered from 15 control women. A modification of the method described by Bartolo et al was used. A standard concentric needle EMG electrode (surface area 0.07 mm², type 13L49 DISA, Copenhagen) was inserted into the external anal sphincter without anaesthetic via a puncture site 1 cm lateral to the anal orifice to a depth of approximately 25 mm. This was connected via preamplifiers to an oscilloscope (Medelec MS9a, Woking, Surrey, UK). The tonic electrical activity of the sphincter was monitored using a time base of 10 ms/cm with the gain at 100 μV/cm and filter settings of 20 Hz–10 kHz. Single motor units firing at a steady rate were identified using the delay and trigger facilities incorporated in the apparatus. Approximately 100 consecutive action potentials of the same motor unit were digitally averaged on one channel of the oscilloscope and the process repeated on the second channel. When two identical traces were obtained on both channels, the action potential duration for that motor unit was measured from the first deflection from the baseline to the return of the action potential to the baseline. Stable late components were thus easily identified. Permanent recordings were obtained of at least 20 action potentials from the external anal sphincter representing approximately 10 recordings from each side of the sphincter. This was made possible by minor movements of the tip of the needle electrode in the sphincter. The arithmetic mean of the 20 recorded potential durations was calculated and represented the mean motor unit potential duration for that sphincter. This was used as an index of neuropathy.

**Statistical Analysis**

Differences in the manometric and electrophysiological measurements between the groups were analysed by the Wilcoxon's rank-sum test.

**Results**

**Radiology**

In two patients barium enemas showed a redundancy of the sigmoid colon. No other colonic abnormality was detectable in any patient. In five of the 15
Neurophysiological dysfunction in young women with intractable constipation

Table 1  Manometric data in young women with intractable idiopathic constipation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chronic constipation</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=15)</td>
<td>(n=25)</td>
<td></td>
</tr>
<tr>
<td>MRP (cm H₂O)</td>
<td>101 (4-6)</td>
<td>107 (5-6)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>HPZ (cm)</td>
<td>3-1 (0-1)</td>
<td>3-2 (0-1)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>MVC (cm)</td>
<td>159 (8)</td>
<td>167 (7)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td></td>
<td>(n=10)</td>
<td>(n=10)</td>
<td></td>
</tr>
<tr>
<td>STV (ml H₂O)</td>
<td>348 (56)</td>
<td>230 (35)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>CSV (ml H₂O)</td>
<td>444 (40)</td>
<td>300 (28)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>MTV (ml H₂O)</td>
<td>699 (49)</td>
<td>510 (22)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RC (mlecm H₂O)</td>
<td>14-4 (1)</td>
<td>8-5 (0-6)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

All measurements mean (SE); rectosphincteric reflex present in all patients and controls; MRP=maximum resting (basal) anal canal pressure; HPZ=length of sphincteric high-pressure zone; MVC=maximum voluntary sphincter contraction pressure; STV=rectal volume at sensory threshold; CSV=rectal volume at constant (defecatory) sensation; MTV=maximum tolerable rectal volume; RC=rectal compliance.

Table 2  Electrophysiological data in young women with intractable idiopathic constipation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chronic constipation</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=15)</td>
<td>(n=25)</td>
<td></td>
</tr>
<tr>
<td>Sensory threshold, PAR (volts)</td>
<td>32-7 (1-5)</td>
<td>35-2 (2-9)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Simulation strength, PAR (volts)</td>
<td>103 (5)</td>
<td>112 (6-6)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Latency PAR (ms)</td>
<td>50-7 (1-9)</td>
<td>39 (1-2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Amplitude PAR (μV)</td>
<td>7-1 (1-78)</td>
<td>4-5 (0-68)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td></td>
<td>(n=8)</td>
<td>(n=15)</td>
<td></td>
</tr>
<tr>
<td>External sphincter MUPD (ms)</td>
<td>10-1 (0-7)</td>
<td>8-7 (0-36)</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

All measurements mean (SE); PAR=pudendo-anal reflex; MUPD=mean motor unit potential duration.

Table 2 lists the electrophysiological measurements. In two patients the pudendo-anal reflex was absent (>100 ms). The remainder showed significant prolongation (Figure). Other electrophysiological parameters of the pudendo-anal reflex remained unchanged. The mean motor unit potential duration of the external anal sphincter appeared to be somewhat prolonged in the constipated group although this did not reach statistical significance.

Discussion

There is no consensus regarding the pathophysiology of constipation and it has been suggested that it may be related to abnormally high sphincter pressures,1 1 5 2 ' an internal anal sphincter that fails to relax on rectal distension,1 3 2 2 2 5 impaired rectal sensitivity,2 2  failure of relaxation or paradoxical contraction of the pelvic floor musculature,5 5 12 24 reduced colonic propulsion,2 5 myenteric plexus abnormalities,9 10 15 24 a functional obstruction of the sigmoid colon,8 or a combination of these abnormalities. This study has examined a well defined young to middle aged group of women with severe 'idiopathic' constipation dating from adolescence. The sex and age distribution resembles that reported from other
studies but is different from the sex distribution found in elderly patients with chronic constipation.

Manometric anal sphincter data in this study did not throw much light on the aetiology of this type of constipation. The data are, however, in agreement with other recent reports in a similar group of patients. Hirschsprung's disease had been excluded by manometry and/or biopsy but not anismus which is caused by the paradoxical contraction of the pelvic floor musculature on attempted defecation.

Although the proctometrogram in 10 patients did not show any increase in the initial sensation of rectal distension, the distending volume for the 'constant' sensation at which the urge to defecate is perceived was increased. This is in keeping with the findings of Read et al who postulated different sensory pathways for these sensory modalities. The increase in rectal compliance and maximal tolerable volume in the constipated group was in contradiction to the findings of Roe et al who, however, used a much faster rate of infusion. An increase in rectal compliance and maximal tolerable volume in association with sensory deficits has been described in patients with spinal cord injury and after pelvic nerve damage.

Our studies suggest that some of these patients have a 'functional' megarectum that is often not obvious radiologically. This may be the combined effect of the outlet obstruction that has been described in many such patients and the coexistent sensory deficit of rectal perception of distension. A similar phenomenon has been described in some elderly patients with constipation and impaction, although there are probably many other factors involved in that group.

The electrophysiological results in this study do not suggest any abnormality of the sensory side of the pudendo-anal reflex as both the threshold and stimulation parameters did not significantly differ from control measurements (Table 2), although voltage is less accurate than current in quantifying this. This finding is in accordance with that of other workers in contrast with patients with neurogenic faecal or urinary incontinence who have abnormalities of sensory and motor pathways.

It is recognised that denervation of the striated anal sphincter musculature can result from chronic straining at defecation. The patients in whom mean motor unit potential duration of the external anal sphincter was assessed in this study showed a relative prolongation in this parameter although this did not achieve statistical significance compared with the control group. In contrast, the latency of the pudendo-anal reflex was grossly prolonged in constipation and was in excess of 100 ms in two patients. This finding suggests a significant neurological disturbance in the central part of this reflex arc, its sensory and motor limbs being apparently intact. It is conceivable that interneuronal connections to Onuf's nucleus are at fault and may be responsible for the abnormal response of the pelvic floor at defecation. Both the patients with the 'absent' reflexes had a sacral spina bifida occulta. The external sphincter mean motor unit potential duration (MUPD), however, was not greatly prolonged in these two patients. It should be noted that there is a clear relationship between the latency of the PAR and the MUPD of the external anal sphincter in neurogenic incontinence.

The conus medullaris is intimately concerned in the modulation of colorectal motility and pelvic floor innervation and in the control of micturition. The urological disturbances noted in our patients are further pointers to a possible occult neurogenic sacral spinal cord deficit in this constipated group. These abnormalities have been noted by other workers. Yip et al and Jakobsen et al emphasise the importance of urodynamic evaluation in spinal dysraphism. In a large series of patients Fidas et al reported spina bifida occulta in 50% of patients with stress urinary incontinence compared with an incidence of only 17% in asymptomatic control female subjects. In our series more than 30% of the patients had incidental lower spinal dysraphism. It is likely that the true incidence is much higher and may be an explanation for the neurophysiological abnormalities described. An alternative explanation of the results is that there is nerve damage to the efferent side of the reflex arc. Snooks and colleagues have shown by transcutaneous spinal stimulation that the latency was prolonged to the puborectalis muscle in over half of a group of constipated patients and to the external anal sphincter in over one-third of the patients. Further, the latency after stimulation of the pudendal nerve before contraction of the external anal sphincter was also prolonged in 10 of 24 constipated patients. These findings did not correlate in every patient with evidence of reinnervation of the muscles as shown by single fibre electromyographic measurement of fibre density. Most (20 of 24) of their patients showed evidence of perineal descent and these workers attributed the prolonged latency to nerve damage by stretching without necessarily causing denervation of muscle. Varma, Smith, and McInnes, describing results in incontinent patients in a previous study, quote values for normal conduction time of approximately 8 ms in each of the afferent and efferent limbs of the reflex similar to that found by Snooks and colleagues for conduction in the efferent limb. From this Varma et al assumed that the normal central conduction time was 15–30 ms. They have shown in
that study a similar prolongation of the pudendo-anoal reflex in incontinent patients as occurs in the constipated patients now reported. In the previous study, the abnormal latencies in incontinent patients were attributed to a neuropathy and evidence was found for this in decreased anal resting and squeeze pressures and prolonged mean motor unit potential duration. The same inference could be made here but with less severe impairment of motor function in constipated patients possibly because of varying degrees of descent of the pelvic floor on straining. The main argument against this, however, lies in the combination of bowel and bladder problems which suggests that the function of both these organs is disturbed as a result of a more central cord disorder.

We thank Dr Angus McInnes, Department of Clinical Neurophysiology, Western General Hospital, for his technical advice on the electrophysiological measurements. JSV was supported by a Wellcome Trust Research Grant.


References

6 Krishnamurthy S, Schuffler MD, Rohrmann CA, Pope CA. Severe idiopathic constipation is associated with a distinctive abnormality of the colonic myenteric plexus. Gastroenterology 1985; 88: 26-34.
7 Read NW, Timms JM, Barfield LJ, Donnelly TC, Bannister JJ. Impairment of defaecation in young women with severe constipation. Gastroenterology 1986; 90: 53-60.
10 Barnes PRH, Lennard-Jones JE. Patients with constipation of different types have difficulty in expelling a balloon from the rectum. Gut 1984; 24: 562-3.
37 Denny-Brown D, Robertson EG. On the physiology of micturition. Brain 1933; 56: 149–90.
final and permanent uprooting process from a foreign country, the significance of taking home the small tangible items as a reminder of the previous life. Those who often found readjustment difficult were those who had been least prepared for their return and who perhaps had come home because of illness. Previously strained relationships at home added to the problems of re-entry stress. Dr Jones emphasised the importance of adequate counselling, ideally before return, for those who might find difficulty in readjustment. During discussion after the paper, several participants at the Teach-in identified personally with the problems that the speaker had raised.

The final presentation of the afternoon was the welcome and provocative Case Presentation and Quiz provided by Dr D. R. Bell from the Liverpool School of Tropical Medicine and Hygiene. He took his audience, with humour and skill, through a series of cases of imported disease in which there had been diagnostic difficulty and asked for the answers to a number of questions about them. Most but not all were correctly answered and then only after some further clues had been supplied by Dr Bell.

At the close of the Teach-in Dr S. Phillips of Glasgow summed up the day’s proceedings, and on behalf of the Royal Society of Tropical Medicine and Hygiene thanked all the participants and the audience for the part they had played in making the meeting so enjoyable and successful.

J. A. Gray

Surgical Science for Physicians

The simplest advance in surgical technique may on occasion produce a therapeutic miracle. Thus, for example, the invention of the stapling gun by the Russians and its development in America, has permitted thousands of individuals with cancer of the lower bowel, ulcerative colitis and polyposis to escape the colostomy life by making possible low rectal, ileo-anal and colo-anal anastomoses. Other advances are achieved the hard way by painstaking unravelling of the anatomy and pathophysiology of disordered function which lead to new diagnostic tests and therapeutic solutions. The Surgical Science series aims to highlight fields of surgery which are sometimes regarded by physicians as no-go areas. Some contributions will be without complexity and easily understood. Others will require careful reading and studied appraisal because their fields are complex and involved distortion of anatomy as well as disturbance of function. The second article of the series, which follows, is of the latter variety and cannot be rendered pithy or plain without risk of becoming incomprehensible. It will repay your close attention.

THE EDITOR

THE ANO-RECTUM AND PELVIC FLOOR

J. S. Varma* and A. N. Smith, University Department of Surgery, Western General Hospital, Edinburgh

'I am convinced that it is by frequent interchange of opinion between the physiologist and the physician that the common goal of physiological science and medical art will be most quickly and safely reached.'

Ivan P. Pavlov

Over the last ten years the application of new technology has rewarded investigators concerned with research into the pathophysiology of ano-rectal and lower urinary tract disorders. A consequence has been an explosion of information about the causation of many common problems in proctology and

* Present address: Department of Surgery, The Chinese University of Hong Kong.
urology. Earlier crude techniques have been replaced by refined, often non-invasive, ones and the emphasis has changed from static, isolated measurements to dynamic, simultaneous ones. Thus it is now possible to record simultaneously anorectal pressure, to make electromyographic records of sphincter activity and to visualise the anorectum by radiology. The pressure-volume relationship and sensitivity of the rectum to distension can be monitored continuously in the same way as cystometry. The precise measurement of the latencies of several polysynaptic reflexes which involve the perineal musculature makes feasible physiological evaluation of entire neural pathways. Techniques are now available to assess sensory deficits in functional anorectal and urological disorders which have long been obscure. These methods of measurement of anorectal and pelvic floor function are rapidly emerging from being research tools into being a part of the requirement for proper clinical assessment. The number of patients requiring such investigations is rising as longevity increases and as the range of sphincter-saving surgery extends.

ANATOMY AND PHYSIOLOGY

The pelvic floor consists of a muscular diaphragm which, especially in the erect position, supports the abdominal contents including the urogenital apparatus. The musculature and innervation of the pelvic floor is essential for the control of micturition and defaecation and of sexual function. Factors influencing anal continence include the consistency of the stool, the presence and distensibility of the rectal reservoir, the efficiency of the sphincters and an intact sensory system. The internal anal sphincter is surrounded by the muscles of the external anal sphincter and the pelvic floor and these are under voluntary control.

The major component of the pelvic floor is a pair of symmetrical compound sheets of striated muscle, the levator ani or pelvic diaphragm (Fig 1). Continuity

![Diagram of Pelvic Floor Components](image_url)

**Figure 1**

Illustrates the composition of the pelvic floor. The diaphragm formed by the levator ani muscles, on each side, is weakened in the mid-line by the passage of urogenital structures and ano-rectum through it. The innervation is again depicted (from Snooks and Swash 1986, by permission).
between the sheets is defective in the midline where viscera pass through (Fig 2). Each is intimately related to the striated muscles of the anal canal, vagina and urethra. The angulation of the bowel at the anorectal junction produced by contraction of the puborectalis portion of the pelvic floor muscles is vital to the control of defaecation. The puborectalis, in common with the other components of the pelvic floor musculature and the external anal sphincter, is unusual in being continuously active even at rest. The level of activity changes in response to alterations in intra-abdominal pressure but the anorectal angulation remains relatively constant and so continence is preserved. This characteristic of the pelvic floor muscles depends on a spinal reflex and hence on intact innervation.

The cell bodies of the neurones controlling the striated muscles of the pelvic floor lie in the ventral horn of the conus medullaris. These neurones, known euphemistically as Onuf's nucleus, have been studied extensively in animals. The pelvic floor and external anal sphincter muscles receive their motor innervation from the sacral plexus via two distinct routes (Fig 1). The pudendal nerve arises

![Figure 2](image-url)

**Figure 2**
Shows the general relationship of the pelvic viscera and the motor innervation of the pelvic floor. The extra-pelvic course of the pudendal nerve, and the separate nerve supply of the puborectalis from the S4 nerve root above the levator muscle are depicted (from Snooks and Swash 1986, by permission). The figure also illustrates the angulation at the ano-rectal angle produced by pull of the puborectal part of the pelvic floor muscle.
from the anterior primary rami of the second, third and fourth sacral nerves. It branches across the ischiorectal fossa to supply the external anal sphincter. Direct branches of the third and fourth sacral nerves remain on the visceral side of the pelvic floor and supply the puborectalis muscle and the more peripheral parts of the levator ani. Electrophysiological studies show that, apart from a small area of overlap in the midline posteriorly, the nerves above the pelvic floor and the pudendal nerves supply only the ipsilateral muscles.

The most important part of the smooth musculature of the rectum and anal canal is the internal anal sphincter which is responsible for about 85 per cent of the resting pressure in the anal canal in health. This sphincter is under autonomic control through the sympathetic (hypogastric) and the parasympathetic (sacral) pathways. Inhibition brought about by rectal distension (the recto-anal or rectosphincteric inhibitory reflex) is predominantly an intramural reflex mediated via the myenteric plexus, although it is subject to some sacral control.

Within the proximal anal canal the junction between ectoderm and endoderm mucosa constitutes the anal transitional zone, measuring approximately 10–15 mm and situated just proximal to the dentate line. This area is richly supplied with various kinds of nerve endings and its sensory function is important to continence. Urinary continence at rest is dependent on the striated muscle of the bladder neck and the external sphincter composed of slow twitch fibres that have tonic activity at rest. These are supplied directly by the pelvic nerves from the sacral segments S2-S4. The peri-urethral striated muscle sphincter functions reflexly to augment urethral closure when intra-abdominal pressure is raised by coughing, laughing, straining etc. This muscle receives its motor innervation from the perineal branch of the pudendal nerve. Reflex activity of the peri-urethral musculature is mediated via sensory afferents in the bladder, urethra and pelvic floor and motoneurones in the conus medullaris (S2-S4). The sensory innervation of the urethral mucosa derives predominantly from the perineal branch of the pudendal nerve. A branch from the motor roots of S3 and S4 reaching the pelvic floor via its visceral surface also carries sensory fibres from the posterior urethra and anal canal. The inferior rectal nerve, a branch of the pudendal nerve, supplies the external anal sphincter, the lining of the lower part of the anal canal and skin around the anus. Anatomical or functional deficits in the sensory, central or motor pathways of reflexes involving the urethral and anal sphincters may, therefore, compromise continence.

The parasympathetic innervation (Fig 3) of the urinary bladder and left colon and rectum derive from sacral segments S2, S3 and S4 via the pelvic nerves. From the inferior hypogastric plexus nerve fibres run forwards to innervate the bladder, and upwards and out of the pelvis to innervate the rectum and left colon. This innervation is of paramount importance in the co-ordinated contraction of the smooth muscle of the bowel and bladder. It also carries sensory fibres from these viscera. It is, therefore, conceivable that damage to this autonomic innervation during pelvic surgery can result in functional disorders of the colon; for example, during hysterectomy the inferior hypogastric (pelvic) plexus which, in the female is placed on each side of the rectum, uterine cervix, vaginal fornix and posterior aspect of the urinary bladder and extends into the base of the broad ligament of the uterus, is susceptible to injury.
INVESTIGATION: METHODS AND INTERPRETATION

Sphincter manometry

Pressure measurements within the anal canal provide information about the integrity of the internal and external anal sphincters. Resting pressure is maintained predominantly by the internal sphincter, while the external sphincter contributes to the voluntary contraction or 'squeeze' pressure. The length of the anal sphincters can also be determined manometrically. The most common methods of measurement have been open-tipped tubes and closed balloon systems connected by fine tubes to strain gauges outside the anal canal. Although

![Figure 3](image-url)

The plan of the autonomic innervation of the gastrointestinal tract and in particular of the colon, rectum and other pelvic organs.
these systems have provided the information on which concepts of anorectal physiology are based, they possess disadvantages. A miniature microtransducer system that provides a continuous pull-through pressure profile of the anal sphincters\(^{10}\) can replace fluid-filled tubes and external transducer relays (Fig 4). The measurements are highly reproducible (mean coefficient of variation 4.4–5.7 per cent) and accurate. In addition, measurement of the area under the

![Continuous Pull-Through Sphincter Profilometry](image)

**Figure 4**
Anal sphincter profilometry showing 4 pull-through procedures with random transducer orientation and measurements derived from each.

![Distending Balloon](image)

**Figure 5**
Rectal balloon and anal canal transducer in situ for registering the recto-sphincteric reflex which is the anal sphincter relaxation following rectal ampullary distension.

The high pressure zone provides an index of the function of the internal sphincter. The tube and balloon system can also be used to elicit and measure the reflex relaxation of the internal sphincter, or recto-sphincteric reflex, in response to rectal distension by a balloon in the rectal ampulla (Figs 5, 6). This reflex is absent in Hirschsprung's disease. Anal manometry provides useful information about the function of the sphincters in incontinence, rectal prolapse, constipation,
descending perineum syndrome, solitary rectal ulcer, the irritable bowel syndromes, haemorrhoids and fissure. It is also useful to evaluate the function of the sphincters and rectum before and after certain colorectal operations. Manometry can be supplemented by electrophysiological methods.

**Electrophysiology**

Percutaneous insertion of a needle EMG electrode into external anal sphincter or the puborectalis muscle enables the electrical activity of these muscles to be monitored at rest, on contraction, during straining and in response to rectal distension. The same equipment enables action potentials from individual motor units to be measured and a mean motor unit potential duration to be calculated for that muscle (Fig 7). Following denervation, as in neurogenic faecal incontinence.

![RECTOSPHINCTERIC REFLEX](image)

**Figure 6**

The recto-sphincteric reflex, or the fall in sphincter pressure, after rectal distension: absent in Hirschsprung’s disease or when the intramural plexus has been damaged.

**MEAN MOTOR UNIT POTENTIAL DURATION (MUPD)**

![Mean Motor Unit Potential Duration](image)

**Figure 7**

Typical mean motor unit potential records of the external anal sphincter, showing prolongation in incontinence.
incontinence, the potential duration is prolonged, probably due to re-innervation of muscle from remaining healthy nerve fibres; thus the prolongation is an accurate index of sphincter nerve damage. The method, however, is tedious and time-consuming. A technique of measuring the latency of reflex contraction of the external anal sphincter\(^{12}\) in response to a surface electrical stimulus applied to the dorsal genital nerve, the pudendo-anal reflex, is less tedious. Reflex contraction of the external anal sphincter is mediated via the sacral spinal cord segments S2, S3 and S4 and hence may indicate a disorder affecting these (Fig 8).

**ANATOMICAL BASIS OF THE BULBOCAVERNOSUS AND PUDEANOANAL REFLEX**

![Diagrammatic representation of the anatomical basis of the bulbocavernous and pudendo-anal reflexes.](image)

The latency of the pudendo-anal reflex correlates with the potential duration and provides an index of external sphincter neuropathy (Fig 9).\(^{12, 13}\) At the same time as measuring reflex latencies, information about the sensory side of the reflex can be obtained from measurement of the minimum current reaching the sensory threshold—the electroosensitivity.\(^{14}\)

Direct methods of measuring motor nerve conduction velocities also exist. For example, brief high-voltage stimulation over the distal spinal cord or cauda equina can be used to measure the latency of contraction of the anal or urethral sphincter musculature.\(^{15}\) Similarly, stimulation of the pudendal nerve at the level of the ischial spine by an intra-rectal probe enables the terminal innervation of these muscles to be assessed.\(^{16}\)
The proctometrogram

A large, highly-compliant balloon gives a continuous pressure-volume trace in the empty rectum when it is slowly distended with water using a peristaltic pump (Fig 10). This measures rectal volume and pressure at various stages of perception by the patient and therefore records rectal compliance (Fig 11). Sensory deficits may also be revealed by this test. The mean coefficient of variation of this test is 4.7–7.9 per cent.

Colonic motility

Colonic motility is recorded using tandem balloons or through a triple-lumen, open-ended, perfused catheter placed at sigmoidoscopy so that its openings lie 5 cm apart in the sigmoid colon, recto-sigmoid and rectum (Fig 12). The three channels are connected via pressure transducers to a chart recorder. The recordings which are made in the resting state, after stimulation by food and by various drugs are measured over half-hour periods. The average wave height and percentage time of activity are calculated, from which a motility index can be derived. Colonic motility is increased following stimulation in diverticular disease and in the irritable colon. It is diminished in megacolon.
Physiological tests can be supplemented by clinical and radiological assessment of the colon and rectum by sigmoidoscopy and a barium enema, during which the anorectal angle can be measured. Passage of swallowed radio-opaque markers can be followed radiologically and provide an estimation of total gut transit time.

**APPARATUS FOR RECORDING CONTINUOUSLY MONITORED PROCTOMETROGRAM**

![Diagram of proctometrogram apparatus](image)

**FIGURE 10**

Apparatus used to record a proctometrogram. As the balloon is distended, sensory awareness is provoked; the relationship of distending volume and pressure gives an estimate of compliance.

**FIGURE 11**

Diagrammatic representation of proctometrogram traces—
(a) pressure volume response of the balloon itself
(b) response in a normal patient
(c) trace from an irritable bowel patient
(d) megarectum response
CLINICAL PROBLEMS

Neurogenic faecal incontinence

Previously known as idiopathic faecal incontinence, this usually follows a stretch injury to nerves of the anal sphincter musculature. Early studies on muscle biopsies suggested a denervation disorder. Single-fibre electromyography has confirmed this and implicated injury to the terminal portion of the pudendal nerve (see Fig 1). This may occur as a result of excessive straining at stool or a difficult childbirth. It is evaluated by examination of the pudendo-anal reflex and measurement of the motor unit potential duration. There is diminution in sphincter pressures and prolongation of the pudendo-anal reflex. In severe forms the reflex may be absent. The latency of the reflex in health does not vary with age or sex. Its close correlation with motor potential duration demonstrates its value in the assessment of the innervation of the striated musculature of the anal sphincters. Abnormalities of the reflex also occur in diseases affecting the sacral spinal cord including multiple sclerosis and cauda equina cord compression by discs or malignant disease. The puborectalis muscle, though separately innervated from the external anal sphincter, is also affected in neurogenic incontinence. In many incontinent patients with sphincter denervation the anorectal angle is widened due to weakness in the pull of the puborectalis sling. This can be corrected by a post-anal repair pulling together the relaxed muscle and buttressing the perianal sphincter complex.

Chronic idiopathic constipation of young women

This condition was first described in 1909 by Arbuthnot Lane and treated with total colectomy, a procedure which subsequently fell into disrepute. Combined
proctography and EMG measurement show that inappropriate contraction of the puborectalis muscle, with or without failure of relaxation during attempted defaecation, may be an important cause of this condition. Defects of rectal proprioception with increase in rectal compliance and the development of a megacolon in the distal bowel are described in some of these patients (Fig 13). Many also exhibit abnormalities of the pudendo-anal reflex in the absence of sphincter neuropathy, thus suggesting that the conus medullaris may be at fault. In keeping with this hypothesis, urological disturbances are commonly associated with this disease. Some have an outlet obstruction syndrome due to contraction of the pelvic musculature during defaecation straining ('anismus') instead of the normally induced relaxation. In others abnormalities of the myenteric plexus are demonstrable throughout the colon. Occult neurogenic deficits in the sacral spinal cord associated with a high incidence of lumbosacral dysraphism may also be present similar to those in functional bladder disorders. At the present time subtotal colectomy with ileorectal anastomosis offers the most satisfactory treatment for the severely disabled. A small proportion of patients have the irritable bowel syndrome.

**Figure 13**
Laparotomy finding in chronic idiopathic constipation with megacolon in a young woman.

**Constipation associated with rectal prolapse**

'Complete' rectal prolapse is obvious and may be associated with any of the types of constipation already described. Many patients may nevertheless have faecal incontinence. Women predominate and commonly have undergone a previous hysterectomy or a pelvic floor repair. In a series treated by surgical reduction of the prolapse and fixation of the rectum by wrapping polyvinyl sponge material around it, 30 per cent remained symptomatic, although cured of
the mechanical part of the prolapse. Low resting sphincter pressure profiles and anal canal squeeze pressures remained after rectopexy. These patients still had troublesome faecal incontinence. The study indicated the need to improve distal bowel function by post-anal repair. Despite the loss of bowel sphincter control, few of these patients have urinary incontinence. The reverse is also true in that urinary stress incontinence is not commonly associated with faecal incontinence or rectal prolapse. Gross urinary and faecal incontinence occur together with utero-vaginal prolapse.

In the ‘solitary ulcer’ of the rectum syndrome a dyskinetic contraction of the pelvic floor occurs during straining at stool promoting rectal intussusception at the pelvic floor level. Mucosal ischaemia and local trauma contribute to the formation of indolent ulcers. X-ray proctography during defaecation elucidates the partial mucosal descent.

**Constipation and the irritable bowel syndrome**
In a hospital series 70 per cent of patients with the irritable bowel syndrome were female. The constipation is characterised by uncomfortable abdominal distension, especially after defaecation, the passage of pellet-like stools, sometimes with excess mucus, and by erratic frequent evacuations which may be regarded as ‘diarrhoea’. Tenesmus and straining at stool are common. ‘Stress’ and life events are said to be important in the production and exacerbation of symptoms.

There is no constantly demonstrable disorder of colonic motility, though the entire intestine may be affected by aberrant and excessive contractions which can be observed in a barium X-ray. A more constant feature is hypersensitivity of the bowel to distension which can be revealed by a proctometrogram. Rectal compliance and volumes are significantly reduced.

**Constipation following hysterectomy**
A proportion of women develop intractable constipation after pelvic surgery, especially hysterectomy. Many also have troublesome urinary symptoms. Colorectal motility studies do not demonstrate sphincteric problems or abnormalities of the pudendo-anal reflex but show defects in rectal proprioception. Many of these patients have an ‘atonic’ rectum with increase in compliance. Defects of motility in the sigmoid colon are striking. Basal motility is reduced and the response to stimulation with prostigmine is not only reduced but a paradoxical reversal of the normal proximal to distal motility gradient occurs. This suggests peripheral autonomic denervation, possibly by damage to pelvic parasym pathetic nerves. Further evidence of this is an excessive, hypersensitive motility in response to carbachol. Theoretically, these patients could be treated by resection of the denervated left colon. In practice, however, there is usually damage to the entire colon, some of it being due to laxative induced destruction of the myenteric plexus. At the present time, subtotal colectomy with ileorectal anastomosis gives the most satisfactory results.

**Spinal cord injury**
Dysfunction of the urinary bladder after injury to the spinal cord has long been recognised. With more effective treatment of this problem and longer survival of
patients concomitant functional problems of the colon and rectum now receive more attention.

In a small group of patients sacral ventral root stimulators have been implanted to promote bladder emptying without the need for an indwelling catheter. Because the distal bowel receives its parasympathetic innervation from the same sacral spinal cord segments as the urinary bladder (S2-4), it is possible to study the effects of stimulation of different spinal nerve roots on the motility of the colon, rectum and anus.

The anal sphincter musculature responds maximally to S4 stimulation. The rectum and sigmoid colon show identical responses to root stimulation: S2 stimulation provokes low pressure isolated contractions, S3 stimulation high pressure peristaltic activity and S4 stimulation does not result in phasic contractions but seems to increase the ‘tone’ of the distal bowel.

**Colorectal function in the elderly who are constipated**

Although constipation is common in elderly patients, its pathophysiology is poorly understood. It is particularly distressing when associated with faecal impaction and incontinence. Some may respond to empirical measures such as change of diet, physical activity and stimulation by appropriate purgatives. In others, however, the condition becomes intractable and difficult to treat.

Rectal sensory threshold may be reduced in elderly subjects with chronic constipation. Some, presenting with faecal impaction, have functional megarectums. Others show a reduction in maximal rectal volume and rectal compliance. Differences in resting sphincter pressure and rectosphincteric reflex are not significant. The pudendo-anal reflex may be absent or prolonged. Total gastrointestinal transit time is prolonged and in a few cases colonic stimulation with bisacodyl fails to elicit a sigmoid motor response. Thus constipation in elderly patients is not merely due to delayed transit. Deficits of rectal proprioception, of sacral cord function and of tonicity of the muscle of the distal bowel may be contributory.

**Anorectal function after radiation rectal injury**

Chronic radiation injury of the colorectum may follow radiotherapy for carcinoma of the cervix, prostate or urinary bladder. The symptoms are distressing, urgency of micturition, frequency of defaecation and incontinence. Other complications that may require surgical intervention are haemorrhage, stricture of the rectum or sigmoid colon and fistula.

After radiation rectal injury the main physiological abnormality is in internal anal sphincter function. A significant reduction occurs in basal pressure, sphincter length and the recto-sphincteric reflex. Rectal volume and compliance is often severely reduced. Rectal compliance correlates well with the symptoms and with sigmoidoscopic abnormalities. Biopsies of the rectum show marked abnormalities of the myenteric plexus.

Serious complications may be treated successfully by a colo-anal sleeve anastomosis, i.e. resection of the rectum and restoration of intestinal continuity by anastomosing healthy proximal colon to the anal canal. Physiological studies performed several years after this operation show persistence of some of the pre-operative abnormalities, such as low rectal capacity, and this may explain how symptoms occasionally persist.
Urinary incontinence and the pelvic floor
Electrophysiological techniques and urodynamic measurement may reveal damage to the innervation of striated muscle in the urethral sphincter. The patient then cannot restrain the escape of urine during laughing, straining and coughing. Here the muscle which normally functions as a part of the pelvic floor, is affected similarly to the puborectalis in faecal incontinence. In addition, there appears to be some sensory deficit in the urethra and dorsal genital nerve. The aetiology is probably the same in neurogenic faecal incontinence. There is also evidence that central spinal cord defects associated with occult spina bifida can cause the dysfunction.

Avoiding ileal or colonic stoma by formation of a neo-rectum
Patients with ulcerative colitis can be offered reconstructive surgery which creates a ‘neorectum’ after distal bowel resection. This combines colectomy, mucosal proctectomy and the formation of a Parks’ pouch (S-shaped or J); adjacent loops of the terminal ileum are anastomosed together before being brought down to the preserved sphincter area through the rectal stump from which the mucosa has been stripped. Patients should be tested pre-operatively for future continence by sphincter pressure profile studies. Immediately after operation sphincter pressures may be low but they often return to normal in a few months. The proctometrogram can be used to show a good pouch capacity. For limited distal colitis, local excision with a colo-anal sleeve anastomosis is less successful.

Proctalgia
In both proctalgia fugax and chronic perineal pain the distal bowel should be examined for all the conditions, common and uncommon, which affect it. Close attention should be paid to the detection of simple lesions such as fissure which can be overlooked particularly in women when occasionally they are placed anteriorly. Solitary rectal ulcer, secondary to intractable constipation and pelvic floor outlet obstruction is a commonly missed lesion. In all such bowel problems enquiry should be made about accompanying upset in bladder function and possible spinal disc or other neurological disorders, such as spina bifida occulta, must be excluded by clinical examination and by radiography. Studies of the pressure profile of the distal sphincters, of the proctosphincteric reflex, of the proctometrogram and of distal spinal cord reflexes such as the pudendo-anal reflex may be necessary. Electromyography records should be examined for pelvic floor muscle outlet obstruction and nerve conduction tests of the lumbo-sacral roots are performed to exclude sacral and cauda equina abnormalities. Inappropriate contraction of the pelvic floor in response to straining should be especially looked for since it is a common accompaniment of many other disorders and often causes rectal discomfort and left iliac fossa pain. These tests which are available in specialised ano-rectal clinics have a high diagnostic accuracy and are important aids to correct management.

ACKNOWLEDGMENT
Figures 1 and 2 are taken from Hospital Update, March 1986, by kind permission.
REFERENCES


15. Kiff ES, Swash M. Normal proximal and delayed distal conduction in the pudendal nerves of patients with idiopathic (neurogenic) faecal incontinence.


34 Varma JS, Smith AN. Abnormalities of colorectal function in intractable constipation following hysterectomy. Gut 1985; 26: 581-582.
35 Brindley GS. An implant to empty the bladder or close the urethra. J Neurol Neurosurg Psych 1977; 40: 358-369.
Motility Effects of Electrical Anterior Sacral Nerve Root Stimulation of the Parasympathetic Supply of the Left Colon and Anorectum in Paraplegic Subjects

N. R. Binnie,*† A. N. Smith,* G. H. Creasey, † and P. Edmond†
*University Department of Surgery, Western General Hospital, Edinburgh; and †Spinal Injuries Unit, Edenhall Hospital, Musselburgh, Scotland, United Kingdom

The extent and nature of colonic and anorectal motility responses to S2, S3, and S4 anterior nerve root stimulation were studied in seven paraplegic patients with a Brindley electromicturition sacral implant. After sequential S2, S3 and S4 stimulation wave height activity was increased above basal from the transverse colon to the rectum. The mean motility index response to sequential stimulation was greatest at the splenic flexure. The greatest peak wave height and mean motility index response to individual anterior nerve root stimulation was to S3, which could empty the left colon by a distal motility gradient. S4 anterior root stimulation increased the intrarectal pressure and also raised the anal canal pressure to high levels. (Journal of Gastrointestinal Motility 1990; 2(1):12—17

Key Words: sacral nerve roots; stimulator; implant; colorectal motility; paraplegia.

Introduction
Brindley and colleagues introduced the implantable anterior sacral nerve root stimulator for bladder control in paraplegic subjects (1). Using this device it has been possible to show by activating the second, third, and fourth anterior sacral roots (S2, S3, and S4) that these nerve roots carry the parasympathetic nerve supply in man to the bladder (1), sigmoid colon and rectum (2), and genital organs (3). The S2, S3, and S4 anterior roots also carry the somatic motor supply to the striated muscles of the pelvic floor (4). The effects of the Brindley stimulator on bladder function have been studied with urodynamic observations by Cardozo and associates (5). The effects on the striated anal sphincter and distal colorectal activity have recently been studied for the first time in man (2).

The present study investigates the extent and nature of the motility response to S2, S3, and S4 anterior root stimulation throughout the left colon and anorectum in the area likely to be influenced by the parasympathetic supply in the S2, S3, and S4 anterior sacral nerve roots.

Material and Methods
PATIENTS
In seven subjects, six male and one female, with traumatic spinal cord injury (Table 1), the left colonic and rectal motility was studied after implantation of a Brindley sacral root stimulator. The studies described were carried out at a mean time of 2.6 years after implantation with a range of 1 to 5 years. The six male subjects had the implant to improve bladder emptying and eliminate urinary infection by minimizing residual volume. The one female subject had the implant primarily to aid urinary continence. All subjects gave informed consent for the investigations, and ethical permission was obtained from the Medical Ethics Committee of the Lothian Health Board, Edinburgh, in July 1985.

STIMULATOR
The sacral anterior root stimulators were implanted using the Brindley technique (1). All subjects except...
subject 2 had three root implants, S2, S3, and S4. Subject 2 had electrodes placed on roots S3 and S4 only. Subject 3 had some leakage of cerebrospinal fluid from the site of emergence of the cable from the spinal dura, but this problem resolved spontaneously and was avoided subsequently by the use of a grommet of fine woven polyester at the dural exit site (1).

The stimulator parameters of signal frequency, impulse burst duration, intensity, and stimulation-time gaps were regulated for optimum bladder function. The stimulation electrical waveform was octagonal with a mean wave duration of 3 ± 1.2 seconds with a mean gap between bursts of 3.2 ± 1.4 seconds. The mean signal strength corresponded to 10.6 ± 2.9 V. A standard period of total stimulation of 1 minute for each root level was used during the study of effects on the colon as this best approximated to the time scale normally used for electromicturition. The motor trains of high frequency at high amplitude occasionally used to achieve final emptying of the bladder were not used by all subjects and therefore were not included in this study. Similarly the continuous train of low-frequency, low-amplitude impulses intended to maintain urinary continence by contraction of the external urethral sphincter was not used manually by subject 7 and was therefore not studied on this occasion.

The effects of sacral root stimulation on colonic motility were studied without altering the stimulator parameters, because altering the bladder settings would result in autonomic dysreflexia as clearly demonstrated by Liddan and coworkers (6). This occurs more seriously when the posterior nerve roots are left intact in patients with Brindley stimulators. The autonomic effects that characterize this dysreflexia are hypertension, sweating, and headache and are the response to visceral distention and afferent stimulation. In this series subject 7 had the posterior roots of S3 and S4 severed at the time of implantation to avoid spontaneous bladder contractions between periods of activation of the stimulator, as her main complaint was that of urinary incontinence. Of the six male patients only subject 3 had the S3 posterior roots cut, leaving the others intact. The remaining males did not have any posterior roots cut, as adequate bladder function was obtained using the stimulator without inducing autonomic dysreflexia while leaving intact the option of reflex bladder emptying and reflex penile erections.

**MANOMETRY**

Subjects were prepared for rectal and distal colonic manometric investigations by ensuring an empty proximal colon with the oral administration of one sachet of "Picolax" (sodium picosulphate 10 mg/sachet) followed by one day of a liquid, no-residue diet. On the morning of the investigation any rectal residue was cleared manually and a repeat saline enema was given if required, as subjects with spinal cord injuries have intractable constipation (7).

The motor activity was examined by three liquid-filled systems placed in series, each of which gave readings overlapping with the other from proximal to distal. Checks were done to ensure that manometric responses recorded at the upper end of each zone gave the same response as the distal end of the preceding one from the next recording system.

**TRANSVERSE COLON AND SPLENIC FLEXURE STUDIES**

The proximal studies involved the use of a flexible fiberoptic sigmoidoscope with x-ray image intensifier control to introduce a fluid-filled system with a single 5-ml pressure balloon up to the transverse colon. The system was filled with aqueous radiopaque fluid, to allow accurate identification and placement under radiologic control. Basal (resting) activity was recorded 10 cm proximal to the splenic flexure, followed by recording of pressure responses to sacral root stimulation. The balloon was now withdrawn by a measured 10-cm distance to the splenic flexure, the position was checked radiographically, and the recordings were repeated. A third recording was
taken from the midsigmoid region before the balloon was withdrawn to check comparability of the responses to those in sigmoid colon.

**Sigmoid Colon Motility**

A water-filled system of three 5-ml balloons (HSCI, Precision Drippings Ltd, UK) in series, separated by a fixed distance of 5 cm and connected to separate external pressure transducers with a chart recorder, was used. The balloons were placed in situ at 25, 20, and 15 cm from the anal margin using a rigid sigmoidoscope. Colon motility recordings were taken in the basal resting state and then in response to sacral root stimulation. The maximum pressure achieved in response to stimulation was recorded for each region. The distal balloon recording was used to check that there were comparable responses in the rectal zone.

**Rectal Motility**

In the rectum a water-filled microballoon system with a fine-bore tubing attachment to a strain-gauge pressure transducer with a chart recorder was used (8). The microballoon was placed inside a second, larger balloon, which in turn contained a volume of water equal to 25% of the maximum capacity of the rectum. The pressure in the rectum was recorded at rest and then measured during the response to stimulation of the anterior sacral roots.

**Anal Canal Pressure**

A recording was made at the point of maximum resting pressure in the anal canal, previously determined by station pull-through using a water-filled microballoon system (2).

**Measurements**

The measurements were the peak amplitude, which was measured as the maximum contraction recorded above the baseline, and the motility index, which was the product of the average motility amplitude response and the length of the response with each stimulus period. The basal motility index was derived by taking the basal mean amplitude of the spontaneous waves for a comparable period of time to the stimulated “response” time. The mean amplitude and motility indices are expressed in response to S2, S3, and S4 root stimulation both sequentially and individually. Brindley and associates have suggested that simultaneous stimulation of all the S2, S3, and S4 roots might be best for bowel emptying (9). However, simultaneous stimulation of all these roots was not attempted because of the danger of autonomic dysreflexia (6), as previously described in patients with intact afferent nerve roots, such as those in this study. Since the activity time was largely determined by the duration of the electrical stimulation, it was not a variable that allowed evaluation.

**Results**

**Response to Sequential Stimulation of S2, S3, and S4**

The peak amplitude of the waves at rest was the same throughout the left colon. After sequential S2, S3, and S4 stimulation there was an increase in the average wave heights in all the zones. The smallest waves were in the transverse colon (Fig. 1).

The mean motility index after sequential S2, S3, and S4 stimulation showed a rise above basal in all the zones (Fig. 2). The greatest response to stimulation in the colon was at the splenic flexure. This was significantly greater than in both the sigmoid and transverse colon. The level of rectal stimulation, however, was not significantly different from that of the splenic flexure.

**Response to Individual Root Stimulation of S2, S3, and S4**

Stimulation of the S3 root produced the greatest peak wave height, for all the zones, and the effect was significantly greater than that produced by S2 and S4 stimulation. The heights of the waves produced by S3 root stimulation were greater in the splenic flexure region than in the distal transverse colon but were not significantly different from those in the sigmoid and rectum (Fig. 3).

The mean motility index response was also greatest after stimulation of the S3 root, with the greatest motility effect at the splenic flexure (Fig. 4). Effects of S3 stimulation at the splenic flexure, sigmoid co-
Figure 2. Motility response to sequential S2, S3, S4 stimulation. *Splenic flexure—transverse colon, p < .01. #Splenic flexure—sigmoid colon, p < .01.

Figure 3. Motility response to individual root stimulation for S2, S3, and S4. *S3 response to splenic flexure—transverse colon, p < .05. #Combined S3—combined S2 or S4, p < .01.

Discussion

This paper extends the preliminary findings of Varma and colleagues regarding the effects of the Brindley stimulator on the function of the distal sigmoid colon, rectum, and pelvic floor (2). Quantitative data are presented from studies throughout the left colon of paraplegic subjects and encompassing sequential and individual nerve root stimulation. Following electrical stimulation of the parasympathetic nerve supply to the left colon and anorectum there was an increase in mean height of the motor waves in all the zones examined. The effect on the wave heights was significantly less in the transverse colon. All the other zones were stimulated to similar wave heights when the combined S2, S3, and S4 root effects were examined. The total motility response to sequential S2, S3, and S4 stimulation showed that the splenic flexure and rectum were the maximally affected areas.

For individual root stimulation S3 produced the greatest change in amplitude in all areas in the left colon and rectum. The motility index after S3 stimulation changed to a gradient of activity down the left colon, maximal at the splenic flexure and lessening to the rectum, suggesting that the activation of this root could have propulsive effects caudally.

Rectal motility was greatest with S4 root activation; however, this may reflect not only intrinsic contractions but also a transmitted effect from the contraction of the pelvic floor muscles, since rectal motility is normally less than that of the rectosigmoid when studied by similar methods after gastrocolic stimulation with food (10). The pressure generated by the external anal sphincter and pelvic floor during S4 stimulation is in excess of the maximum voluntary
contraction physiologic range and could contribute to the high rectal pressure recorded.

It seems likely that the motility effects in the left colon could be the result of the direct electrical stimulation of the parasympathetic nerves to effector sites at smooth muscle cells in the left colon and rectum. However, the possibility exists that the electrical stimulation is also activating a pacemaker in the upper part of the left colon, since this area seems to be the site of greatest motility response. The distal gradient of motility established in these cases in the left colon should be effective in emptying fecal contents, particularly if the contractions were peristaltic. Propagated waves were previously demonstrated in the rectosigmoid in the observations on the Brindley stimulator by Varma and his colleagues in 1986 (2). The high rectal pressures following S4 stimulation could delay emptying, particularly if they result from contractions of the pelvic floor (4). The striated contractions cease abruptly on withdrawal of the stimulus while smooth muscle contractions of the rectum tend to persist beyond it and could therefore result in evacuation. In recent notes for surgeons and physicians regarding the stimulator Brindley, Polkey, and Rushton have suggested that anterior sacral root stimulation causes increased colonic activity and in most patients moves fecal material along toward the rectum while simultaneous S2, S3, and S4 stimulation might achieve evacuation (9).

The motility found in the transverse colon in terms of both wave height and motility index after the use of the stimulator to any one or all of the roots regularly rose above basal levels at this site and also became higher than the basal level of the adjacent splenic flexure. If the motor response in the transverse colon began with S2 root activity and it contracted before the major contractions of the splenic flexure were induced by S3 stimulation, filling of the left colon would begin. Further onward propulsion of the fecal stream would, however, be hindered by the greater S3-evoked contractions at the splenic flexure. Radioisotope and transit marker studies indicate a delay in some normal subjects at the splenic flexure and rectum, suggesting that there may be a physiologic barrier to propulsion in normal subjects at those sites (11,12). Furthermore, isotope scintigraphic transit studies (13) confirm that the transverse colon is an area where motility halts before progression of the fecal bolus into the left colon.

The overall implication from these studies seems to be that stimulation of S2, S3, and S4 segments of the cord leads to motor activity throughout the entire area of the pelvic parasympathetic innervation from the transverse colon to the anorectum, with the S3 level being the most effective in activating the left colon. However, it may be necessary to consider that some changes are also produced when neural stimulation is withdrawn, since the storage capacity of the left colon may be a function of inactivity between periods of stimulation.

It is unknown whether the activity in the sacral parasympathetic region is brought about by stimuli arising in all the roots together or whether it is arranged hierarchically from above downward, S2 before S3 before S4 serially. Furthermore, in this study the stimulus parameters chosen for bladder evacuation were accepted for stimulation of the same parasympathetic nerve roots leading to the bowel, as it was feared that attempts to alter those used for bladder control would produce autonomic dysreflexia, especially since the posterior roots were intact. These observations were made in paraplegic subjects with the limitations of early experience with the Brindley device. Several of the patients in this series have subsequently been able to produce stimulus-driven rectal evacuations after slight alteration in their stimulator settings. It is foreseeable that some patients may use the device as much for their bowel problem as for the bladder. Meshkinpour and colleagues (14) found that the large bowel could be affected by an absence of the gastrocolic reflex elicited by a standard food stimulus after spinal cord injury, with later excessive segmentation contractions which are nonpropulsive (15). The patients in this study maintained regular bowel evacuations by the use of alternate-day suppositories and manual evacuation and therefore had been spared the effects of fecal retention.

Acknowledgments

N. R. Binnie was supported by Scottish Hospital Endowment Research Trust grant 720.

References

MOTILITY EFFECTS OF ELECTRICAL ANTERIOR


Use of the pudendo-anal reflex in the treatment of neurogenic faecal incontinence

N R Binnie, B M Kawimbe, M Papachrysostomou, A N Smith

Abstract
An electrical stimulator has been devised to treat neurogenic faecal incontinence caused by pudendal nerve neuropathy and works on the basis of repeated stimulation of the pudendo-anal reflex arc. Although conduction in the pudendo-anal reflex arc may be prolonged, and is so in neurogenic faecal incontinence, it must be shown to be present before the method can be used. This stimulation results in an immediate rise in the pressure in the anal canal and a significant increase in the electromyographic activity of the external anal sphincter. Maintenance of the stimulus over a two month period raised the mean resting pressure significantly in the anal canal and increased the reflex and voluntary responses of the external anal sphincter to coughing and squeezing actions respectively. The length of the sphincter was not affected. There was widening of the mean motor unit potential duration, though this was not significant. The resting electromyogram was enhanced after the course of treatment, indicating greater spontaneous activity in the external sphincter. The changes led to seven of the eight patients studied becoming continent at the end of the treatment.

Neurogenic faecal incontinence is an increasing problem in an ageing population. Not all patients are suitable for a post-anal repair, which is the mainstay of surgical treatment. Various electrical stimulators have been described in the past with the aim of returning function to the external sphincter and pelvic floor. These make use of a surface anal plug electrode or are implanted with a radiofrequency link outside the body. Although some have been successful at first, they have not found continued use, mainly because of wire breakages in the implants and anal pain or inhibition fall, as the recto-sphincteric reflex, in patients with neurogenic faecal incontinence were studied before and after pudendo-anal reflex stimulation treatment and any clinical change was noted.

Neurophysiological tests performed before and after treatment by the stimulator

<table>
<thead>
<tr>
<th></th>
<th>Pre-stimulation (mean (SEM))</th>
<th>Post-stimulation (mean (SEM))</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARL</td>
<td>55.9 (6.9) ms</td>
<td>65.9 (6.8) ms</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>PAR amp</td>
<td>37.5 (10.5) μV</td>
<td>40.5 (9.2) μV</td>
<td>&gt;0.01</td>
</tr>
<tr>
<td>MUPD</td>
<td>12.7 (3.5) ms</td>
<td>12.8 (3.4) ms</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Electromyogram</td>
<td>11.6 (4.9) μV</td>
<td>26.9 (7.3) μV</td>
<td>&gt;0.01</td>
</tr>
</tbody>
</table>

Patients
Eight women with a mean age of 47.5 (range 32-65) years took part in the study, for which ethical permission had been obtained from Lothian Health Board. Parity ranged from 1-5, with a mean of 3-1. All presented with faecal incontinence, were incapacitated socially, and had to wear incontinence pads. During the study each patient acted as her own control. All had an intact pudendo-anal reflex arc with a mean latency of 55.9 ms and a range of 47.2-69.4 ms (Table). The normal latency was mean (SD) of 39 (5.8) ms.

Methods
All measurements were performed at the initial presentation and were repeated after completing an eight week trial of electrical stimulation.

Manometry
A standard water filled microballoon system with external transducer measured the anal canal pressure by a 1 cm station pull through technique. The anal sphincter high pressure zone reflected the functional length of the anal sphincter, whose maximum resting pressure was recorded. The reflex contraction pressure of the external sphincter during a maximum cough was recorded at the point of maximum resting pressure, as was the maximum voluntary squeeze pressure of the sphincter.

Manometric recordings were also made of the inhibitory fall, as the recto-sphincteric reflex, in the resting pressure within the anal canal on rapidly distending the rectal ampulla with a balloon containing 50 ml of air. The anal sphincter pressure was also measured in response to dorso-genital nerve stimulation at the parameters to be used in the subsequent treatment.

Electrophysiology
An anal plug electrode was used with an electromyographic integrator to obtain amplitude measurements of the external anal sphincter resting electromyogram and the electromyo-
gram was also recorded during dorsal nerve stimulation. The pudendo-anal reflex latency and the response amplitude were recorded after applying over one hundred consecutive synchronised impulses to the dorso-genital nerve using an electromyographic multi-function apparatus (Medelec MS 92a, Woking, Surrey, England). The mean motor unit potential duration of the external anal sphincter was calculated from the mean of 20 motor unit potential durations taken at four sites around the anal sphincter circumference. These were obtained with a concentric needle electrode, using the signal trigger and delay function of the recording equipment. The number of phases in each motor unit potential were counted and the fraction or overall percentage of polyphasic units was calculated for each subject. Each part of a motor unit which lay between two crossings of the base line, including the part of the potential between the onset and the first crossing, was termed a phase. A polyphasic unit has greater than four phases. Anal sphincter mapping was performed at the time of motor unit potential duration acquisition using a concentric needle electrode to show that the external anal sphincter ring was intact in all cases.

**ELECTRICAL STIMULATOR**

The portable stimulator, which has a rechargeable nickel cadmium battery power source, provided a train of square wave stimuli to the dorso-genital nerve with fixed frequency of 1 Hz and a duration of 0.1 ms (Fig 1). Saline-soaked felt electrodes were used to apply the skin stimulus in the mid-line at the base of the clitoris identical to that used for the pudendal reflex test. A sub-maximal tolerable stimulation voltage of mean (SD) 135 (15) V was used, which was two or three times the sensory threshold. The immediate effect of activating the stimulator was to cause a significant rise (n=8) in the external anal sphincter electromyographic activity from mean (SEM) 11.6 (1.7) μV to 44.9 (1.9) μV (p<0.01), with a corresponding significant rise in the anal canal pressure from mean (SEM) 49.1 (4.0) cm H₂O to 89 cm (10.4) cm H₂O (p<0.01). Treatment lasted for five minutes on three occasions per day for an eight week course and was self-administered.

**STATISTICS**

The statistical evaluation for the measurements of the high pressure zone, maximum resting pressure, maximum voluntary squeeze contraction, and cough reflex contraction pressure was done by a Student's t test using logarithm conversion of the data of the paired observations before and after treatment. The remaining data were analysed by the Wilcoxon signed rank test for paired data.

**Results**

**MANOMETRY**

The anal canal high pressure zone, representing functional anal sphincter length (Fig 2), was increased from mean (SEM) 1.9 (0.2) cm to 2.6 (0.3) cm after the period of stimulation, but not significantly (p>0.05).

The patients with faecal incontinence had individual resting pressures below 60 cm H₂O, which represented their "continence threshold." In the anal canal this pressure was significantly increased from mean (SEM) 49.1 (4.0) cm H₂O to 89 cm (10.4) cm H₂O.
Use of the pudendo-anal reflex in the treatment of neurogenic faecal incontinence

The pudendo-anal reflex latencies with a mean (SEM) of 52.9 (2.4) ms were prolonged when compared with the normal range of 39 (0.94) ms, and were indicative of neurogenic injury (Table). The pudendo-anal reflex response amplitude (Table) was significantly increased from mean (SEM) 37.5 (3.7) μV to 49.5 (3.3) μV (p<0.01) after the period of stimulation.

The motor unit potential duration of the external anal sphincter was prolonged or widened with a mean (SEM) of 12.7 (1.2) ms when compared with the accepted normal range of 6.9 (0.2) ms (Table). There was also a high number of polyphasic motor unit potentials recorded from the external anal sphincter in the treated subjects with a mean (SEM) of 25.9 (9.4)%, the normal being 12%, both of which results are in keeping with reinnervation of the muscle after a previous neurogenic insult. The motor unit potential duration values were not affected by the course of electrical stimulation with a mean (SEM) of 12.7 (1.2) ms before and 12.8 (1.2) ms after stimulation (p>0.05).

The resting or basal integrated electromyogram of the external anal sphincter was increased significantly from mean (SEM) 11.6 (1.7) μV to 26.9 (2.6) μV after the course of stimulation. The external anal sphincter electromyographic response and the pressure responses to activation of the stimulator were also retested. There was a significant increase in the electromyographic response (n=8) from mean (SEM) 44.9 (4.9) μV to 72.3 (5.4) μV (p<0.01) with a concomitant significant increase in the pressure response from to 61.2 (4.5) cm H₂O (p<0.01) after the course of electrical stimulation (Fig 3).

The pressure elicited by the reflex contraction of the external anal sphincter in response to coughing, the cough reflex contraction pressure (Fig 4), was significantly increased from mean (SEM) 80.6 (8.2) cm H₂O to 106.1 (11.2) cm H₂O after the period of stimulation (p<0.01).

The maximum voluntary squeeze contraction of the external anal sphincter (Fig 5) was also increased significantly from mean (SEM) 112 (12.1) cm H₂O to 150 (17.3) cm H₂O after the period of stimulation (p<0.01) (Table). The anal canal pressure reduction which followed provoking an internal sphincter recto-sphincteric reflex was not significantly altered by the course of dorsal nerve stimulation (from mean (SEM) 43.8 (9.9) cm H₂O to 45.4 (9.1) cm H₂O after treatment).

Electrophysiology

The pudendo-anal reflex latencies with a mean (SEM) of 52.9 (2.4) ms were prolonged when compared with the normal range of 39 (0.94) ms, and were indicative of neurogenic injury (Table). The pudendo-anal reflex response amplitude (Table) was significantly increased from mean (SEM) 37.5 (3.7) μV to 49.5 (3.3) μV (p<0.01) after the period of stimulation.

The motor unit potential duration of the external anal sphincter was prolonged or widened with a mean (SEM) of 12.7 (1.2) ms when compared with the accepted normal range of 6.9 (0.2) ms (Table). There was also a high number of polyphasic motor unit potentials recorded from the external anal sphincter in the treated subjects with a mean (SEM) of 25.9 (9.4)% the normal being 12%, both of which results are in keeping with reinnervation of the muscle after a previous neurogenic insult. The motor unit potential duration values were not affected by the course of electrical stimulation with a mean (SEM) of 12.7 (1.2) ms before and 12.8 (1.2) ms after stimulation (p>0.05) (Table).

The resting or basal integrated electromyogram of the external anal sphincter was increased significantly from mean (SEM) 11.6 (1.7) μV to 26.9 (2.6) μV after the course of stimulation. The external anal sphincter electromyographic response and the pressure responses to activation of the stimulator were also retested. There was a significant increase in the electromyographic response (n=8) from mean (SEM) 44.9 (4.9) μV to 72.3 (5.4) μV (p<0.01) with a concomitant significant increase in the pressure response from

Figure 3: The maximum resting pressure recorded in the anal canal before and after the course of dorsal genital nerve stimulation, showing p value and SEM.

Figure 4: Maximum pressure recorded in the anal canal during the reflex response to a cough before and after the course of dorsal genital nerve stimulation, showing p value and SEM.

Figure 5: The maximum pressure recorded in the anal canal during a maximal voluntary squeeze contraction of the sphincter before and after the course of dorsal genital nerve stimulation, showing p value and SEM.
marked clinical improvement and became continuous (SEM) 8.9 (10-4) cm H₂O to 128 (13.3) cm H₂O (p<0.01). Seven of the eight subjects had after stimulation.

The pelvic floor and external anal sphincter at rest are in a state of continuous tonic contraction, dependent on a spinal reflex arc completed through the conus medullaris by afferent and efferent pathways in the sacral 2, 3, and 4 segments of the spinal cord. The integrity of the arc can be tested by the pudendo-anal reflex, elicitation of which, in patients with faecal incontinence, produces a measurable contraction of pelvic floor and external sphincter but with an increased latency from stimulation to response. This has been used as an indicator of neurogenic damage. Traction injury to the pudendal and pelvic nerves is associated with dysfunction of the pelvic floor and external anal sphincter which can result in faecal incontinence. Injury to these nerves also occurs during excessive straining with perineal descent such as occurs during labour. Both types of injury tend to be incomplete, with preservation of the anatomical pathway sufficient for elicitation of the reflex and for using it for treatment. When there is a partial denervation the remaining nerve fibres attempt to reinnervate the muscle fibres by sprouting. Reinnervation of the pelvic floor can take up to two years to be complete depending on the site and degree of the nerve injury.

The women in this study all had reduced spontaneous activity in the external anal sphincter at rest, as was reflected in the low spontaneous integrated electromyographic activity. There was also a weak reflex pressure response to coughing and a reduced voluntary squeeze contraction of the external anal sphincter. This manometric picture coupled with the electromyographic evidence of prolonged pudendo-anal reflex latency, prolonged mean motor unit potential duration, and increased polyphasic potentials confirm the neurogenic nature of the external anal sphincter dysfunction. Where there is a normal rectosphincteric reflex, rectal filling relaxes the internal anal sphincter. There is then little compensatory action of the external sphincter, which is demonstrably weaker in its barrier action as shown by the poor pressure responses to voluntary and stress reflex contractions of the striated muscle.

Treatments for neurogenic faecal incontinence reflect the spectrum of the condition, which ranges from occasional soiling to frank incontinence. Dietary changes and medication have been advocated to give some predictability of bowel habit. Pelvic floor exercises with physiotherapy are used for urinary stress incontinence but the results are variable. Voluntary sphincter responses can be improved by training devices, and biofeedback has been claimed to be effective.

The surgical procedure of post-anal repair was devised by Parks, who reported results of 72% fully continent and 12% continent for solid stool, although Keighley reported a lower figure for full continence of 63% with a further 21% continent for solid stool. The use of electrical stimulation for diagnosis in patients with denervated muscle has been practised for over a hundred years. The application of Faradic stimulation for the therapy of the anal sphincter has been regarded as unpleasant and without much effect, and Caldwell designed an implantable device for anal sphincter stimulation but with the serious technical problem of cable breakage.

The present method of stimulating the pelvic floor and external anal sphincter makes use of the pudendo-anal reflex and has followed from the observation that the external sphincter contracts during the recording of the reflex. The reflex shows no signs of habituation over several minutes of stimulation. A stimulator was therefore designed to produce trains of stimuli similar to those used in the test situation.

All the women in the study were shown to have neurogenic faecal incontinence due to pudendal nerve neuropathy and had a prolonged but intact pudendo-anal reflex before the period of electrical stimulation of the pudendo-anal reflex. After eight weeks of treatment seven out of eight subjects became fully continent of faeces and flatus while one remained continent of flatus only. There was no change in the pudendal reflex latency or in the length of the sphincter. The maximum resting anal canal pressure was measured above the 60 cm H₂O pressure which was the 'continence threshold' for the eight patients and the 'protective' cough and squeeze pressures associated with the external sphincter activity were significantly improved.

The improvement in sphincter function is reflected in the enhanced resting electromyogram, which should help raise the spontaneous activity to that in a normal external anal sphincter. The effectiveness of the return of sphincter function needs explanation. It may have resulted from hypertrophy of the remaining innervated muscle fibres giving the sphincter an enhanced activity and thus perhaps making the subjects more aware of its contraction. There was widening of the motor unit potential duration in some patients but this was not significant, indicating that further or reinnervation of the sphincter is an unlikely mechanism. Loss of tone in the pelvic floor could perpetuate the lack of spontaneous activity in the spinal reflex arc since afferent input to the sacral cord is essential for its activity to persist. Simple tightening of the pubo-rectalis portion of the pelvic floor in a post-anal repair, for example, would not persist unless the muscle could actively maintain this position afterwards and electromyographic studies show increased resting activity after the repair in keeping with a reactivation of the pudendo-anal reflex arc. The raised electromyographic and pressure levels during the activation of the stimulator at the end of treatment showed how far a two months' course of treatment can build up these related effects.

In neurogenic faecal incontinence, the
pudendo-anal reflex is almost always present though prolonged, and its presence must be confirmed before an electrical sphincter stimulator dependent on it is used. The evidence suggests that this reflex can be harnessed by repetitive electrical stimulation to aid the restoration of the control of defaecation. The action is likely to be due to stimulation of the external anal sphincter rather than the internal sphincter. The mean basal pressure in the anal canal, which measures both sphincters, has risen probably not changed because the values obtained on inhibiting it in the recto-sphincteric reflex were not increased. Therefore, it can be deduced that the pressure effect is predominantly on the external sphincter, perhaps accompanied by one on the pelvic floor.

This type of stimulation differs from Faradism, which has been abandoned because it is short-lived and its effects were achieved through the stimulation of local nerve endings only. Studies are proceeding to ascertain the contribution of the present method of pelvic floor stimulation in promoting clinical effects such as the duration of continence and its associated pressure changes, including whether reflex stimulation can be applied to pudendal neuropathy of varying degrees of severity.

Mr N R Rinnie was supported by a Scottish Hospital Endowments Research Trust grant (HERT 720). Dr M Papachrysostomou is supported by the Scottish Home and Health Department Biomedical Research Committee.

Effect of hysterectomy on bowel function

T Taylor, A N Smith, P M Fulton

Hysterectomy is a common, comparatively safe operation. Many complications are known, but its possible relation with bowel function is less well reported. We performed a case-control study to see whether hysterectomy had any long term effect on bowel function, and whether this was associated with altered urinary function.

Patients, methods, and results

We studied women in two general practices in north Edinburgh who had had a hysterectomy for benign disease two to eight years previously. Each woman was randomly matched by age and sex with another woman from the same practice. By reading practice records we excluded from the control group women who had had extensive abdominal operations and those with the irritative bowel syndrome. We devised a simple questionnaire to assess bowel function. It was adapted from those used in other studies² and validated in a sample of the women. One hundred pairs of women were sent questionnaires; 96 women who had had a hysterectomy and 95 controls responded, giving 91 matched pairs. Their age range was 32 to 63 (mean 51.4) years. At least 75 of every 3rd day bowel motions were sent questionnaires; 96 women who had had a hysterectomy and 95 controls responded, giving 91 matched pairs. Their age range was 32 to 63 (mean 51.4) years. At least 75 of every 3rd day bowel motions

Patients who had had a hysterectomy more commonly reported infrequent bowel motions. Fourteen of these women had a bowel motion every four days or less, compared with six controls (Wilcoxon signed rank test on paired data, p<0.05). The women who had had a hysterectomy were more likely to use laxatives and have hard stools, although the differences between the groups were not significant. Twenty one women who had had a hysterectomy but only 10 controls said that they were constipated when the other member of the pair did not. This difference, although not significant, was unlikely to have occurred by chance (p=0.07, McNemar's test). Fifteen women who had had a hysterectomy but only four controls had consulted a doctor about constipation (Wilcoxon signed rank test on paired data, p<0.05, McNemar's test).

We thank Professor John Cooper and other members of the Nottingham case register, particularly Dr Sarah White, Pat Mounser, Norah Davis, and Richard Gancaryzk, for their help in preparing and checking data from the case register for this survey in statistical bulletins. We also thank Karen Robinson of the Department of Health and Social Security for help in obtaining national figures and for estimating the average number of beds used daily in NHS mental health hospitals.

References


(Accepted 30 May 1989)
may take large amounts of laxatives for postoperative constipation, leading to the "catarctic colon." If this had been so in our study we would have expected more use of laxatives by the women who had had hysterectomy than we found, although such use might have been underreported deliberately. Another possible mechanism is pelvic autonomic denervation due to an intraoperative manoeuvre, traction during the operation, or realignment of the pelvic organs after removal of the uterus.

Urinary dysfunction is a well recognised complication of hysterectomy and is thought to be due to disruption of the nerve supply to the bladder. We found a highly significant association between persistently reduced bowel frequency and persistently increased urinary frequency after hysterectomy. This supports the hypothesis that they may have a common aetiology—namely, autonomic denervation of both viscera, which have a closely related nerve supply in the pelvis.

We thank Dr A A Robertson, Dr A Donald and partners, Dr M A Eastwood, and Mr J Knowles (medical records officer) for their help with this study. We also thank Dr J W Yarnell for giving us a copy of his questionnaire.


(Accepted 29 April 1989)

---

Radioiodine in human thyroid glands and incidence of thyroid cancer in Cumbria

Colin Bowlt, Peter Tiplady

Concern is increasing over the association between ionising radiation and cancers in populations living close to nuclear installations such as Sellafield in Cumbria. Because the external radiation in Cumbria is only marginally above the national average any appreciable additional dose would have to come from manmade sources of radioactivity.

Both iodine-129 and iodine-131 are discharged from Sellafield into the sea and the atmosphere and since the early 1960s have probably contributed equally to the small additional dose to the thyroid above that of natural background radiation. We measured 129I activity in thyroid glands in the population of Cumbria and related them to the incidence of thyroid cancer in the area. Inevitable delays in carrying out these measurements excluded an assessment of 131I, which has a half life of eight days (that of 129I is 15 million years).

Methods and results

Measurements were made on 130 thyroid glands taken opportunistically at necropsy from adults (mean age 67) dying from various causes in Cumbria between November 1984 and September 1987. The thyroid samples were homogenised and dried, and 129I activity was measured in a thin walled scintillation detector over 100 minutes. Background levels (which varied during the examination) were subtracted from the count rate for the sample, and occasional negative values resulted. The figure (left) shows 129I activity in individual thyroid glands plotted against the distance of the patients' homes from Sellafield. Levels of radioactivity decreased with distance (Spearman's r = -0.392, p<0.001).

We also examined the incidence of thyroid cancer, using data from the Northern regional cancer registry for 1969-86. Age standardised registration rates and ratios were calculated by applying the national values for the midpoint of the period. Surprisingly, there was a positive correlation between the distance from Sellafield and the incidence of cancer, with higher incidence being found with greater distance (Spearman's r = 0.541, p<0.0007) (figure (right)). In the 40 out of 285 parishes where thyroid cancers occurred the incidence varied from 0.39 to 40.46/100 000. Calculations using the Poisson distribution, however, showed only two parishes with significant increases in thyroid cancer: one was 16 km from Sellafield (two cases registered v 0.1 expected, p<0.01) and the other 24 km away (four cases registered v 0.5 expected, p<0.01). In Cumbria

---

![Image of map showing Cumbria and Sellafield with radioactivity levels and thyroid cancer incidence data]

*Left: 129I activity in thyroid tissue taken at necropsy related to distance of patients' homes from Sellafield. Right: registrations of thyroid cancer in Cumbria, 1969-86. SRR = Standardised registration ratio*
Effects of hysterectomy on bowel and bladder function

T. Taylor¹, A. N. Smith² and Mary Fulton³

¹ Gastrointestinal Unit, University of Edinburgh, Western General Hospital, Edinburgh
² University Department of Surgery, Western General Hospital, Edinburgh
³ Department of Community Medicine, University of Edinburgh Medical School, Edinburgh, UK

Accepted: 2 August 1990

Abstract. A case control study compared the bowel habit of 91 post-hysterectomy women with paired controls from the same family doctor practice. More cases had an abnormal bowel frequency, a firmer stool consistency and assessed themselves as having abnormal bowel function, predominantly constipation after hysterectomy, than controls. Significantly more cases than controls had consulted a doctor because of constipation but there was no significant difference in laxative usage. There was a significant short-term association between decreased bowel frequency and increased urinary frequency after hysterectomy. This became highly significant in those patients who developed chronic symptoms. Oophorectomy, unilateral or bilateral, did not significantly affect bowel habit other than to intensify the change in stool consistency. The hypothesis is discussed that the post-hysterectomy effects on bowel and bladder function may have a common aetiology in a degree of autonomic denervation of both viscera.

Methods

One hundred women who had had a hysterectomy for benign disease 2–8 years previously were identified in two Edinburgh practices. An upper age limit of 65 at the time of entry to the study was set. The plan of the study was to compare hysterectomy cases with controls from the same area and hence social background. Each case was age-sex matched by taking the next woman born in that year from the practice list. Ninety-one pairs of cases and controls agreed to participate in the study and returned a questionnaire given to each member of the pair. Women with major abdominal surgery were excluded from the control group as were those irritable bowel syndrome.

The questionnaire which was a simple, self-administered one, was devised to allow assessment of both bowel and urinary function. It included a brief section on past health and current medication as well as asking about frequency of defaecation, stool consistency, laxative use and had a self-assessment of bowel habit in which the subjects were asked whether they considered themselves to be normal, constipated or to have loose motions. They were also asked if they had consulted a doctor about constipation, experienced any urinary dysfunction or incontinence, and whether there was any postoperative effect of hysterectomy on bowel and urinary frequency. The questionnaire was adapted from ones used in other studies for assessing bowel and bladder function [5, 6].

Ten women chosen at random for direct interview showed no significant difference in their responses from those in their postal questionnaire. Ten other women with severe symptoms, when reinterviewed, showed 29% responses indicating more severe constipation than formerly, 5% with less severe symptoms and 66% identical responses to the questions formerly asked. A comparative group

Introduction

A number of female patients presenting with severe constipation date its onset from a hysterectomy. Thirty-four such patients have been investigated by us in the past two years as tertiary referrals for the assessment of colorectal function. Increasingly, they require surgical management by sub-total colectomy when medical measures have failed.

Long-term sequelae of hysterectomy on bladder function, notably frequency and incontinence, are well documented [1, 2]. It is claimed that their severity increases with the extent of the pelvic procedure but possible effects on bowel function have been studied less extensively [3, 4].

Intractable constipation after hysterectomy could be the severe end of a spectrum of more general bowel disorder and it remains to be determined how many supposedly unaffected hysterectomy patients have a changed bowel habit. Gurnari et al. [3], reviewing this subject in 108 female patients after gynaecological surgery, showed that chronic constipation and urinary incontinence occurred more frequently the more radical the operation performed. They attributed the increased risk of complications to surgical injury of intrapelvic nerve fibres. We have described in a preliminary report the frequency of posthysterectomy constipation [4]. This study describes in greater detail aspects of the bowel disturbance and its relationship to altered urinary function after hysterectomy and examines whether oophorectomy done at the same time contributes to the effects on pelvic function.
of 20 women treated by D and C at a similar time to the hysterectomy group, stated that this procedure had had no effect on their bowel function.

Statistical analysis

Statistical analysis was by a chi-squared test or a McNemar’s test for paired comparisons.

Results

Bowel habit of controls

The bowel habit of the control group was broadly comparable to that of the well known study of Connell et al. [5] as indicated in Table 1, though the questions asked and the composition of the groups were slightly different.

Comparison of bowel function between post-hysterectomy cases and controls

Table 1 established various criteria for normality, for example, a range of bowel frequency from three times per day to a bowel movement every third day, the passage of a formed stool and little recourse to laxatives. Matched pairs of cases and controls were analysed in respect of whether they fell into a ‘normal’ or an ‘abnormal’ category by the above criteria.

(a) Bowel frequency. Eighteen cases but only 7 controls had an abnormal bowel frequency when their pair did not (p<0.05, McNemar’s test); the majority had a bowel frequency of every fourth day or less (14 cases, 6 controls).

(b) Stool consistency. Twenty-six cases but only 9 controls reported abnormal stools when their pair did not (p<0.01, McNemar’s test).

(c) Laxative use. Fifteen cases used laxatives fortnightly or more frequently but only six controls did so when their matched pair did not. The differences were not statistically significant (p>0.05, McNemar’s test).

Patients’ own assessment of bowel function

Twenty-seven cases felt that they had an abnormal bowel function after hysterectomy but only 10 controls, when their pair had normal bowel function. This difference was highly significant statistically (p<0.01, McNemar’s test). Furthermore, 20 of the 27 assessed themselves as constipated but only 8 of the 10 controls. Fifteen cases but only 4 controls assessed themselves as severely constipated because they had consulted a doctor because of constipation, when their pair had not, the difference being significant (p<0.05, McNemar’s test).

Correlation of bowel and bladder dysfunction

Cases were asked if their bowel or urinary frequency had been altered after hysterectomy (Table 2). Twenty-two claimed that their bowel frequency had reduced and 37 out of 85 said that their urinary frequency had increased in the short term after the operation, including 15 who noticed both changes. There is a significant association (p<0.05, Chi-squared test) between decreased bowel and increased urinary frequency. Not all of these changes persisted, however. Ten claimed that they had a permanent increase in urinary frequency (Table 3), including 8 who had noticed both changes. This association was highly significant (p<0.01, Chi-squared test).

Correlation of bowel function after oophorectomy

Bowel function was examined in hysterectomy patients, 56 of whom had had an abdominal hysterectomy alone and compared with 33 patients who had had an oophorectomy in addition to their hysterectomy. Two patients who had had a vaginal hysterectomy were excluded from analysis in this section. Bowel frequency, laxative use and self-assessment of bowel function

| Table 1. Control group: bowel habit compared with Connell et al. (1965) [5] |
|-----------------|-----------------|-----------------|-----------------|
| Bowel frequency | Formed stool    | Total number    | Laxatives more   |
| 3x daily        | every 3rd day   | using laxatives | often than weekly |
| Present study   | 92%            | 81%            | 22%             | 4.5%          |
| Connell et al.  | 98% a          | 90%            | 34.4% b         | 16.8% b       |
| (1965) [5]      |                |                |                 |               |
| a Varied 3 times daily to 3 times weekly |
| b Age 30–69 |

<table>
<thead>
<tr>
<th>Table 2. Post-hysterectomy: correlation of short-term changes of bowel and bladder function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary frequency</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Increased</td>
</tr>
<tr>
<td>Not increased</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Not increased</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>(x², p&lt;0.05)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Post-hysterectomy: correlation of long-term changes of bowel and bladder function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary frequency</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Increased</td>
</tr>
<tr>
<td>Not increased</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Not increased</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>(x², p&lt;0.01)</td>
</tr>
</tbody>
</table>
showed no statistically significant difference between the two groups. Nevertheless, women who had an oophorectomy in addition to their hysterectomy were more likely to have an abnormal, firmer stool consistency; 10 women had abnormal stools after oophorectomy compared with 1 control when their pair had not ($p<0.05$, McNemar’s test).

There was no significantly increased tendency to have associated bowel and bladder changes in patients who had an oophorectomy and a hysterectomy compared to hysterectomy alone. Unilateral and bilateral oophorectomy were compared for bladder and bowel disturbance and did not have any statistically significant differences but the numbers were small.

**Discussion**

Bowel function varies markedly between populations and within a given population. The bowel habit of our control group is similar to those previously reported [5], the largest difference being a reduction in the use of laxatives, perhaps part of the general decline in their use and the general popularity of high-fibre diets [7]. Our previously recorded results showed that women who have had a hysterectomy were more likely to have less frequent bowel actions than an age-matched control group with a trend towards constipation [4]. The present survey suggests that women who have had a hysterectomy are more likely to have an abnormal bowel function which extends not only to an abnormal frequency of defaecation and abnormal stools but to an increased tendency to consult a doctor about constipation. The bowel disturbance is not, however, severe enough to require increased recourse to laxative use.

Bladder and bowel symptoms were associated in our group of patients. The increased frequency of micturition and decreased frequency of bowel action presenting after operation but not before suggest a common aetiology for the two problems. The one considered most likely to explain this occurrence is an interference of the autonomic innervation of both viscera at risk of trauma in the pelvis. The recovery of some of the cases with an increased association of the two changes in the remainder with the passage of time intensifies the suspicion of a possible link through autonomic nerve disturbance at operation.

Other possible mechanisms to be considered are the psychological disturbance of hysterectomy but recent prospective studies have shown that women are not likely to become depressed after hysterectomy [8] and are even likely to be less depressed than pre-operatively [9]. Some women may initially take laxatives for post-operative constipation and precipitate a vicious circle of laxative abuse causing bowel atony resulting in the so-called ‘cathartic colon’. If this were so more laxative use by the cases would be expected [10].

For the cases who had had an oophorectomy, the only statistically significant difference was that women who have had one or more ovaries removed were likely to have an abnormal stool consistency. This might be taken as evidence towards a hormonal pathogenesis for changed bowel function because of a slower intestinal transit. Women with slow transit constipation have been found to be more likely to have raised serum prolactin and lower plasma oestriadiol levels [11]. Against this, it has been shown that women who have a hysterectomy have an earlier menopause [12]. There was no difference between the ages of hysterectomy cases and controls with abnormal bowel function and hysterectomy cases and controls with normal function. Cases and controls in this study had a similar obstetric history with the consequence that obstetric difficulty did not contribute to any difference in the clinical features.

A mechanism for a similar pelvic nerve disturbance to the one we envisage has been described by Catchpole [13] in relationship to lower anterior resection. After this operation he found evidence of a partial autonomic denervation of the lower bowel. Cases of intractable constipation after hysterectomy have been found to have a seriously disturbed motility in the left colon but with no upset in pelvic floor or sphincter function [14].

The parasympathetic innervation of the urinary bladder and left colon is derived from the sacral segments S2, 3 and 4, via the pelvic nerves from the inferior hypogastric plexus, and nerve fibres run forwards to innervate the bladder and lower rectum and also pass upwards out of the pelvis to innervate the upper rectum and left colon. These fibres carry sensory fibres from both viscera. It is conceivable that damage to the autonomic innervation during pelvic surgery can result in functional disorders of the colon from possible damage to the inferior hypogastric (pelvic) plexus which, in the female, is placed on each side of the rectum, uterine cervix, vaginal fornix and posterior aspect of the urinary bladder and extends into the base of the broad ligaments of the uterus. Furthermore, Christensen and Schulze-Delrieu describe intramural pelvic nerves which enter the bowel wall in the pelvis and ascend through as much as 80% of the length of the colon [15]. They describe numerous ganglia within the pelvic parasympathetic outflow, some lying down within the pelvic nerves on the mucosal surface, even of the distal colon and others distributed throughout the pelvic plexus. The location and orientation of these intramural pelvic nerves make them potentially subject to trauma. Events like constipation and childbirth, they suggest, could stretch them to produce a mechanical cause for a neuropathy. We believe that a similar stretch mechanism causing pelvic nerve damage may be responsible for the bowel function changes after hysterectomy.
References


Mr. A. N. Smith
University Department of Surgery
Western General Hospital
Edinburgh EH4 2XU
UK
Disordered colorectal motility in intractable constipation following hysterectomy

Colorectal and anal sphincter motility and electrophysiology were investigated in 14 women with profound constipation following hysterectomy and compared with an asymptomatic group of control subjects. Twelve patients complained of significant urinary symptoms. No differences in the motor function of the anal sphincters were detectable. The latency of the pudendoanal reflex was unchanged after hysterectomy. Proctometrograms demonstrated significantly increased rectal volumes and compliance in the hysterectomy group together with deficits of rectal sensory function. In the base state a significant proximal-to-distal sigmoid colon motility gradient existed only in the control group. Following stimulation with Prostigmin®, this gradient was enhanced in the control group but paradoxically reversed in the hysterectomized patients, thus constituting a functional obstruction. Denervation supersensitivity was demonstrable in two patients tested with carbachol provocation but not in control subjects. These findings suggest dysfunction in the autonomic innervation of the hindgut in some patients who had undergone hysterectomy, resulting in severe constipation.

Keywords: Autonomic nerves, constipation, hysterectomy, denervation hypersensitivity

Hysterectomy is a frequently performed operation with few outward sequelae and the results of surgery are usually judged with regard to the pelvic pathology for which the procedure was undertaken. Descriptions of functional side-effects following the operation have been mainly confined to the lower urinary tract1-7 and were initially attributed to coincidental urinary tract infection or alteration in the support of the bladder offered by the uterus and pelvic floor. Injury to the innervation of the urinary bladder and its sphincters, however, may play an important part in the development of these complications8,9.

This study was prompted by the observation that some patients referred for investigation of intractable constipation appeared to have developed this problem following pelvic surgery and related their late-onset constipation to hysterectomy. These patients appear to represent only a very small proportion of women who undergo the operation for various disorders. In the light of previous observations of urological1,2,4,5,6,11 and colorectal12-14 dysfunction following some forms of pelvic surgery, the motility of the sigmoid colon, rectum and anal sphincters was studied under basal and stimulated conditions to explore the physiology of constipation following hysterectomy.

Patients and Methods

Formal approval was obtained from the ethical committee of the North Lothian District, Lothian Health Board, Edinburgh, in June 1985 for the investigations described in this study. Informed consent was obtained from all participants.

Physiological studies of the motility of the sigmoid colon, rectum and anal sphincters were performed in 14 women suffering from intractable constipation following hysterectomy and were compared with results from an asymptomatic group of matched control subjects. The mean age of the patients with constipation was 36±8 years and the mean duration of symptoms was 6±1 years. All patients related the onset of their severe constipation to hysterectomy. This had been performed via the abdominal route in 12 patients and vaginally in two, all for benign disease. Oophorectomy had not been performed in any of the patients. The frequency of defaecation ranged from one spontaneous bowel motion per week to no bowel motion in a whole month without the use of enemas. Dietary and drug adjustments to relieve the constipation had proved unsuccessful. Twelve of the patients had troublesome urinary symptoms necessitating urodynamic assessment. These comprised stress incontinence in five patients, frequency in three, urge incontinence in two and atonic retention in two.

Fourteen approximately age-matched women with minor anorectal conditions gave consent for similar studies. None of them had suffered from constipation.

Radiology

Double contrast barium enemas were performed in all the patients. The control group was not subjected to this investigation.

Manometry

The manometric studies were conducted in a fasted state in the morning, the patients having been given the opportunity to empty the bowel beforehand. No other bowel preparation was used. All except necessary oral medications were withdrawn 48 hours before the motility investigations. Anal sphincter manometry was performed using conventional methods9,15 to measure basal and squeeze pressures, sphincter length and the presence of the rectosphincteric reflex. Proctometrograms16 were obtained in all patients to measure volumes and pressures at sensory threshold, constant sensation and maximal rectal distension. Rectal compliance was calculated from the trace obtained as mL/cm Hg O. Motility of the sigmoid colon was monitored by means of a triple-lumen soft-rubber tube (internal diameter of each lumen was 1 mm) placed via a sigmoidoscope, the side openings lying at a distance of 15, 20 and 25 cm from the anal verge. The water-filled tubes were connected via external pressure transducers to a multichannel chart recorder, the system being regularly flushed throughout the test. Basal motility index was calculated from the tracings obtained over a 20 min period using Connell’s method9,17. The heights, waves and frequency of the motility traces were converted to x-y co-ordinates by the use of a computer (Hewlett-Packard 85 with Summagraphics attachment, Hewlett-Packard, West Lothian, UK) for mathematical computation of the motility indices. Prostigmin® (neostigmine; Roche Products Ltd., Welwyn Garden City, UK) was then injected subcutaneously in a dose of 0.01 mg/kg and the motility was further monitored over a similar period of time, beginning 5 min after the Prostigmin injection. Two subjects in each group also underwent motility studies following a subcutaneous injection of carbachol (500 μg).
Table 1 Manometric and electrophysiological data in 14 hysterectomized and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hysterectomy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of anal high pressure zone (cm)</td>
<td>2.7(0.3)</td>
<td>2.6(0.5)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Maximum anal basal pressure (cmH(_2)O)</td>
<td>92.3(5.1)</td>
<td>91.4(5.6)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Anal pressure response to cough (cmH(_2)O)</td>
<td>106(26)</td>
<td>89(31)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Maximum anal squeeze pressure (cmH(_2)O)</td>
<td>120(16)</td>
<td>108(36)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Rectal sensory threshold (mH(_2)O)</td>
<td>224(120)</td>
<td>420(80)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Rectal constant sensation (mH(_2)O)</td>
<td>306(68)</td>
<td>452(180)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Rectal maximal tolerable volume (mH(_2)O)</td>
<td>478(86)</td>
<td>680(120)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Rectal compliance (mL/cmH(_2)O)</td>
<td>9.2(4.3)</td>
<td>24(12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Latency of pudendoanal reflex (ms)</td>
<td>37.2(5.8)</td>
<td>39(6.2)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Values are mean(s.e.m.)

Figure 1 Basal colonic motility in 14 hysterectomized patients (●) and in controls (○). * P>0.1

Electrophysiology

Seven patients and all controls underwent measurement of the latency of the pudendoanal reflex as an index of the integrity of the conus medullaris and its somatic outflow to the anal sphincter musculature. The phenomenon of anismus was tested for in all subjects by recording the integrated electromyograph of the sphincter musculature with an anal plug electrode, and an anismus index was calculated.

Statistics

Statistics were performed using Wilcoxon’s non-parametric analysis. Paired comparisons were made for the motility indices before and after administration of Prostigmin, the remaining data being analysed by the unpaired formula.

Results

Radiology

Double contrast barium enemas showed no abnormality in 11 patients, megacolon in one and a redundant colon in two patients.

Manometry

Table 1 compares the manometric and electrophysiological data between the two groups. There were no significant differences in sphincter function. Rectal compliance and volumes appeared significantly increased in the group that had undergone hysterectomy, some of these patients demonstrating severe defects in rectal perception to distension.

The studies on colonic motility gave the following three observations. First, in the basal or resting state a significant proximal-to-distal motility gradient was demonstrable in the control group but not in the hysterectomy group (Figure 1). Second, following stimulation with Prostigmin the proximal-to-distal motility gradient was further accentuated in the control group, increases in motility occurring at all three sites. In the hysterectomy group, a lesser increase in motility occurred and there was a paradoxical reversal of the motility following stimulation in this group, i.e. there was now a significant distal-to-proximal motility gradient (Figure 2). The cumulative motility increase with Prostigmin was significantly less in the hysterectomy group (Figure 3). Third, a qualitatively hypersensitive motility response to carbachol was demonstrable in the two patients with constipation but not in the control subjects (Figure 4).

Electrophysiology

The pudendoanal reflex latency was delayed in one patient although statistically the differences between the two groups were not significant (Table 1). There was no difference in the anismus index between the two groups.

Figure 2 Prostigmin stimulated colonic motility in 14 hysterectomized patients (●) and in controls (○). * P>0.1; ** P<0.01
Constipation following hysterectomy: A. N. Smith et al.

Discussion

Dysfunction of the urinary bladder following pelvic surgery, including hysterectomy, has been previously documented. Other forms of pelvic surgery may lead to sexual dysfunction, presumably secondary to autonomic nerve damage. The clinical observation that a small proportion of women develops intractable constipation following hysterectomy has been substantiated by a larger clinical study. The parasympathetic innervation of the urinary bladder, left colon and rectum derives from sacral segments S2, S3, and S4 via the pelvic nerves. From the inferior hypogastric plexus nerve fibres run forward to innervate the bladder and upwards and out of the pelvis to innervate the rectum and left colon. This innervation is of paramount importance in the co-ordinated contractions of the smooth muscle of the bowel and bladder. It also carries the sensory fibres to these viscera. It is conceivable that damage to this autonomic innervation during pelvic surgery may result in functional disorders of the colon.

Long and Bernstein discussed the possible sites of nerve injury during pelvic surgery, with particular reference to sexual dysfunction. The inferior hypogastric (pelvic) plexus in the female is placed on the side of the rectum, uterine cervix, vaginal fornix and anterior aspect of the urinary bladder and extends into the base of the broad ligament of the uterus; it is presumably susceptible to injury during hysterectomy. Adamson and Aird produced experimental megacolon in animals by cutting the pelvic nerves. White et al. described severe bladder and bowel dysfunction in patients with acute damage to the sacral segments of the spinal cord or the lower sacral nerves, with the development of an atonic bowel. Scott and Cantrell demonstrated functional changes in the colon following section of its pelvic parasympathetic nerve supply in the dog. These observations and those of the present study suggest that constipation in this group of patients may occur as a result of incidental injury to the autonomic parasympathetic innervation of the left colon and rectum. This conclusion is substantiated by abnormalities of bladder function noted in the same patients.

The response to carbachol is typical of denervation supersensitivity. The motility response to Prostigmin is diminished but not abolished. This would be expected in an organ with incomplete damage to its innervation. The paradoxical reversal of motility in the constipated group following Prostigmin stimulation is difficult to explain but constitutes a functional obstruction at the rectosigmoid level. Presumably, either the proximal extrinsic innervation is more susceptible to damage and/or is more sensitive to the same injury compared with the innervation to the rectum. There is good anatomical evidence to suggest that rectal motility is more...
dependent on its intrinsic innervation than the more proximal colon which has a considerable extrinsic nerve supply.\(^3\) Severance of the extramural pelvic nerves in dogs results in degeneration of the ascending intramural colonic nerve fascicles.\(^34\) Christensen and Schulze-Delrieu have suggested that these ascending nerves of the colon are potentially at risk during surgical procedures.\(^33,34\) The extramural pelvic nerves are derived from the plexus of autonomic nerves, which convey parasympathetic fibres from the pelvic plexus to the pelvic organs.\(^35\) Afferent fibres from the pelvic viscera join the pelvic splanchnic nerves, which are the main source of the parasympathetic innervation of the colon.\(^35\) The extramural pelvic nerves in dogs results in denervation of the ascending intramural colonic nerve plexus.\(^35\) Severance of the extramural pelvic nerves in dogs results in degeneration of the ascending intramural colonic nerve plexus.\(^35\)

Roe et al.\(^35\) were unable to demonstrate differences in motility between a hysterectomized constipated group and another in whom slow transit constipation had occurred de novo.\(^36\)

The lack of abnormalities at the sphincteric level is not surprising. The external anal sphincter is innervated by the somatic motor pudendal nerves and is therefore not affected by autonomic nerve damage. In this study the motor innervation of the external anal sphincter appeared functionally intact as assessed by manometric data.\(^36\) The internal anal sphincter has an extrinsic innervation which is largely dependent on the function of the intrinsic myenteric plexus which is also responsible for the rectosphincteric reflex.\(^21,24,40,41\) It must be noted, however, that the external urethral sphincter appears to be more susceptible to dysfunction following hysterectomy.\(^42\)

Resection of the rectum alone can result in motility disturbances of the left colon.\(^43\) It would seem appropriate to treat such patients by left hemicolectomy together with anterior resection of the rectum. In view of the long duration of symptoms in many patients and the resulting laxative abuse, the entire colon may become functionally abnormal due to the long-standing stasis and we prefer to perform a subtotal colectomy with ileorectal anastomosis.

The lack of abnormalities at the sphincteric level is not surprising. The external anal sphincter is innervated by the somatic motor pudendal nerves and is therefore not affected by autonomic nerve damage. In this study the motor innervation of the external anal sphincter appeared functionally intact as assessed by manometric data. The internal anal sphincter has an extrinsic innervation which is largely dependent on the function of the intrinsic myenteric plexus which is also responsible for the rectosphincteric reflex.\(^21,24,40,41\) It must be noted, however, that the external urethral sphincter appears to be more susceptible to dysfunction following hysterectomy.\(^42\)

Resection of the rectum alone can result in motility disturbances of the left colon.\(^43\) It would seem appropriate to treat such patients by left hemicolectomy together with anterior resection of the rectum. In view of the long duration of symptoms in many patients and the resulting laxative abuse, the entire colon may become functionally abnormal due to the long-standing stasis and we prefer to perform a subtotal colectomy with ileorectal anastomosis.\(^\text{[Reference 25]}\)

26. Ekstrom J, Mottberg L. Functional evidence for sparing of...
Highly selective vagotomy with duodenal dilatation in patients with duodenal ulceration and gastric outlet obstruction

S. G. Pollard, P. J. Friend, D. C. Dunn and J. O. Hunter

Department of Surgery, Addenbrooke’s Hospital, Hills Road, Cambridge CB2 2QQ, UK

Correspondence to: Mr S. G. Pollard

Since it was described in 1970-1,2, highly selective vagotomy has become an established treatment for duodenal ulceration. Many, however, would regard the presence of gastric outlet obstruction as a contraindication to the procedure3,4.

Patients and methods

Forty-two patients undergoing surgery between 1973 and 1983 for chronic duodenal ulcer and gastric outlet obstruction under the care of a single consultant surgeon (D.C.D.) are presented. All patients underwent highly selective vagotomy combined with duodenal dilatation in 34 and duodenoplasty in eight. The patients formed part of a total experience of 217 highly selective vagotomies performed during this period for duodenal ulcer disease.

In all patients an initial digital assessment of the gastric outlet was performed at operation by attempting to invaginate the gastric and duodenal walls through the lumen of the pylorus. In 50 cases this was not possible and a 2 cm gastrotomy was made in the gastric antrum and the gastric outlet measured using Hegar dilators.

Following the criteria of Kirk for the normal calibre of the gastric outlet, obstruction was defined as an outlet measuring < 15 mm in diameter at operation. In eight patients suspected of having stenosis the outlet was 15 mm or more and the gastrotomy was closed without further action.

The group with stenosis consisted of 31 men and 11 women with an average age of 48 years (range 24-70 years). The mean duration of ulcer-type pain in the group was 13.2 years (range 6 months to 30 years) and the mean duration of symptoms of gastric outlet obstruction when present was 11.5 months (range 2 weeks to 5 years).

All patients suffered chronic ulcer pain with failure of medical treatment. Thirty patients presented the clinical picture of pyloric obstruction with vomiting of food, some with a sucission splatch after eating. A further eight patients had radiological evidence of obstruction (three volumes of resting juice, dilated stomach with narrowed outlet of food in the stomach despite fasting) although clinical symptoms were not apparent. The remaining four patients were not suspected of having stenosis before operation but had a definite narrowing of the gastric outlet at laparotomy.

In the 42 patients with stenosis, the outlet was narrowed to an average diameter of 10-7 mm (range 3-14 mm) and was dilated by an average of 8-7 mm (range 4-15 mm) to an average diameter of 19-4 mm (range 15-25 mm). Splitting of the duodenum occurred during dilatation in eight. This was repaired transversely over a Hegar dilator with interrupted sutures as a single-layer duodenoplasty and an omental patch oversewn.

Insulin testing of vagal integrity on the tenth postoperative day was negative in all cases, suggesting adequate parietal cell denervation. A positive response was defined as a basal acid output of > 2 mmol/h or an increase of > 1 mmol/h following hypoglycaemic stimulation.

Each patient was reviewed annually for up to 10 years in a gastric follow-up clinic and assigned a Visick grade by a physician (J.O.H.) who was not aware whether stenosis had been present.

Results

The average length of hospital stay for the 42 patients was 7-7 days (range 4-22 days). There were no major postoperative complications and no postoperative deaths.

Of the 30 patients with symptomatic stenosis, 27 (90 per cent) had no further trouble with stenosis and 36 of the 42 in the study group (86 per cent) have had no further trouble with duodenal ulceration. Three of the 42 patients (7 per cent) have had clinical and subsequent radiological evidence of recurrent stenosis, two of whom suffered recurrent ulceration and have undergone truncal vagotomy and antrectomy. The third patient developed symptoms of transient gastric outlet obstruction without evidence of recurrent ulceration.

A further four patients have suffered recurrent ulceration alone after 1-6 years on the basis of ulcer-type pain, confirmed endoscopically. Two responded to courses of H2-receptor antagonists, one remains on long-term treatment and one patient has required a gastrectomy.

One man underwent gastrectomy for carcinoma of the gastric antrum 5 years after highly selective vagotomy.

At their most recent clinic visit, 41 patients (98 per cent) were graded Visick 1 or 2. This includes four patients who underwent further surgery (two for recurrent ulceration with stenosis, one for recurrent ulceration alone and one for gastric carcinoma) and three patients who have required H2-receptor antagonists for recurrent ulceration. One patient (2 per cent) was graded Visick 3 because of heartburn; biliary reflux was demonstrated on endoscopy.

The incidence of recurrent ulceration in the 175 patients undergoing highly selective vagotomy alone for uncomplicated duodenal ulceration during the same period was 14 per cent.

Discussion

Gastric outlet obstruction occurs in 7-35 per cent of patients with duodenal ulcer disease and is commoner in the Third...
World\(^4\). The incidence in our series was 19-4 per cent of 217 patients undergoing surgery for chronic duodenal ulcer.

Since it was first described\(^1,2\), highly selective vagotomy has become an accepted operation in the surgical treatment of uncomplicated duodenal ulceration and has repeatedly been shown in prospective randomized trials to be superior to both truncal vagotomy with drainage and selective vagotomy with drainage procedures in terms of postoperative mortality and morbidity and postvagotomy symptoms\(^6\).\(^9\).

In the presence of gastric outlet obstruction, the treatment of choice is not clear. In a recent symposium there was unanimous disapproval of the use of highly selective vagotomy in the presence of gastric outlet obstruction because of concern regarding restenosis\(^3\). Vagotomy with pyloroplasty has been advocated in preference to highly selective vagotomy with dilatation on the basis that the risks of dumping and diarrhoea are preferable to the risk of restenosis\(^4\).

The use of highly selective vagotomy with duodenal dilatation for gastric outlet obstruction from duodenal ulceration was first reported in 15 patients in 1973 by Johnson et al.\(^10\). In 1976 Kennedy reported good results from highly selective vagotomy combined with formal duodenoplasty without dilatation\(^11\). In 1978 Delaney showed that even tight stenoses could be dilated without fear of restenosis\(^12\) and that, even with long-standing outflow obstruction, gastric tone and emptying will return to normal within 3 months of highly selective vagotomy combined with duodenal dilatation or duodenoplasty\(^13\).

Our rate of recurrent stenosis compares favourably with that of other series that use digital dilatation\(^14,1\)\(^5\) and is comparable with the results of the only other group that has routinely dilated the stenosis up to 20 Fr Hegar\(^16\), i.e. beyond the diameter of the normal outlet\(^5\). The long-term results also compare favourably with those for alternative procedures\(^15\), particularly in terms of patient acceptability, although we accept the potential pitfalls of comparing our results with historical controls.

References


Paper accepted 7 May 1990
Effect of Electrical Anterior Sacral Nerve Root Stimulation on Pelvic Floor Function in Paraplegic Subjects

N. R. Binnie,* A. N. Smith,* G. H. Creasey,† and P. Edmond†

*University Department of Surgery, Western General Hospital, Edinburgh, and †Spinal Injuries Unit, Edenhall Hospital, Musselburgh, Scotland

The effect of the Brindley stimulator on pelvic floor function has been studied in seven paraplegic subjects by standard manometric, radiologic, and electrophysiologic methods. There was no difference in the maximum resting pressure in the anal canal between the stimulated group and paraplegic subjects without sacral stimulators acting as controls. The fall in pressure in response to the rectosphincteric reflex as a percentage of the original resting pressure was significantly less, indicating a proportional effect on the external sphincter. There was less descent of the pelvic floor at rest in the stimulated group, but no difference in the pudendoanal reflex latency, motor and potential duration, or resting electromyogram activity of the external anal sphincter. The maximum resting pressure in the anal canal, the pudendoanal reflex response amplitude, and the external anal sphincter electromyogram activity increased, however, with the duration of the implant. The S4 root had the dominant effect on the pelvic floor, with decreasing effects from the S3 and S2 roots on the pressure and integrated electromyogram activity generated by the external anal sphincter. The anorectal angle had not changed at rest in the group with the stimulator, but S4 root stimulation made it more acute than S3 or S2 root stimulation. The results suggest profound effects of S4 anterior root stimulation on the pelvic floor with additional effects of S3 and S2 anterior roots on pelvic function. (Journal of Gastrointestinal Motility 1991; 3(1):39–45)

Key Words: sacral nerve roots, stimulator, implant, pelvic floor, paraplegia.

Introduction

Paraplegic subjects have no voluntary control over the activation or inhibition of the pelvic floor muscles and therefore lack voluntary control of urinary and fecal continence. The Brindley anterior sacral root stimulator gives a degree of voluntary control over bladder emptying and urinary continence by its activation of the parasympathetic supply to the bladder and the somatic efferents to the pelvic floor sphincters, respectively (1). In the original study this was supplemented in a few cases by posterior nerve root division to achieve deafferentation of the bladder, thus abolishing spontaneous bladder contractions with the objective of increasing the degree of urinary continence.

Although the Brindley stimulator was introduced for the control of urinary continence, effects on bowel function are readily noticed by most patients using it. This takes the form of increased frequency of defecation, accompanied by a faster transit (2). Paradoxically, the moisture content of the fecal bolus is less, suggesting that the rapidity of transit in the colon is not uniform. Studies have shown left colon motility patterns increasing from the splenic flexure downward, and this motor activity was mainly evoked by S3 anterior root stimulation with smaller effects in the transverse colon, leading to a possible delay in transit at the splenic flexure (3). S4 anterior root stimulation contracted the pelvic floor as recorded by Varma et al. (4), suggesting that this is another area of motility holdup. The anorectal sphincters have been shown to be innervated predominantly by S4 nerve roots, with a significant contribution from S3 and a lesser one from S2, establishing a similar control to that of the urethral sphincter.
Material and Methods

PATIENTS
Seven paraplegic patients with a Brindley stimulator implant were studied. The six males and one female ranged in age from 20 to 50 years and had cord lesions from C5 to T3. All but one patient had complete lesions, and this patient had had the two S3 and S4 posterior nerve roots divided. All the subjects used the implanted Brindley stimulator to achieve bladder emptying. Continence was aided by regular voiding every 4 hours using the activated device.

The control group comprised seven paraplegic subjects of similar age and level of spinal cord injury (3). All subjects gave informed consent to a protocol agreed upon by the Ethics Committee of Lothian Health Board. The stimulator usage was as described in Binnie et al. (3). The subjects were prepared by ensuring that the rectum was empty by digital examination and manual evacuation as required before proceeding with the investigations.

STATISTICS
Each patient was his own control in the “on-off” situation; in these cases the statistical analysis was by the Wilcoxon rank test for paired data. For the long-term comparisons, the Kendall rank correlation for nonparametric data was used.

MANOMETRY
The anal sphincter pressure measurements were performed using standard methods as described by Varma and Smith (6).

To determine the rectosphincteric reflex, a micro-balloon was placed at the site of anal canal maximum resting pressure and a second balloon of 2 x 1 cm was rapidly inflated with 50 ml of air in the rectum, 10 cm from the anal margin. The reflex reduction in anal canal pressure was recorded as the rectosphincteric reflex amplitude.

The rectal capacity and intrarectal pressure at maximum volume were established using the continuous infusion proctometrogram technique (7). This allowed calculation of the rectal compliance.

ELECTROMYOGRAPHY
The pudendal reflex latency was recorded from the external anal sphincter with an anal plug electrode after stimulation of the dorsal genital nerve (8).

The mean motor unit potential duration (MUPD) of the external anal sphincter was taken as the mean of four quadrant MUPD estimations around the circumference of the external sphincter (9).

An anal plug electrode was placed in the anal canal and a record of the spontaneous or basal integrated electromyogram (EMG) activity at rest was made with the EMG signal integrator (Electromed 4880/MX216). Thereafter the EMG activity during root stimulation was recorded.

RADIOLOGY
The proctometrogram anorectal catheter and balloon system was filled to 100 ml with a radiopaque fluid. With the subject in the left lateral position and after correct lateral alignment, using fluoroscopy, an x-ray proctogram film was taken at rest before a second film was taken during S4 root stimulation. The x-ray films were then studied and the anorectal angle plus the pelvic floor position were calculated. The anorectal angle was at the intersection of a line drawn along the luminal axis of the anal canal and a second line drawn along the distal border of the rectum. The pelvic floor position was calculated as the distance of this angle point along a line at right angles to the pubococcgeal line.

Results

MANOMETRY
The length of the anal sphincter high-pressure zone and maximum resting pressure in the anal canal were not significantly different in the stimulator and in the control groups. The maximum anal canal pressures during stimulation (Fig. 1) of anterior roots S2 (102 cm H2O ± SEM 26.3 cm H2O), S3 (200 cm H2O ± SEM 14.4 cm H2O), and S4 (248 cm H2O ± SEM 21.2) show that the response is significantly higher with S4 root stimulation (p < 0.01). There was a significant correlation between the maximum exter-
Table 1. Results of Anorectal Manometric Investigations in Brindley Group and Control Group with Spinal Cord Injuries

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Brindley Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPZ (cm)</td>
<td>2.7 ± 0.2</td>
<td>2.4 ± 0.2</td>
</tr>
<tr>
<td>MRP (cm H2O)</td>
<td>68.3 ± 6.5</td>
<td>53.6 ± 4.3</td>
</tr>
<tr>
<td>MPstim (cm H2O)</td>
<td>248.7 ± 21.3</td>
<td>75 ± 5.6</td>
</tr>
<tr>
<td>RSR (cm H2O)</td>
<td>53.3 ± 5.6</td>
<td>41.7 ± 4.6</td>
</tr>
<tr>
<td>RSR% (%)</td>
<td>78 ± 1.8</td>
<td>87.3 ± 2.3</td>
</tr>
<tr>
<td>MRV (ml)</td>
<td>493 ± 76.0</td>
<td>480 ± 21.9</td>
</tr>
<tr>
<td>PMRV (cm H2O)</td>
<td>49.6 ± 2.5</td>
<td>51 ± 1.7</td>
</tr>
<tr>
<td>RC (ml/cm H2O)</td>
<td>10 ± 1.7</td>
<td>9.1 ± 0.5</td>
</tr>
</tbody>
</table>

HPZ = high-pressure zone of the anal canal; MRP = maximum resting pressure in the anal canal; MPstim = maximum anal canal pressure during stimulation of S4 root; RSR = rectosphincteric reflex inhibition of the internal anal sphincter; RSR% = RSR fall in pressure as a percentage of the MRP; MRV = maximal rectal volume or capacity; PMRV = intrarectal pressure at MRV; RC = rectal compliance (during proctogram).

Table 2. Results of the EMG Investigations in Brindley Group and Control Group

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Brindley Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAR (ms)</td>
<td>39.2 ± 2.0</td>
<td>37.8 ± 1.8</td>
</tr>
<tr>
<td>PARD (ms)</td>
<td>18.0 ± 1.4</td>
<td>17.1 ± 1.4</td>
</tr>
<tr>
<td>PARA (μV)</td>
<td>35.7 ± 3.4</td>
<td>30.0 ± 1.0</td>
</tr>
<tr>
<td>EMG rest (μV)</td>
<td>13.0 ± 1.7</td>
<td>12.1 ± 1.2</td>
</tr>
<tr>
<td>EMG stim (μV)</td>
<td>167.9 ± 13.0</td>
<td></td>
</tr>
<tr>
<td>MUPD (ms)</td>
<td>7.4 ± 0.9</td>
<td>7.4 ± 0.8</td>
</tr>
</tbody>
</table>

PAR = pudendoanal reflex latency; PARD = pudendoanal reflex response duration; PARA = pudendoanal reflex response amplitude; EMG rest = external anal sphincter EMG at rest; EMG stim = external anal sphincter EMG during stimulation of S4 root; MUPD = mean motor unit potential duration of external anal sphincter.

The rectosphincteric reflex was present in all subjects and controls. The reflex reduction in pressure of anal canal maximum resting pressure induced by the rectosphincteric reflex was not significantly different between stimulator and control subjects. However, there was a significant difference in the amount of pressure reduction as a percentage of original anal sphincter maximum resting pressure for stimulator subjects (78% ± SEM 1.9%) and control subjects with spinal injuries (87.3% ± SEM 2.3%) (p < 0.05).

The mean maximum rectal volume (Table 1) to the point of balloon expulsion and rectal compliance was not significantly different between stimulator and control subjects, although one had a megarectum capacity (870 ml).

ELECTROMYOGRAPHY (TABLE 2)

The pudendoanal reflex latency was within the accepted normal range of 38.5 ± 5.8 ms (8, 10–12) for both Brindley and control subjects. The pudendoanal reflex response duration and response amplitude were not significantly different. The resting EMG was similar in both groups, as was the motor unit potential duration of the external anal sphincter. (See Table 2.)

There was a direct correlation between the pudendoanal reflex response amplitude and the duration of stimulator usage (r = 0.98, p < 0.001) (Fig. 3). There was also a direct correlation between the maxi-
The maximum external anal sphincter EMG activity in response to S4 stimulation and the duration of the stimulator implant \((r = 0.79, p < 0.05)\) (Fig. 4).

**Discussion**

There was significantly less descent of the pelvic floor at rest in relation to the pubococcygeal line in the Brindley stimulator subjects \((-22.8 \pm 1 \text{ mm})\) than in the control subjects with spinal injury \((-31.9 \pm 1.7 \text{ mm}) (p < 0.05)\) (Fig. 6). During stimulation of the S4 anterior root, there was a significant elevation of the pelvic floor to 4 mm above the pubococcygeal line \((p < 0.01)\) (Fig. 7).

The mean motor unit potential duration and pudendal reflex latencies were within the accepted normal ranges for these muscles, 5 to 7 ms (9, 17). Prolongation of the pudendal reflex and motor unit potential duration are associated with neurogenic impairment of the muscles of the pelvic floor, giving reduced sphincter pressures and resulting in neurogenic fecal incontinence (12, 18, 19). The two females studied here were not in the high-risk group for neurogenic fecal incontinence, which is usually associated with multiparity and middle age (20).

The anorectal angle at rest showed no significant difference between the stimulator group \((122.2^\circ \pm 5^\circ)\) and the control group \((125.9^\circ \pm 5.3^\circ)\). However, the difference in the position of the pelvic floor at rest in the two groups did achieve significance \((p < 0.05)\), with the stimulator group having less perineal descent. These changes should enhance fecal continence but if exaggerated could obstruct defecation. However, by altering the parameters of stimulation, the obstructive effect on the anorectal angle could be lessened, and with sufficient rectal pressure defecation should occur.

Several methods are described for assessing the anorectal angle and pelvic floor descent, including barium-soaked gauze swabs (21) and rubber tubing (22) with the patient in the lateral position. Balloon proctography with the patient sitting can show pelvic floor weakness (23). Synthetic barium-impregnated stool made with potato starch is now more commonly used in dynamic defecography studies (24). It is generally agreed that cine-radiology with the patient in the sitting position and using this type of radiopaque the internal sphincter or a reduced level of resting activity in the external sphincter in the control group. The resting pressure in the external anal sphincter in the stimulator group contributed the normal residual 20% to 30% of the maximum resting pressure (15, 16).

In contrast to this finding, there was no difference reflected in the integrated resting EMG activity of the external anal sphincters between both groups. The mean motor unit potential duration and pudendal reflex latencies were within the accepted normal ranges for these muscles, 5 to 7 ms (9, 17). Prolongation of the pudendal reflex and motor unit potential duration are associated with neurogenic impairment of the muscles of the pelvic floor, giving reduced sphincter pressures and resulting in neurogenic fecal incontinence (12, 18, 19). The two females studied here were not in the high-risk group for neurogenic fecal incontinence, which is usually associated with multiparity and middle age (20).

The mean motor unit potential duration and pudendal reflex latencies were within the accepted normal ranges for these muscles, 5 to 7 ms (9, 17). Prolongation of the pudendal reflex and motor unit potential duration are associated with neurogenic impairment of the muscles of the pelvic floor, giving reduced sphincter pressures and resulting in neurogenic fecal incontinence (12, 18, 19). The two females studied here were not in the high-risk group for neurogenic fecal incontinence, which is usually associated with multiparity and middle age (20).

The mean motor unit potential duration and pudendal reflex latencies were within the accepted normal ranges for these muscles, 5 to 7 ms (9, 17). Prolongation of the pudendal reflex and motor unit potential duration are associated with neurogenic impairment of the muscles of the pelvic floor, giving reduced sphincter pressures and resulting in neurogenic fecal incontinence (12, 18, 19). The two females studied here were not in the high-risk group for neurogenic fecal incontinence, which is usually associated with multiparity and middle age (20).
synthetic stool of similar water content to normal stool gives more physiologic conditions and allows repeatable objective assessment of the function of the pelvic floor (25). The present pelvic floor studies were performed in the left lateral position, and it is accepted that the pelvic floor is not normally particularly stressed in this position (22). However, the atomic nature of the pelvic floor in paraplegics makes it easier to demonstrate perineal descent in the left lateral position than in patients without spinal cord injuries. The use of a balloon allows the contrast to be held in the rectum because paraplegic subjects have no voluntary control over defecation.

Acute stimulation of the S2 3 4 anterior roots caused synchronous contraction of the pelvic floor, puborectalis, and external anal sphincter, with associated elevation of the pelvic floor, narrowing of the anorectal angle, and immediate rise in anal sphincter pressure. The S4 root had the dominant effect with decreasing effect from S2 and S3 (3,4). There was close correlation between the duration of the

Figure 5. (A) Photograph of a lateral x-ray proctogram taken in the left lateral position in a subject with spinal cord injury with a Brindley stimulator while the stimulator was inactive. The reference pubococcygeal line has been drawn. (B) Photograph of a lateral x-ray proctogram taken in the left lateral position in the same subject while the Brindley stimulator was active. The reference pubococcygeal line has been drawn.

Figure 6. Position of the pelvic floor estimated by the anorectal angle point in relation to the pubococcygeal line at rest in control subjects with spinal cord injuries and Brindley stimulator subjects (p < 0.05).
implant and the maximum pressure ($r = 0.81$) plus integrated EMG activity ($r = 0.93$) generated by the external anal sphincter in this study. This, together with the observed similar correlation of the increase in amplitude of the pudendoanal reflex response with time of implant ($r = 0.98$), is in keeping with possible "hypertrophy" of the striated muscles of the pelvic floor during the time of the implant. The use of electrical stimulation of intact lower motor neurons to paralyzed or immobilized skeletal muscle is known to reverse substantially atrophy due to disuse and to restore contractile force (26,27).

There is also increased resistance to fatigue with increased levels of oxidative enzymes used in aerobic metabolism together with increased capillary density and a transformation of fast-twitch type II to slow-switch type I muscle fibers (28,29). Functional electrical stimulation (FES) is taken to mean the restoration of useful movement or sensation by the electrical stimulation of excitable tissue, and many benefits have been claimed in a variety of conditions (30). Some paraplegic subjects have developed trained quadriceps by participating in a daily program of FES (31). Their thigh muscle stiffness was not significantly different from that of untrained muscles. Stiffness of the trained muscles decreased immediately after passive movement and increased immediately after electrical stimulation in a similar way to untrained muscle. If the limb was not moved passively after stimulation, then the stiffness persisted until the limb was moved by the physiotherapist, after which there was a quantifiable reduction in stiffness and in the EMG activity associated with the stretch reflex. The persistent stiffness was thought to be due to a plastic-like molding property of muscle phoxotrophy at the chemical actin/myosin binding level, which could maintain the muscle position or stiffness without EMG activity.

This novel concept could be applied to the pelvic floor of the Brindley subjects, in whom there appeared to be alteration in the position of the pelvic floor after stimulation without any increase in resting EMG activity. The only method of passively stretching the pelvic floor would be the downward transmission of abdominal pressure, and without this the pelvic floor stiffness would persist. Another effect of such pelvic floor stiffness would be to hinder micturition immediately after electrical stimulation. In support of this latter, three of the stimulator subjects have required urethral sphincterotomy to facilitate electromicturition with the stimulator.

Acknowledgements

Mr. N. R. Binnie was supported by Scottish Hospital Endowment Research Trust grant 720.

References

1. Brindley GS. An implant to empty the bladder or close the urethra. J Neurol Neurosurg Psychiatry 1981;44:9–18.


The importance of the orientation of the electrode plates in recording the external anal sphincter EMG by non-invasive anal plug electrodes

N.R. Binnie, B. M. Kawimbe, M. Papachrysostomou, N. Clare and A. N. Smith

University Department of Surgery, Western General Hospital, Edinburgh, UK

Accepted: 1 November 1990

Abstract. Two non-invasive anal plug electrodes of similar size have been compared, one with the electrode plates orientated circularly in the anal canal and the other with the plates in the long axis of the anal canal. There was a significant increase in the amplitude in the EMG signals recorded at rest and during squeeze from the external anal sphincter with a longitudinally placed electrode in 117 patients. Inappropriate contraction of the external anal sphincter when straining at stool was more readily detected using the longitudinal electrode in 52 patients investigated for intractable constipation. The longitudinal electrode detected the amplitude of the response to the elicitation of a pudendo-anal reflex more readily than the circular electrode. When in 12 of the 117 the pudendo-anal reflex EMG signal was either absent or not detected with the circumferential plug electrode, the longitudinal electrode detected the presence of a low amplitude response in 11 of these. When the non-invasive longitudinal electrode was compared to invasive fine wire stainless steel electrodes, a correlation was found for external anal sphincter resting EMG (r = 0.99, *p* < 0.01), voluntary squeeze EMG (r = 0.99, *p* < 0.001) and strain EMG (r = 0.91, *p* < 0.01). The longitudinal anal plug electrode thus facilitates surface acquisition of EMG activity.

Résumé. Deux électrodes anales non invasives de contact d’un diamètre similaire ont été comparées, l’une avec les plaques d’électrode orientées circumfernement dans le canal anal et l’autre avec les plaques suivant le grand axe du canal anal. Il existait une augmentation significative de l’amplitude des signaux électriques enregistrés au repos et durant la contraction du sphincter anal externe pour les électrodes placées longitudinalement chez 117 patients. Une contraction inappropriée du sphincter anal externe durant la défaillance était plus facilement détectée en utilisant des électrodes longitudinales chez 52 patients explorés pour constipation irréductible. L’électrode longitudinale détectait l’amplitude de réponse au déclenchement du réflexe pudendo-anal plus facilement que l’électrode circulaire, mais chez 12 des 117 malades le signal électrique du réflexe pudendo-anal était soit absent, soit n’était pas détecté avec une électrode circonférentielle tandis que l’électrode longitudinale détectait la présence d’une réponse de basse amplitude chez 11 d’entre eux. La comparaison entre l’électrode longitudinale non invasive et l’électrode invasive par fil d’acier inoxydable fin montrait une corrélation pour l’EMG de base du sphincter anal externe (r = 0.91, *p* < 0.01), le tracé de contraction volontaire (r = 0.99, *p* < 0.001) et le tracé de défaillance (r = 0.91, *p* < 0.01). Ainsi l’électrode longitudinale par plaque améliore l’enregistrement de l’activité électromyographique.

Introduction

Anal plug electrodes usually have two circular electrode plates circumferential to the anal plug which thus lie parallel to the external anal sphincter muscle fibres. Due to the increased longitudinal conductivity of muscle, it is accepted that bipolar surface electrodes for recording striated muscle EMG are usually placed in the direction of the muscle fibres [1]. Each electrode is connected to either side of a balanced amplifier while a third electrode connects the patient to ground [2]. Because of this theoretical implication, an anal plug electrode was constructed with two electrode plates placed along the long axis of the anal plug, the electrodes being equally separated on the circumference. The electrode plates were thus separated along the length of the external anal sphincter muscle fibres. A series of anal-rectal electrophysiological investigations was done to compare the two types of anal plug electrodes which differed with their circular and longitudinal arrangements. These included recording the integrated EMG activity of the external anal sphincter at rest, during voluntary squeeze and during straining, and while eliciting the pudendo-anal reflex latency response. Patients with anismus [3] who have an inappropriate contraction of the external anal sphincter can be recognised by detecting a rise in the external anal sphincter EMG activity when straining at stool. The nor-
normal response to straining at stool should be relaxation of the pelvic floor and external anal sphincter with a reduction in the EMG activity. The pudendo-rectal reflex latency assesses the integrity of the reflex arc from the dorsal genital nerve to the S234 component of the sacral cord and the efferent pudendal nerve conduction time to the external anal sphincter [4].

A further aim of the study was to compare the more sensitive of the two types of non-invasive anal plug electrode with invasive fine wire stainless steel electrodes.

Patients

One hundred and seventeen patients participated in the comparison of the orientation of the plates of the two plug electrode plates and had studies done at rest and during squeeze and strain manoeuvres. These 117 patients were 94 females (mean age 55.4 ± 9.3 years) and 23 males of mean age 31 ± 6.2 years. These patients, in addition, all had a pudendo-rectal reflex study. Of the 117 patients, 52 patients showed, during straining, possible anismus effects. The patients who were being investigated for obstructive defaecation were represented by 38 females of mean age 48.2 ± 11.5 years and 14 males (mean age 32.4 ± 5.7 years).

Eight consecutive subjects attending the ano-rectal laboratory participated in a comparison of the more sensitive of the two plug electrodes with the fine-wire method. All patients gave informed consent for the procedures involved.

Materials

Electrodes

The electrode referred to as the circumferential electrode is the Disa 13k 78/79 (Disa Electronics, Bristol) (Fig. 1 a). The longitudinal anal plug electrode has two 0.25 cm × 2 cm stainless steel electrode plates placed in parallel on the longitudinal axis of the neck of the plastic anal plug, separated equally on the circumference [5]. The electrode plates are thus separated in the direction of the external anal sphincter muscle fibres (Fig. 1 b). The plastic plug is machined to the appropriate shape with an overall length of 7 cm, a bulbous distal end 1.5 cm diameter and the neck of the plug being 2 cm in length and 0.5 cm in diameter.

The fine wire stainless steel electrodes [6, 7] were placed in a hypodermic needle with the ends protruding. The wires were insulated with a teflon coating and approximately 0.25 cm of the tips were bared and hooked over to allow the position to be maintained in the muscle on withdrawal of the needle.

Methods

Integrated EMG

All the subjects had investigation of rest, squeeze and strain EMG performed using either the circumferential electrode first and then the longitudinal one or else this was done in the reverse order, the order being varied but not formally randomised.

For the wire electrode study the subjects were placed in the left lateral position and the fine wire stainless steel electrodes introduced into the external anal sphincter in the mid-line posteriorly with a hypodermic needle to a depth of 1.5 cm. The needle was then withdrawn leaving the hooked electrodes in place in the external muscle.
Correlation of external anal sphincter rectified EMG (µV) during straining, recorded with invasive wire electrodes and non-invasive longitudinal anal plug electrode.

The wires were connected to an isolated EMG integrator (Ormed 4880, MX216) and the recorder calibrated to read the required EMG range (0–50 µV). After insertional EMG activity ceased the resting EMG activity in the external anal sphincter was recorded. The subject was then asked to contract the external anal sphincter and the squeeze EMG was recorded. The subject was finally asked to strain as if at stool and the strain EMG was recorded. This procedure was repeated twice to confirm the results. The wire electrodes were now withdrawn and the anal plug electrode to be compared was inserted into the anal canal for the investigations to be repeated.

Pudendo-anal reflex

The pudendo-anal polysynaptic reflex arc incorporates the sensory pudendal nerve, the S234 spinal cord and the efferent pudendal nerve to the external anal sphincter. The Medelec MS92a stimulus triggered response unit records the time delay from skin stimulus to the EMG response in the external anal sphincter. The time to onset of the digitally averaged response to at least 100 stimulus impulses is taken as the pudendo-anal reflex latency. The sensitivity of the incoming signal amplifier is selected to the most appropriate sensitivity for the amplitude of the incoming EMG signal from the muscle. If the amplifier sensitivity is set too high the display store will be overloaded and the signal peaks will be flattened. The amplitude of the pudendo-anal signal response in microvolts (µV) is therefore equal to the volts per division times the screen divisions, and this can be measured electronically within the apparatus. Finally, a paper copy of the pudendo-anal reflex response can be printed out with all that information included.

Statistical analysis

The anal plug electrode and fine wire electrode tests were compared by deriving p values and a correlation coefficient [8].

Results

Orientation of electrodes

The rectified EMG amplitudes recorded from the external anal sphincter with the longitudinal electrode were significantly higher than those recorded with the circumferential electrode during rest and squeeze activity (Fig. 2). In 52 patients with obstructive defaecation there was an inappropriate contraction rectified EMG voltage when straining. The inappropriate EMG change was detected more readily by the longitudinal electrode than by the circular one (p<0.01) (Fig. 2). In the 117 patients who had the pudendo-anal reflex response studied, the signal latency obtained from the external anal sphincter was identical with the circular and longitudinal electrodes (45.3±2.3 ms). There was, however, a significantly higher response amplitude when the responses were recorded with the longitudinal electrode (p<0.01) (Fig. 3). In keeping with this, the sensitivity of the incoming signal amplifier of the EMG apparatus could be significantly reduced by a factor of 10. Figures 4a and b show the enhancement of the EMG voltage obtained with the longitudinal electrode compared to the circular one during the elicitation of the pudendo-anal reflex. There were 14 females (age 66.7±8.6 years) in whom no pudendo-anal reflex could be detected using the circumferential electrode although the response was present with the longitudinal one.
Invasive versus non-invasive

There was a significant correlation between the rectified EMG voltage recorded with the longitudinal anal plug electrode and the fine wire electrode for the external anal sphincter resting EMG \( (r = 0.99, p < 0.01) \), the squeeze EMG \( (r = 0.99, p < 0.001) \) and the strain EMG \( (r = 0.91, p < 0.01) \) (Fig. 5). The direct correlation persisted between the two techniques in both the normal situation with reduction of EMG on straining, and in the abnormal state of anismus when there was inappropriate contraction of the external anal sphincter on straining at stool.

Discussion

The familiar hour-glass-shaped anal plug electrode was originally made by Hopkinson for anal muscle stimulation with two parallel circumferential electrode plates 1 cm apart placed at either end of the neck of the electrode at the presumed site for stimulation of the “recto-pubalis” muscle [9]. However, the circular external anal sphincter and loop of pubo-rectalis muscle at the anorectal junction are arranged such that their muscle fibres lie in the same circle or loop shape, respectively. The longitudinal conductivity of muscle tissue is 5 to 15 times larger than in the transverse direction [1]. Recording electrodes should therefore be placed longitudinally with respect to muscle [10]. This is at variance with the design of the Hopkinson electrode used in the treatment of female urinary incontinence [11] and the currently available anal plug electrodes used for surface recording of the EMG activity of the external anal sphincter (Disa 13k78/79).

Electrophysiological investigation of the pelvic floor can provide detailed information on the pelvic floor muscle motor unit potential duration and single fibre density [12]. The pudendo-anal reflex latency investigation is well tolerated, is much less invasive and is a useful ano-rectal test in patients with neurogenic faecal incontinence [4]. This study shows that an anal plug electrode with longitudinal electrode plates significantly improves the detection of the external anal sphincter EMG signal response on eliciting the pudendo-anal reflex.

When healthy skeletal muscle is completely relaxed it has no detectable EMG activity [2]. The pelvic floor, external anal sphincter and external urethral sphincter are unusual in that they have continuous tonic EMG activity at rest [13], provided that the reflex arc is intact [14, 15]. The detection of changes in EMG activity in the pelvic floor can be recorded with a concentric needle electrode [16]. The longitudinal electrodes detected these responses better than the circular ones and may be used to measure the reduction in EMG activity during normal defaecation, to detect failure of this in obstructive defaecation or anismus [3]. The use of artefact-free fine wire electrodes is to be regarded as the “gold standard” for diagnosing inappropriate contraction of the external anal sphincter during dynamic studies while straining as if at stool [7]. The presence of an anal plug within the anal canal might also induce non-physiological responses in the external anal sphincter. However, the significant direct correlation with the invasive fine wire electrode at rest \( (p < 0.01) \), during squeeze \( (p < 0.001) \) and straining \( (p < 0.01) \) shows that this is not so. The inappropriate increases in the rectified EMG during straining in obstructive defaecation or anismus were detected as readily with the longitudinal anal plug electrode as they were with the fine wire electrodes.

Acknowledgements. Mr. N. R. Binnie was supported by a Scottish Hospital Endowment Research Trust Grant (No. 720). Mr. B. M. Kaimbe was supported by a Janssen Pharmaceutical Research Fellowship. Dr. Maria Papachryssotomou was supported by a Scottish Home and Health Department Clinical and Biomedical Research Grant (K/MRS/501/202).

References


Prof. A. N. Smith
University Department of Surgery
Western General Hospital
Edinburgh EH4 2XU
UK
Constipation Associated with Chronic Spinal Cord Injury: The Effect of Pelvic Parasympathetic Stimulation by the Brindley Stimulator

N. R. Binnie, FRCS, A. N. Smith, MD, FRCS, G. H. Creasey, FRCS, P. Edmond, FRCS

University Department of Surgery, Western General Hospital, Edinburgh, Spinal Injury Unit, Edenhall Hospital, Musselburgh, East Lothian, UK.

Summary

Ten subjects with severe constipation due to complete spinal cord injury (SCI) had pro-longed oro-anal transit time (p<0.01), diminished faecal water content (p<0.05) and a reduced frequency of defaecation (p<0.01) compared to 10 non-SCI subjects. Paraplegic with an implanted Brindley S234 anterior sacral nerve root stimulator had a significant increase in frequency of defaecation (p<0.01), compared to the SCI group while the faecal water content was less although not significantly so. The Brindley stimulator group also showed a more rapid colonic transit than the SCI group but this did not reach statistical significance. SCI is associated with constipation which therefore appears to be favourably influenced by the Brindley S234 anterior nerve root stimulator. The effects produced are compatible with stimulation of left colonic motility, which facilitates the emptying of the distal colon, but also suggest that part of the response restricts transit in some areas of the colon or rectum. Since the motility changes induced by the Brindley stimulator do not affect the right colon a relatively greater residence time of the faecal bolus in this part of the large bowel would enhance water absorption.

Key words: Paraplegia; Colonic transit time; Faecal water; Implant; Stimulator.

Constipation is commonly present after spinal cord injury (SCI) and usually takes a chronic intractable form. This study assesses the degree of constipation in a group of SCI subjects by measuring the oro-anal transit time, the faecal water content and the frequency of defaecation, and comparing the results obtained with a group of non-spinal injured control subjects. In a third group of subjects a Brindley S234 anterior sacral nerve root stimulator had been implanted. These subjects were similarly studied to assess the effect of activating the sacral parasympathetic nerve supply to the distal colon and rectum.

Correspondence to Professor A. N. Smith, University Department of Surgery, Western General Hospital, Edinburgh, UK.
Brindley introduced the implantable anterior sacral nerve root stimulator for bladder control in selected paraplegic subjects. After suitable lumbo-sacral laminectomy the appropriate anterior sacral nerve roots are placed within the electrodes. The electrodes are attached to a passive subcutaneous receiver which is activated by an external radio-frequency transmitter. Using this device it is possible to empty the bladder or close the urethra. It is also possible to activate the sigmoid colon and pelvic floor. In this study the stimulator parameter of signal frequency, impulse duration and intensity plus the stimulation free time gaps were regulated for optimum bladder function.

Binnie et al. have shown sequential S2, 3 and 4 anterior nerve root stimulation increases the motility responses from the transverse colon to the rectum in paraplegic subjects. The greatest response was to S3 root stimulation which could empty the left colon by a distal motility gradient. The effects produced are compatible with stimulation of left colon motility and the emptying of the distal bowel. They also suggest however that part of the response may restrict transit in some areas of the colon and rectum.

In view of the pronounced motor effects on distal bowel function it was decided to compare paraplegic subjects treated with a Brindley stimulator with untreated spinal injury subjects in respect of parameters of intestinal motor function such as transit time, faecal water content and frequency of defaecation.

Subjects

Three groups were studied as follows: (a) a control group of 10 healthy volunteers comprising of 8 males and 2 females with no history of gastrointestinal disease or SCI, mean age 29·1 years with a range 22–38 years; (b) the second group of 10 subjects comprising 9 males and 1 female had complete SCI ranging from level C4 to T10. Their mean age was 34·1 years with a range from 20–45 years. The mean time since SCI was 8·1 years (range 1–20 years); and (c) the third group consisted of 7 SCI subjects with implanted sacral anterior nerve root ‘Brindley’ stimulators. There were 6 males and 1 female in this group with a mean age of 36·3 years ranging from 20–50 years. The levels of SCI ranged from C5 to T3 with a mean time since injury of 7·4 years (range 1–21 years) and mean time since stimulator implant of 2·6 years (range 1–5 years).

Methods

Subjects entering the study took no laxatives for at least 2 days prior to the study and refrained from aperients throughout the study period. They were fasted for 8 hours before commencing the transit studies and after completion of the oro-caecal transit time continued on a normal diet.

Oro-caecal transit time

The method used was that of Bond et al since it was easy to repeat in subjects with a SCI. They were prepared for oro-caecal transit time estimation by an 8 hour overnight fast before a baseline end expiratory 20 ml breath sample was taken prior to breakfast. Ten grams of lactulose in 15 ml water was given with a standardised
breakfast of cereal with milk followed by tea or coffee plus toast with preserve (500 calories). The orally administered nondigestible carbohydrate lactulose is fermented in the caecum and within 8 minutes of reaching the caecum the product gas hydrogen appears in the exhaled breath. The patient did not eat or drink and smoking was not permitted thereafter until the test was completed. The end expiratory breath samples were repeated every 15 minutes until the rise in breath hydrogen due to the arrival of the lactulose in the caecum was recorded.

Oro-anal transit time

This was estimated by the single ingestion of fifty 2 mm cube radio-opaque ‘Hinton’ pellets. The stools were collected from then onwards, were stored in a sealed container with the time and date recorded, and subsequently X-rayed to reveal the numbers of the markers passed. This process was continued until at least 80% of the pellets had been passed. The time to the 80% recovery point was taken as the oro-anal transit time. In the paraplegic subjects the stool collection was by manual evacuation plus occasional spontaneous rectal evacuation. A rectal digital examination was performed each day after breakfast and any rectal residue was collected into the stool specimen containers.

Faecal water content

The faecal water content was derived by weighing the stool specimen before and after freeze drying using the technique as described by Eastwood.

Frequency of Defaecation

The frequency of defaecation was noted from the time of ingestion of the transit markers until completion of the oro-anal transit time.

Statistical analysis

As an alternative to the usual one way analysis of variance the Kruskall-Wallis test was used to analyse the data for the three groups in each of the four investigations performed. Where this was significant pairwise Mann-Whitney-Wilcoxon tests were performed with the Bonferroni correction. The Mann-Whitney-Wilcoxon test gives 95% confidence intervals (c.i.) for the difference in medians and these are quoted where significant.

Results

Oro-caecal transit time

There was no significant difference between the oro-caecal times for the controls (2-95 hrs +/- SEM 0.15 hrs) and the SCI group (3.4 hrs +/- SEM 0.34 hrs (p > 0.05)) or between the controls and the Brindley stimulator group (3.4 hrs +/- SEM 0.34 hrs (p > 0.05)). Similarly there was no significant difference between the SCI group and the Brindley stimulator group (p > 0.05).
Figure 1  Oro-anal transit time in controls, spinal cord injury and Brindley stimulator groups. The means and standard error of the means are shown. The number of superimpositions of data points are as indicated.

Figure 2  Faecal water content of controls, spinal cord injury and Brindley stimulator groups. The means and standard error of the means are shown. The number of superimpositions of data points are as indicated.

Oro-Anal transit time

The oro-anal transit time (Fig. 1) in the controls was 68.7 hours ± SEM 7.6 hours and was significantly shorter than in the SCI group which was 187.3 hours ± SEM 27.7 hours (p < 0.01) (c.i. -166.0, -66.0). The control oro-anal transit time was also significantly shorter than that in the Brindley implant group 135.6
Figure 3 Frequency of defaecation of controls, spinal cord injury and Brindley stimulator groups. The means and standard error of the means are shown. The number of superimpositions of data points are as indicated.

hours +/- SEM 7·5 hours (p < 0·01) c.i. –94·0, –34·5 (Fig. 1). The oro-anal transit time in the Brindley stimulator group was shorter than in the spinal cord injury group but not significantly so.

Faecal water content
There was a significant difference between the faecal water content (Fig. 2) of the controls (69·7 +/- SEM 0·7%) and the SCI group (63·9% +/- SEM 1·6%) (p < 0·05) (c.i. 2·0, 10·0). There was similarly a difference between the controls and the Brindley stimulator group (58·1% +/- SEM 0·9%) (p < 0·01) (c.i. 9·0, 14·9) (Fig. 2). The faecal water content in the SCI group was not significantly higher than in the Brindley stimulator group.

Frequency of defaecation
The frequency of defaecation (Fig. 3) or stools per day was significantly different between the controls 1·12/day +/- SEM 0·14/day and the spinal cord injury group 0·37/day +/- SEM 0·07/day (p < 0·01) (c.i. 0·5, 1·1) and between the spinal cord injury group and the Brindley implant group 0·78/day +/- SEM 0·08/day (p < 0·01) (c.i. –0·67, –0·17). There was however no significant difference between the frequency of defaecation in the controls and the Brindley implant group.

Discussion
Studies on human subjects with low spinal cord or sacral lesions by Denny-Brown and Robertson concluded that the mechanism controlling defaecation was medi-
ated through the sacral spine and its peripheral nerves which is in agreement with later works. The absence of postprandial colonic myoelectrical and motor activity in the colon has been demonstrated by Glick et al. The absence of the postprandial response is thought to be due to lack of parasympathetic neural continuity to the left colon and rectum via the sacral outflow in the 2nd, 3rd and 4th anterior sacral nerve roots. In keeping with this theory, left colonic and rectal status has been shown to be one of the main causes of delay in gastrointestinal transit time following SCI.

Since vagal innervation is not compromised in SCI it might be expected that the oro-caecal transit times in SCI subjects would not be changed compared to nonspinal injured controls. The results in this study showed no significant difference in small bowel transit time between controls and the SCI group or between controls and the Brindley stimulator group. The Brindley stimulator acts on the anterior roots of the sacral nerves S234 and thus affects only the sacral parasympathetic outflow and would not directly influence the foregut. There was no difference between the oro-caecal transit times in the SCI group and the Brindley stimulator group.

The presence of constipation with slow transit in SCI subjects is now accepted. In this study there was a significant prolongation of oro-anal transit time between controls and both the SCI group and the Brindley stimulator group. The oro-caecal times were normal thus leaving the delay to be accounted for by prolonged colonic transit time. The colonic delay has been recorded in the left colon and rectum. The Brindley stimulator activates the sacral parasympathetic outflow and might be expected to influence the left colon and rectum. The calculated mean colonic transit time in the Brindley stimulator group was 132-2 hours +/- SEM 7-4 hours while the mean colonic transit time in the SCI group was 183-9 hours +/- SEM 27-6 hours. This difference was however not statistically significant.

The frequency of defaecation was reduced in the SCI group compared with the controls but returned to a frequency comparable to the control one with the Brindley stimulator. The increased frequency of defaecation in the Brindley stimulator group when compared to the SCI group possibly reflects the motor influence of the stimulator on the left colon and rectum.

The faecal water content was significantly less in both the SCI group and the Brindley stimulator group when compared to controls. The overall colonic transit time is shorter and frequency of defaecation is increased for the Brindley group compared to the SCI group while the faecal water content is paradoxically less in the Brindley group, although this latter finding did not achieve statistical significance with the Bonferroni correction. A possible explanation for the reduced faecal water content in the Brindley group may lie in the pattern of colonic motility induced by the stimulation of the left colon and rectum.

Previous results suggest that the left colon is made to contract in a manner resembling peristalsis which would promote colonic and rectal emptying by the Brindley stimulator, although the pelvic floor which also contracts would tend to prevent emptying. The pattern of motility produced in the colon when the stimulator is activated suggests relative hold-up in the right colon since the transverse colon motility, although stimulated, is affected much less than that of the left colon which has its maximum activity beginning at the splenic flexure as the pelvic parasympathetic nerves S2, 3 and 4 to the left colon are stimulated. These effects alter
the transit of the faecal bolus in different parts of the colon. Non-physiological hold-up in the distal transverse colon would encourage the absorption of water in the right colon resulting in a more firm stool. Once beyond the splenic flexure, the motility encourage by the Brindley stimulator would compensate for any proximal delay and increase the frequency of defaecation and reduce the total colonic transit time.

The predominant effect of the Brindley stimulator on colonic function is therefore the more frequent passage of a formed stool associated with a more rapid colonic transit time. It may prove possible in the future to adapt the Brindley stimulator, not only for urinary bladder control, but also for improvements selectively in the bowel function of paraplegic patients.

Acknowledgements

Mr N. R. Binnie was supported by a Scottish Hospital Endowment Research Trust Grant, Grant No. 720. The spinal stimulators were implanted by Mr Phillip Harris, FRCS, Department of Clinical Neurosciences, Western General Hospital, Edinburgh.

References

Outlet obstruction constipation (anismus) managed by biofeedback

B M Kawimbe, M Papachrysostomou, N R Binnie, N Clare, A N Smith

Abstract
Fifteen subjects presenting with intractable constipation due to obstructive defecation, mean (SEM) duration 8·8 (1·8) years, had the inappropriate contraction and electromyographic changes in the pelvic floor muscles and external anal sphincter typical of this condition. An electromyographically derived index was used to grade its severity. A self applied biofeedback device was used to allow electromyographic recording of the abnormal external anal sphincter. The subjects were encouraged to reduce the abnormal electromyographic activity on straining after instruction and training. The procedure was intended as a relearning process in which the non-relaxing activity of the pelvic floor was gradually suppressed. Biofeedback training was maintained on a domiciliary basis for a mean time of 3·1 weeks and resulted in a significant reduction in the anismus index (mean (SEM) 69·9 (7·8)% before biofeedback, mean 14 (3·9)% after biofeedback, p<0·01). There was an associated reduction in the time spent straining at stool and in the difficulty of defecation and an increased frequency of defecation. Defecatory video proctograms in six subjects showed improvements in the anorectal angle during straining and evacuation. The clinical benefit to the patients persisted after a mean follow up of 6·2 months.

Inappropriate contraction of the posterior portion of the pelvic floor musculature when straining to defecate can produce a form of constipation which is caused by the anorectal 'outlet' obstruction which ensues. This implies failure of the inhibition of the pelvic floor muscle which occurs in normal defecation together with a spasm of the pelvic floor which creates the conditions for the severe constipation of this state known as anismus. The affected subjects strain excessively at stool with the higher centres unaware of the incoordination of the pelvic floor. The inappropriate external anal sphincter contraction can be detected by modern non-invasive electromyographic techniques. The claim has been made that biofeedback training can promote defecation by restoring the capability of inhibiting the anomalous contraction of the pelvic floor. This is done by learning to suppress the activity of the non-relaxing part of it. A self applied electromyographic device, Myotron 120 (Physiological Feedback Systems, Vijftig Bunderweg 1, Dorst (NB), The Netherlands) allows the subject to see or hear the electromyographic response of the external anal sphincter muscle during straining, and the feedback of biological information is the basis of the training technique. The aim of the study was to assess the effect of using such self applied recording as a biofeedback means of domiciliary treatment in a group of subjects with anismus using subjective improvement and objective evidence as measures of the outcome.

Patients
Fifteen subjects, 12 women and three men, median age 45 years, range 22–76 years, presented with intractable constipation and excessive straining at stool due to difficulty in evacuating the rectum. The mean (SEM) duration of the presenting complaint was 8·8 (7·1) years. All subjects had some perineal discomfort at defecation and one had an anterior rectal mucosal prolapse. Each underwent proctoscopy and rigid sigmoidoscopy to exclude other associated pathology such as rectal prolapse or solitary rectal ulceration. All were asked to stop taking their medication at the start of treatment.

Methods
ANORECTAL MANOMETRY
Standard manometric methods were used to measure the length of the anal sphincter high pressure zone, the maximum resting pressure, and the rectosphincteric reflex relaxation of the internal sphincter. A continuous infusion proctometrogram technique was used to assess sensory awareness, maximal rectal capacity, and the rectal compliance. In a further test the proctometrogram balloon was filled to the level of sensory awareness and the subject invited to attempt to expel the balloon voluntarily. This was repeated as a training exercise up to 10 times in each subject with the object of increasing the subject's rectal sensory awareness.

ELECTROPHYSIOLOGY
The pudendal reflex latency and the external anal sphincter motor unit potential duration was measured using a standard concentric needle electrode technique.

DETECTION OF ANISMUS
The subject lay in the left lateral position with a ground electrode wrapped round the right thigh. An anal plug electrode connected to an isolated electromyographic integrator was placed in the anal canal. The resting electromyography was recorded from the external anal sphincter before the squeeze recording and the strain recording after bearing down as if at stool. An anismus
TABLE I

Anorectal manometry and electromyographic results before and after biofeedback and at later follow up in 15 subjects (mean (SEM))

<table>
<thead>
<tr>
<th>Test</th>
<th>Before biofeedback</th>
<th>After biofeedback</th>
<th>Follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High pressure zone in anal canal (cm)</td>
<td>3-1 (0.2)</td>
<td>3-0 (0.2)</td>
<td>3-1 (0.2)</td>
</tr>
<tr>
<td>Maximum resting pressure in the anal canal (cm H2O)</td>
<td>92-3 (5.1)</td>
<td>9-14 (5.6)</td>
<td>92-9 (5.5)</td>
</tr>
<tr>
<td>Rectosphincteric reflex (cm H2O)</td>
<td>66-4 (4-6)</td>
<td>66-2 (4-5)</td>
<td>66-1 (3-8)</td>
</tr>
<tr>
<td>Maximum rectal volume of capacity (ml)</td>
<td>448 (21)</td>
<td>443 (22)</td>
<td>445 (23)</td>
</tr>
<tr>
<td>Rectal compliance ratio of volume/intraluminal pressure (ml/cm H2O)</td>
<td>7-6 (0.4)</td>
<td>7-6 (0.5)</td>
<td>7-7 (0.5)</td>
</tr>
<tr>
<td>Pudendoanal reflex latency (ms)</td>
<td>42-3 (1.7)</td>
<td>42-4 (1.7)</td>
<td>42-5 (1.8)</td>
</tr>
<tr>
<td>Motor unit potential duration of the external anal sphincter (ms)</td>
<td>8-8 (0-6)</td>
<td>8-7 (0-7)</td>
<td>8-9 (0-8)</td>
</tr>
</tbody>
</table>

index was calculated from strain electromyographic voltage—rest electromyographic voltage \* squeeze recording—rest electromyographic voltage \* 100.  

ELECTROMYOGRAPHIC BIOFEEDBACK

The subjects came to the anorectal motility laboratory for training and met the doctor and the technician carrying out the study. They were shown a diagrammatic representation of their problem and the objectives of the biofeedback treatment were explained. The anal plug electrode was placed in the anal canal and connected to the biofeedback device. The Myotron was calibrated and the resting electromyographic recording was noted. The subjects now contracted the external sphincter and recorded the squeeze, which was displayed as µV in excess of the original resting recording. Then, bearing down as if at stool, the subjects took particular note of the straining recording. The electromyographic activity could also be monitored continuously by means of a built in loud speaker in which the frequency of the sound waves varied proportionately with the electromyographic level. At successive straining attempts and by altering the method of straining as required to become purposeful, the subject tried to relax the pelvic floor and to reduce the straining recording down to or below the resting recording and thus correct the anismus dysfunction by restoring the normal defecation inhibition of the pelvic floor.

Subjects then took the device home with the aim of using it for two sessions per day. They were to attempt defecation only on the morning occasion, the second session being a reinforcement exercise. The Myotron had a simple set of instructions attached to it since some subjects were uncertain of some of the steps and details of the procedure or became confused by the sequence of events.

The duration of domiciliary biofeedback treatment was in multiples of two weeks, depending on the subjects’ symptoms and whether they thought they would benefit from continuing biofeedback. The group was, on the whole, highly motivated and all went through the learning exercise and period of training. They particularly appreciated the availability at all times of the female technician in the team. Eight subjects used the device for two weeks, six for four weeks, and one for six weeks. They also kept a diary record of the number of stools passed per week, the time spent straining at stool, the degree of difficulty in passing stools, and noted any perineal pain or discomfort. The last two symptoms were scored as indices on an analogue scale of 0, 1 = mild, 2 = moderate, 3 = severe. The subjects who had begun to keep a diary of these events before starting biofeedback continued to do so throughout the treatment and continued for two weeks afterwards before attending the laboratory for review.

RADIOLOGY

Video-proctograms were performed using a mixture of barium potato mash mixture for six subjects. The anorectal angle was measured at rest, on squeezing to contract the sphincters, and on straining (bearing down) to simulate evacuation.

FOLLOW UP

All subjects were reviewed between three and six months after the assessment at the end of biofeedback treatment when the anorectal function tests were repeated. Two subjects were seen again at one year and a further two were reviewed at over 15 months, giving an overall mean (SEM) follow up time of 6-2 (4-6) months.

STATISTICS

Statistical analysis was performed on the data using the non-parametric Wilcoxon signed rank test for paired data.

Results

ANORECTAL MANOMETRY

There were no significant differences in the results of the standard anorectal manometric investigations before and after biofeedback or between biofeedback and follow up tests (Table I).

ANORECTAL NEUROPHYSIOLOGY

The pudendoanal reflex was present in all subjects with a mean (SEM) latency of 42-3 (1.7) ms (Table I). The mean motor unit potential
Outlet obstruction constipation (anismus) managed by biofeedback

### Table II

<table>
<thead>
<tr>
<th>Test</th>
<th>Before biofeedback</th>
<th>After biofeedback</th>
<th>Follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anismus index</td>
<td>69.9 (7.8)</td>
<td>14.0 (3.9)</td>
<td>14.6 (3.7)</td>
</tr>
<tr>
<td>Perineal pain at defecation</td>
<td>2.3 (0.2)</td>
<td>0.5 (0.2)</td>
<td>0.4 (0.2)</td>
</tr>
<tr>
<td>Difficulty at defecation</td>
<td>2.8 (0.1)</td>
<td>1.1 (0.2)</td>
<td>0.6 (0.1)</td>
</tr>
<tr>
<td>Time spent straining at stool</td>
<td>12.7 (1.2)</td>
<td>5.6 (0.8)</td>
<td>4.5 (0.5)</td>
</tr>
<tr>
<td>No. bowel motions per week</td>
<td>5.2 (0.8)</td>
<td>8.8 (1.0)</td>
<td>7.4 (0.7)</td>
</tr>
<tr>
<td>Ability to expel rectal balloon or balloon expulsion test</td>
<td>2</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

Duration of the external anal sphincters was 8.8 (0.6) ms. The widest motor unit potentials were in subjects with the longest history of anismus ($r=0.82$, $p<0.01$).

### ANISMUS AND BIOFEEDBACK

The anismus index before and after biofeedback and at the latest follow up is given in Table II.

**Discussion**

Anorectal outlet obstruction due to anismus or anismus like activity follows the loss of the normal inhibition of the pelvic floor that occurs while straining to defecate. In addition to their abnormal electromyographic responses the subjects in this series presented with intractable constipation. A sample of these showed typical radiological signs of this condition such as the acute anorectal angle becoming more acute with squeezing actions of the external sphincter and pelvic floor muscle combined with the same angle failing to open out to an obtuse angle with straining or bearing down movements to prepare for the evacuation of the faecal bolus. Radiological verification of these effects and the consistently abnormal electromyographic changes showed that the patients with intractable constipation had anismus or were in an anismus like state. We know that the electromyographic changes alone may not be consistent and are also found in other conditions such as severe constipation, perineal pain, and the solitary rectal ulcer syndrome. The failure of the pelvic floor and external anal sphincter to relax is compounded by their inappropriate contraction. The descriptive term ‘anismus’ has been applied to this part of the phenomenon and is suspected if the history...
includes excessive straining during defecation with difficulty in evacuating the rectum, often requiring self digitation of the rectum. The condition is confirmed objectively by anorectal manometry which initially shows a rise in sphincter pressure with straining and the electromyographic studies showing increased activity with straining. Defecography shows an accentuation of the puborectalis indentation at the anorectal angle with straining.

Electromyographic changes suggesting anismus were detected in all subjects using a flexible anal plug electrode to record the abnormal electromyographic changes indicative of the inappropriate contraction of the pelvic floor muscle when straining. There was a significant correlation between the duration of the presenting complaint of excessive straining and the mean motor potential duration of the external sphincter. This implies that straining caused a traction injury to the pudendal nerve and that some reinnervation was occurring, which in turn prolonged the mean motor potential duration of the affected muscle.

Attempts to overcome the obstructive effects of the non-relaxing puborectalis muscle at defecation in true anismus have been varied. Pharmacological blockade of the sympathetic innervation has been tried when pelvic floor spasm affects the bladder. Puborectalis relaxation by local injection of botulinus toxin has been shown to be effective in correcting anismus, but the effect is relatively short lived and needs to be repeated. Various surgical methods such as partial division of the puborectalis muscle have been advocated to allow obstructed defecation to proceed, but against this approach is the overriding importance of maintaining continence.

As anismus subjects are unaware of the inco-ordination of the pelvic floor, biofeedback offers a simple and minimally invasive technique for relearning how to suppress the non-relaxation of the pelvic floor. The Myotron 120 device is ideally suited for retraining anismus subjects. It is small, compact, easily operated, and relatively inexpensive. An experienced tutor needs to instruct the subjects on what they are required to do and aiming to achieve with the device. The clinical aim is trouble free defecation, which is not always accompanied by complete resolution of the anismus muscle abnormality.

In our series a minor degree of electromyographic anismus remained and was acceptable as it was asymptomatic. The subjects maintained a reduction in the anismus index over a two year period. When tested after the biofeedback training period the fall in the anismus index was accompanied by less time spent in straining, more bowel movements per week, and less perineal pain and discomfort. They more readily expelled a balloon bolus from the rectum and generally spent more time over defecation, feeling that there was clinical improvement in their defecation capability.

Our radiological studies confirm that the anorectal angle is acute in anismus subjects and becomes increasingly so on contraction of the sphincters as in squeezing movements, nor does this angle open out in the mimicked defecation of

---

**Figure 4:** Degree of difficulty at defecation.

**Figure 5:** Time spent straining at stool (mean (SEM)).

**Figure 6:** Time spent on the toilet (mean (SEM)).
Outlet obstruction constipation (anismus) managed by biofeedback

Before biofeedback After biofeedback Follow up

![Graph showing bowel motions per week](image)

straining or bearing down. After biofeedback treatment the anorectal angle significantly 'opened out' on straining. Some subjects found it difficult to expel the barium mixture, unlike the balloon in the laboratory experiments, whether due to embarrassment or some element of the anismus like state continuing. In patients with defecation problems defecography may detect anatomical abnormalities and give some insight into the pathophysiology of defecation, but has been thought to lack clinical relevance in establishing the diagnosis and progress. What remains is to determine the longterm duration of the improvement and to acquire more information about the mechanism of the anismus defect as well as the nature of other anismus like states. It is not known how biofeedback reverses the anismus state or whether biofeedback training abolishes it directly or promotes indirectly a compensatory phenomenon.

BMK was supported by a Janssen Pharmaceutical Research Fellowship and MP is supported by a Scottish Home and Health Department Clinical and Biomedical Research Grant (K/MRS/500128). NRJ was supported by a Scottish Hospitals Endowment Research Trust Grant (No.720).

Neurological Disorders

A. N. Smith and N. R. Binnie

Neurological lesions

Lesions associated with colonic and rectal dysfunction and with problems of the pelvic floor of neurological causation will be considered in the following order: central, spinal, nerve roots, peripheral nerves and ganglion nerve cells, with functional disorders which have neurological involvement but cannot be classified anatomically.

Central Lesions

In most central lesions the colon is most affected but there is a general inhibition of gastrointestinal motor function (Wilson 1976). Whether this is an exaggeration of the normal inhibitory factors modulating colonic motility or because excitatory factors are suppressed due to the withdrawal of vagal stimuli or the absence of gastro-colic reflex is unknown.

Central neurological lesions have many features in common with paralytic ileus. The right colon is most commonly affected; the dominant slow wave frequency falls from 11/min to 3/min in the right colon. Spike bursts are of low amplitude initially but later become normal by increasing in amplitude and propagating distally. The recovery phase is associated with the passage of flatus and faeces (Cordon et al. 1986). In addition, there is delayed gastric emptying and involvement of the small intestine suggesting a lack of vagal activity. In postoperative ileus, however, the recovery is rapid especially in the stomach and small bowel, whereas in the colon it is delayed and less predictable (Rothnie et al. 1963).

Patients with major head injuries, raised intracranial pressure or posterior fossa tumours commonly exhibit delayed gastric emptying, atonic abdominal distension and evidence of absent colonic motor activity which fluctuates with the depth of unconsciousness.

Central neurological lesions such as in Parkinson's disease are often associated with constipation. Micturition is usually more severely affected than bowel function, which is partly due to incoordination of pelvic floor muscle activity. This is a direct effect on the extra-pyramidal control of muscle activity in the levator ani plates and thus not associated with any changes in the pelvic floor reflexes which are slightly prolonged.

Drugs used for the treatment of Parkinson's disease may also produce intestinal pseudo-obstruction because of the hypomotility resulting from their anticholinergic activity.

Colonic ileus occurs in the treatment of depression by psychotropic drugs such as the tricyclic antidepressant compounds, for example amitriptiline (Burks 1988) and imipramine. These compounds prevent re-uptake of catecholamine centrally and at peripheral nerve endings and also have pronounced anticholinergic action at both sites. The effect is reversible and intestinal motility returns within 24-48 hours of withdrawal of the compound.

The internal ionic movement of all cells is
closely regulated for the maintenance of normal function. Potassium depletion suppresses the function of neurones and affects acetylcholine transmission from central cells to their peripheral counterparts. Conduction delay causes ileus, which predominantly affects the colon by altering transmission to intestinal smooth muscle. The ileus resolves when the hypokalaemia is treated. There is usually a delay in bowel transit because of decreased acetylcholine stimulation of smooth muscle. There is also an accompanying bladder atony which can be measured on cystometrograms.

The effect of a cerebrovascular accident on gut and pelvic floor function is variable. There is an initial ileus which resembles spinal shock or pseudo-obstruction (Reynolds and Eliasson 1977) and is thought to represent temporary cessation of the conduction of the central impulses from the hypothalamus and basal nuclei to the periphery. The subsequent development of any colorectal disorder depends on the degree and extent of the central nervous system lesion and the relative sparing of autonomic centres necessary for the recovery of function. Other important factors are the effect of antihypertensive drugs, the general level of consciousness and the degree of disturbance of cerebral arterial perfusion. With clinical improvement the abnormal motility pattern improves; a deterioration in the clinical state usually leads to prolonged hypomotility and constipation and suggests progressive neural damage with little possibility of recovery.

Geriatric patients without stroke may have similar abnormalities as stroke patients since they commonly have severe cerebrovascular disease. Both a central and a peripheral neurogenic aetiology can be represented in the bowel disturbance. Clinically, the patients present in two groups (Varma et al. 1988), one with a megarectum and faecal impaction and the other showing colonic hypertonicity which may precipitate faecal incontinence if the sphincters are inadequate.

This has been investigated in a group of elderly patients (Fig. 9.1) with chronic constipation who were compared with an asymptomatic group. Proctometrograms were performed to measure initial rectal volume, maximal tolerable volume and rectal compliance. Anal sphincter pressure and reflexes were measured by conventional techniques. There was significant impairment of rectal sensory threshold in the elderly constipated patients.

A third of the patients in the group studied showed a megarectum which probably contributed to rectal impaction and dyschezia (Read and Abouzekry 1986). Two-thirds showed the opposite and had a significant reduction of maximal rectal volume and rectal compliance to the point of extruding the measuring balloon. There was no difference in the sphincter length and the rectosphincteric responses. Some patients had an absent or prolonged pudendo-anal reflex indicating delay in neural transmission through the S2, S3 and S4 segments of the spinal cord or its efferent supply to the pelvic floor. Oro-anal transit times were prolonged mainly due to rectal stasis.

The classification of two main groups presenting with chronic constipation, one with a functional megarectum and possible megacolon and the other with a hypertonic irritable bowel type of syndrome, similar to that observed in young patients, is compatible with a central lesion allowing escape of two separate spinal cord patterns of activity. Both groups appear to suffer additionally from defects of anorectal proprioception, probably mediated by receptors in the striated muscle of the pelvic floor or in the pararectal tissues. Anorectal sensory deficits (Read et al. 1985) may also compromise the sampling reflex involved in defaecation (Duthie 1975). The patients are best treated by suppositories to empty the rectum high-fibre diets and the prokinetic agent cisapride.
which improves smooth muscle tone in the hypotonie form, or by drugs such as mebeverine which relax smooth muscle activity in the hypertonic form.

Spinal Lesions

Spinal Cord Injury

Spinal cord injury leads to faecal incontinence in the phase of spinal shock. Classically, the resting anal canal pressure is low (Meunier and Mollard 1977) and the anal reflex is absent at this stage, but is the first reflex to return in the recovery phase (Roboch 1917; Pedersen et al. 1978). Faecal incontinence is later followed by intractable constipation, often associated with the development of an acquired megacolon and megarectum.

Guttman (1970) and Connell et al. (1963) and later Meshkinpour et al. (1985) found that motility returned to the pelvic colon after a phase of inhibition during the period of spinal shock. The pelvic colon then develops greater motor contractions than the proximal colon, reversing the normal motility gradient. There is some doubt as to whether these contractions are peristaltic, since the distal bowel is only occasionally emptied spontaneously and the clinical picture has some of the elements of a pseudo-obstruction.

Meshkinpour and colleagues (1983) also found a marked absence of gastro-colic reflexes after spinal cord injury. The colon exhibits non-propulsive segmentation contractions which lead to a functional obstruction. At an early stage the colon shows an increased compliance and dilates. Many patients need suppositories and enemas to empty the lower bowel and find it preferable to continue constipation with bypass incontinence.

With improved general care and survival of spinal cord injury patients, late problems of bowel dysfunction are often encountered (Guttman 1973). To improve bladder function and regain control over bladder emptying, Brindley introduced implantable electrodes with a system of radiofrequency stimulation of the sacral nerve roots which carry the motor pelvic parasympathetic nerves to the bladder (Brindley et al. 1982). Since the pelvic parasympathetic nerves are also distributed to the left colon and anorectum, this implant promotes stimulation of the distal bowl as well as the bladder (Fig. 9.2). Peristaltic contractions of the entire left colon are evoked by stimulation of the sacral parasympathetic outflow S2, S3 and S4. The effects are maximal with S3.

![Fig. 9.2. Maximal pressure response in the sigmoid colon (cm H2O pressure) in response to stimulation of sacral anterior nerve roots S2, S3 and S4 sequentially in 5 paraplegic subjects, compared with basal figures in response to the activation of an implanted Brindley stimulator. (Reproduced with permission from Varma et al. (1986).)](image)

![Fig. 9.3. Mean motility indices in the transverse colon, splenic flexure, sigmoid colon and rectum after individual sacral root stimulation. The S3 root produces the greatest response at the splenic flexure, while S4 produces a marked rectal pressure rise. (Reproduced with permission from N. R. Binnie et al. (1990) Motility effects of electrical anterior sacral nerve root stimulation of the parasympathetic supply of the left colon and anorectum in paraplegic subjects. *Journal of Gastrointestinal Motility* 2:12–17.)](image)
stimulation and are most intense at the splenic flexure (Fig. 9.3) with the motility response gradually decreasing in the distal colon. These contractions are propulsive and promote emptying. S4 effects are greater on the anorectum but they also contract the pelvic floor and tend to be obstructive in nature. However the effects on the pelvic floor may be important in maintaining continence. The effect of S2 stimulation is weak but always above basal levels (Varma et al. 1986). The Brindley stimulator is presumed to produce these effects by acting directly on the parasympathetic innervation, and by relaying impulses to nerve endings in the left colon and rectum, but the effect might equally follow the activation of a pacemaker in the left colon. The colon is thought to have several pacemaker sites throughout its length with a dominant site residing in the left colon below the splenic flexure (Christensen et al. 1974).

Spinal injuries above the level of the conus medullaris isolate the brain and higher centres from local control which is maintained by independent activity of nerve cells in the sacral spinal cord. Low injuries affect the end of the spinal cord at the S2, S3 and S4 level and annul independent activity of cells in this area. Whatever the level of the lesion, all injuries tend initially to have faecal incontinence but later the lack of motility of the left colon in both groups leads to intractable constipation. Weber et al. (1985) suggested that the pons was a possible supraspinal area for control of colonic and anorectal motility, and that when pontine control was lost the differentiation between high and low spinal lesions was also lost, resulting in a tendency towards a similar clinical state.

High lesions theoretically should allow preservation of the innervation of the distal colon and should lead to "automatic" evacuation. This is more pronounced in the case of bladder function (Klein et al. 1969; Wyndale et al. 1985) and is rarely possible for bowel function which is further affected by the somatic paralysis of the trunk and limb muscles, and loss of afferent sensation resulting in suppression of expulsive efforts and the information required for automatic defaecation. Rectal sensation to balloon distension is lost in both high and low lesions, and is felt as a vague abdominal discomfort rather than localized to the low pelvis or perineum (Frenckner and Ihrle 1976a, b).

Many spinal injury patients learn to predict when the rectum and bladder are nearing maximum distension by recognizing the signs and features of autonomic dysreflexia (Crawford and Frankel 1971; Lindman et al. 1980) such as pounding headache, hypertension, hemifacial sweating or even piloerection in one forearm. Some have been successful in using these manifestations as reliable indicators of the need for bowel or bladder emptying. Changes in electrical resistance of the skin surface have also been used in such predictions. Most patients gradually develop severe constipation, occasionally associated with overflow faecal incontinence requiring stimulant drugs, repeated enemas, suppositories and manual evacuation.

Paraplegic subjects show a marked delay in oranal transit, mainly due to prolonged colonic transit (Menardo et al. 1984). The maximal rectal capacity and compliance is increased in proctometrograms and is accompanied by a loss of sensory awareness of the distending balloon (Barnes and Lennard-Jones 1985). Absence of the cortical somatosensory evoked potentials suggests complete cord transection.

Electrophysiology studies show an intact pudendo-anal reflex arc when the lesion is above the level of the first lumbar vertebra, the conus medullaris is spared and therefore there is no peripheral nerve conduction defect (Binnie 1990). There is a normal MUPD and a normal cauda equina conduction velocity. A normal sacral reflex arc confirms the integrity of the efferent nerves and is important in selecting patients for a Brindley neuroprosthetic device to aid micturition and defaecation (Brindley et al. 1982).

A delayed pudendo-anal reflex latency (Table 9.1) suggests inter alia damage at the level of the conus medullaris and thus a low lesion. Some of these patients have delayed cauda equina conduction as tested by direct stimulation over the lumbosacral nerve roots and recording the ensuing electrical events in the external anal sphincter. The pudendo-anal reflex may be absent or delayed, indicating either complete or partial damage respectively. The mean motor unit potential duration is prolonged by reinnervation of the sphincters and pelvic floor (Bartolo et al. 1983). Direct examination shows a reduced maximal resting pressure and an x-ray proctogram shows a widened anorectal angle. Patients with high lesions may show the same changes despite having an intact S2, 3 and 4 arc and a degree of spontaneous EMG activity at rest in the anal sphincter, suggesting that higher influences other than the intact sacral reflexes are required to maintain normal resting tone in the striated muscle part of the anal sphincter.

A summary of tests done for high and low lesions is given in Table 9.1, with the reservation
Neurological Disorders

Table 9.1. Investigations performed in 79 spinal cases

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Upper</th>
<th>Lower</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anal transit time</td>
<td>Both prolonged</td>
<td>10.4 (3.5–25 days)</td>
<td>3.5 (2–4.5 days)</td>
</tr>
<tr>
<td>Faecal water centres</td>
<td>Both reduced</td>
<td>57% (48%–63%)</td>
<td>67% (58%–74%)</td>
</tr>
<tr>
<td>Anal sphincter length</td>
<td>Unaffected</td>
<td>2.7 (2–4 cm H₂O)</td>
<td>2.5 (2–4.5 cm H₂O)</td>
</tr>
<tr>
<td>Maximum resting pressure</td>
<td>“Normal”</td>
<td>60 (30–85) cm H₂O</td>
<td>95 (70–130) cm H₂O</td>
</tr>
<tr>
<td>Pudendal reflex</td>
<td>Unaffected</td>
<td>37.4 (284–46 ms)</td>
<td>38 (31–45 ms)</td>
</tr>
<tr>
<td>MUPD external sphincter</td>
<td>Normal</td>
<td>5.3 (4.7–10.6 ms)</td>
<td>4.6 (4–6.8 ms)</td>
</tr>
<tr>
<td>Cauda equina conduction velocity</td>
<td>Normal</td>
<td>68 (58–76 m/s)</td>
<td>57 (46–69 m/s)</td>
</tr>
<tr>
<td>Sensory evoked potentials from anus to cortex</td>
<td>Absent</td>
<td>Not recordable</td>
<td>78 (65–88 ms)</td>
</tr>
<tr>
<td>Anorectal angle on x-ray</td>
<td>At first normal</td>
<td>107 (85–130°)</td>
<td>87 (78–105°)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients mean/range</th>
<th>Control mean/range</th>
</tr>
</thead>
</table>

1 Upper motor neurone lesions: tetraplegia (C3–8), 20; paraplegia, 26. Lower motor neurone lesions: lumbosacral abnormalities, 23; spina bifida, 5; sacrococcygeal, 5.

that many of the patients with high or low lesions ultimately show the same defects. However, the value of the tests is threefold:

1. Those which assess the severity of the physiological disturbance: oro-anal transit is a useful indicator of the extent of colonic motor function impairment. Measurement of small bowel transit (Bond et al. 1975) allows a corrected caeco-anal transit but since small bowel transit is only on average 3.5 hours compared with the many days of caeco-anal transit, in practice the oro-anal measurement is the one most often used (Hinton et al. 1969). The faecal transit is assessed by comparing the weight of aliquots of wet and dried stool. Since water absorption occurs during transit and is roughly proportional to it, the extent of the change of the faecal moisture may be used to assess the degree of constipation (Eastwood et al. 1984). In spinal injury patients this may fall from the normal moisture of around 70% to 55% in severe cases with difficulty in faecal evacuation (Binnie et al. 1988a).

2. Those indicating deranged bowel control. An important clinical indicator of low lesions affecting the conus medullaris is the absence of reflex contraction of the external anal sphincter. Sphincter pressure has often been reported as normal in paraplegia (Denny-Brown and Robertson 1935). The mean resting pressure measured in the anal canal can be low in both high and low lesions in the initial spinal shock phase. Thereafter, the mean resting pressure tends to settle above 60 cm H₂O for high lesions, as a result of the continued contraction of the internal sphincter.

made possible through continuing activity in the myenteric nerve plexus and from continued reflex activity of the external sphincter ani (Gowers 1877). Pressures recorded with modern transducers, however, show that these tend to be reduced below the normal range, and may fall further, below the 60 cm H₂O necessary for the control of continence in low level lesions as a result of the paralysis of the external sphincter, which contributes approximately 20% of the maximum resting pressure (Bennett and Duthie 1964).

3. Differentiation between high and low lesions may be initially possible on a proctometrogram. Patients with a high lesion have a hypertonic response (White et al. 1940) while patients with lesions involving the sacral spinal cord or cauda equina exhibit a hypotonic response. As a result of loss of afferent impulses reaching higher centres because of the cord transection and chronic distension, high level lesions subsequently become hypotonic like the low lesions.

Connell et al. (1963) found that the resting and stimulated motility of the pelvic colon was also diminished in patients with high cord transection but was significantly increased in those with low cord lesions. It is often not feasible to use this information in diagnosing individual patients.

The majority of patients with paraplegia respond to cisapride, a prokinetic agent, which enhances motility by redressing the balance of the autonomic nervous system tone in favour of parasympathetic stimulation to the bowel (Binnie et al. 1988a). It reduces the oro-anal transit time and increases the frequency of defaecation in 10 para-
plegic patients without producing diarrhoea or continuous incontinence. Cisapride also reduces the maximal rectal capacity and decreases the compliance of the colon through an improvement in rectal tone.

Some patients have a diminished awareness of the stimulus of anorectal contents which is in keeping with an incomplete spinal injury (Binnie et al. 1988b). The reduction of filling sensation results in sudden urgency of defaecation if the rectum fills before an awareness of this is appreciated. Rectal filling promotes relaxation of the internal sphincter and the consequences of this are faecal soiling. The internal anal sphincter particularly relaxes reflexly in the presence of distension by rectal contents (Gowers 1877). The volume of rectal contents necessary to produce this may be less than the volume at which the rectal sensation is registered and the need for defaecation appreciated.

Using biofeedback techniques the patient can be trained to use the relaxation produced by balloon distension of the rectum to reinforce voluntary control and reflexes (Constantinides and Cywes 1983). This allows time to contract the external sphincter to offset the fall in pressure due to relaxation of the internal anal sphincter, thus avoiding soiling and incontinence. During training, when manometry shows a fall in anal canal pressure (Engel et al. 1974), the patient tries to oppose impending rectal evacuation by voluntary contraction of the external anal sphincter (Cerulli et al. 1979). Biofeedback training can be successful in partial lesions when the patient can voluntarily contract his muscles and restore the pressure necessary for bowel control (Wald 1981). The volume of the rectal balloon is gradually reduced to a level that can be perceived by the subject. Over the course of a few weeks he should acquire a more normal limit for rectal sensation before defaecation and can dispense with the device at a point at which he has the assurance of greater sphincter control.

Cauda Equina

Cauda equina lesions are often incomplete and differ greatly in their effect on bowel function. The sacral parasympathetic fibres run with the anterior sacral nerve roots and may be damaged as one or several of the roots are compressed in their vertical course in the spinal canal before emerging through the sacral foramina. The arrangement of the roots and their accompanying parasympathetic fibres favours partial rather than complete involvement by compression or traction. Some roots may be spared even in severe lumbosacral injuries as it is rare to have actual severance of the entire cauda equina. Both the parasympathetic innervation to the sphincter and the motor innervation

Fig. 9.4. Filling defect in a myelogram from a patient with a central lumbar protrusion. The patient had a reduced maximal anal resting pressure, a prolonged pudendo-anal reflex latency and a delayed cauda equina conduction velocity following stimulation over LV1 but not LV4, thus localizing the lesion to between these vertebral levels.
of the anorectum and pelvic floor may thus escape
the more severe problems which occur at the
slightly higher level of the conus medullaris. There
may be preservation of some sensory awareness of
rectal distension but this may have an abnormal
quality as a dysaesthesia. Other causes of the
cauda equina syndrome include pressure lesions
from prolapsed intervertebral discs, lumbosacral
fractures and haematomas.

Central lumbar disc protrusion (Fig. 9.4) causes
compression of nerve roots as the spinal cord ends
at the lower limit of the first lumbar vertebra. The
lower the level of the lesion, the greater is the
incidence of faecal incontinence because of the
compression of S2, S3 and S4 roots. Damage at
this site would cut off most of the nerve supply to
the pelvic viscera (so that the bladder is affected as
well as the bowel), pelvic floor and external
sphincters. The sensory loss to the skin is
restricted to the saddle area and may be asymmetri
cal because of the varying nerve root involvement.
The reflex contraction of the external anal
sphincter is lost. The mean internal anal sphincter
resting pressure is usually low (Meunier and Moll
1977). Paralysis of the external sphincter
through loss of the S2, S3 and S4 contribution also
contributes to the reduction in the overall mean
resting pressure. The proctosphincteric (rectal
inhibitory reflex) reflex is present, though the
relaxation of the internal sphincter provoked by
rectal distension is deeper and lasts longer
(Frenchner 1975).

The barrier to incontinence requires a sphincter
response of approximately 60 cm H2O, and
collapse below this level increases the likelihood
of faecal soiling. There is also an increased max-
imal tolerable rectal volume with increase of
compliance as measured by the proctometrogram
(White et al. 1940). The latency in the cauda
equina nerve conduction times following skin
stimulation over LV1 and LV4 sites is detected by
the EMG response to the external anal sphincter
(Snooks and Swash 1988). This shows:

1. Conduction delay or complete absence of re-
   sponse when an electrical stimulus is adminis-
   tered at the LV1, with a normal LV4 con-
   duction if the lesion is between the sites of
   stimulation. The spinal latency ratio will be
   increased:

<table>
<thead>
<tr>
<th>Latency to external anal sphincter after stimulation at L1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency to external anal sphincter after stimulation at L5</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
</tr>
</tbody>
</table>

(after Snooks and Swash 1984)

2. In asymmetric lesions one side may have its
   innervation response retained and thus partial
   preservation of its function and nerve con-
   duction.

3. The test may also be used to observe any
   recovery in instances where the initial appraisal
   erroneously suggested a complete cauda
equina lesion due to a compression haema-
toma, oedema or temporary bony com-
pression, or from displaced vertebral fractures
which have undergone early reduction.

An electrical stimulus of the order of 750 to 1000
volts is given as a shock impulse over 100 μs
directly over the LV1 and LV4 skin. The con-
duction time and velocity of the impulses are
computed from the distance between the stimu-
lation site at LV1 and LV4 and the difference in
the latency times to the external anal sphincter
EMG response.

Occasionally during investigation of patients
with faecal incontinence the electrophysiological
features of cauda equina lesions emerge in
patients with no clinical signs of cauda equina
disease (Snooks et al. 1985). If the anal reflex is
absent in patients with anorectal incontinence, it
suggests a spinal lesion and merits further neuro-
logical investigation, including myelography to
localize potentially surgically remediable lesions.

Measurement of the mean motor unit potential
duration gives an indication of reinnervation in
individual cases of the cauda equina syndrome.
Because the proctometrogram only gives sec-
ondary information about sensory awareness to dis-
tension and may be abnormal due to the degree of
rectal dilatation or megarectum already present,
electromucosal sensitivity is a better determinant
for defective sensation and conduction in the
efferent neural pathway from the rectum. Somato-
sensory testing can be used to check the afferent
pathways from the sacral and lumbar sensory root
levels to the cortex and may be absent or delayed
in cauda equina lesions. By varying the level at
which the skin stimulus is applied to the sacral and
lumbar region, an indication may be obtained of
the site of the lesion according to the arrival or
absence of impulses initiated in the lumbosacral
region, recognized at a cortical level with scalp
electrodes. Repeat examination may show a
degree of recovery indicating the presence of a
partial lesion. Patients with a cauda equina syn-
drome are prone to constipation as well as faecal
incontinence, which may in fact be an overflow
incontinence.

It is not uncommon for some of these patients
with cauda equina syndrome to develop a partial
or complete rectal prolapse. When faecal inconti-
nence is the dominant problem, and the pelvic
Developmental Anomalies of the Spine

Spondyloepiphyseal dysplasia (SED) produces features of a severe spondylolisthesis of the 7th cervical vertebra and lower spinal segment. Spondyloepiphyseal dysplasia in the lumbar region has been described in association with a bony abnormality of the spinal arch which normally matures to form the articular processes and neural arches at the lumbar and sacral levels. The clinical features result from the bony deformity or failure of bony development of the neural arches at the lumbar and sacral levels. Whether the clinical features result from a bony deformity or failure of bony development of the neural arches at the lumbar and sacral levels is not known. It is difficult to determine the exact nature of the soft tissue deformity which is probably responsible for the lack of neurological control. There is no doubt, however, that the bony deformity is associated with symptoms (Alva et al. 1967). It is difficult to explain the late onset of symptoms when the structural deformity has obviously been present since birth. It has been suggested that the symptoms are precipitated by unrecognized neurogenic damage during childbirth or by toxic factors such as alcohol (Fidas et al. 1989).

Furthermore, there is no correlation between the bony defect and a single neurological abnormality. The degree of traction on nerve roots or compression from associated lesions such as lipomas and dermoids appears to determine the nature of the abnormality (James and Lassman 1981). The single most useful investigation of patients with the fully established syndrome causing intractable constipation is radiological examination of the pelvis, especially of L4 to L5, to determine the state of fusion of the bony arches. If there are normal sacral segments, the likelihood of development symptoms as a result of failed neurological maturation is high.

The severity of the problem in patients with comparable arch defects also varies widely. Patients with severe bony defects can be symptom free whereas others with minimal bony abnormality have severe symptoms (Fidas et al. 1987). A myelogram may reveal root tethering in such cases.

In symptomatic patients, anorectal assessment is directed at external sphincter function and motility in the rectal and anorectal area, which show a low resting pressure and a megarectum with faecal retention respectively. The common end result of faecal soiling and frank incontinence is due to sphincter incompetence and loss of sensory conduction. The maximum squeeze and cough pressures are reduced or absent, while the internal sphincter relaxes in the presence of rectal distension through a preserved recto-anal inhibitory reflex allowing faecal soiling to occur. The pudendo-anal reflex is absent or has a prolonged latency. Decreased sensory awareness can be measured by the proctometrogram which shows a raised maximal capacity, rectal distension and increased compliance. There may also be variable cauda equina nerve conduction defects depending upon the extent of the lesion (Fig. 9.5).

Sometimes, instead of pelvic floor paralysis, there is outlet obstruction or anismus. It is possible that in the incontinent group the efferent motor fibres to the pelvic floor are damaged while in the anismus group there is a sensory nerve abnormality of the pelvic floor muscles through the motor neurones in the Onuf's nucleus which increases the contractile activity (Onuf 1901).

Fidas et al. (1989) came to the conclusion, when considering spina bifida occulta and its associated urodynamic abnormalities, that these were not directly related to anomalous bone growth per se and suggested abnormal development of the tail bud in early gestation. It is perhaps in this area that an explanation might be found for the severe constipation of young women who have no radiological bony structural abnormality in their distal spine. Their constipation is severe and intractable, necessitating enemas, suppositories and purgatives after the failure of all simple measures such as a high-fibre diet and stool softeners. The colonic problems interfere with their work, their careers and their social lives. The pudendo-anal reflex is absent in some or grossly delayed in others, which tends to suggest a conus medullaris anomaly (Varma et al. 1988). The condition has been strongly associated with concomitant urinary evacuation problems (Bannister et al. 1988).
US. Spina bifida occulta and partial sacral agenesis

A variable picture of bowel upset. The sphincter function was reduced as the motor component of the lesion was ineffective at stimulation over LV1, and caused by the dysraphism at the lumbar level. A sensory component was caused by spinal agenesis and was in turn associated with a gross rectal agenesis.

Other investigations in the same group of patients have sought anomalous secretion of products, varying disturbance of oestrogen or progesterone or even a visceral autonomic neuropathy. Many of these young women come to subtotal colectomy with ileorectal anastomosis which affords relief of symptoms, but this should only be done if sphincter function is normal.

Spinal Cord Disease

The commonest spinal cord disease causing bowel dysfunction is multiple sclerosis, and constipation in this disease can equal the severity of the "constipation of young women syndrome", but faecal incontinence may be equally distressing. The diagnosis of multiple sclerosis may be clinically obvious but occasionally the first presentation is with bowel symptoms. The increasing constipation has been attributed to diminished colonic motility (Glick et al. 1982) and absent postprandial stimulation of the sigmoid colon but a secondary megacolon may also supervene. Rectal prolapse is not uncommon especially if there is pelvic floor paresis. Pudendo-anal reflex is lost if the conus is involved but this is a rare finding. As the condition worsens there is a severe loss of sensation of rectal filling which can be detected on a proctogram.

Confirmation of the spinal involvement and the presence or absence of afferent sensation can be determined directly by electromucosal sensitivity tests or by tests of afferent conduction upwards through the spinal cord to cortical levels.

A few patients with normal sphincter control have been treated by surgery for the megacolon by a subtotal colectomy and ileosigmoid anastomosis. Two patients with severe constipation in our series were treated in this manner. Two years later, one requested an ileostomy because of progressive faecal incontinence. The other has a satisfactory result thus far. Three other multiple sclerosis patients without a secondary megacolon have been treated conservatively with cisapride with clinical improvement.

Poliomyelitis which affects the anterior motor neurones of the spinal cord was formerly a condition which caused serious bowel problems and it still does so in some parts of the world, notably Africa, India and the Far East. Bowel symptoms are commonly the result of a severe attack which paralyzes the abdominal musculature. This results in defaecation impairment due to inability to raise the intra-abdominal pressure necessary for expulsion through an otherwise paralysed pelvic floor.

Conduction in the spinal cord may be abnormal in the diabetic patient but the more dominant picture is that of an autonomic or peripheral neuropathy (Battle et al. 1980).
The Effect of Spinal Anaesthesia and Other Anaesthetic Agents

Local anaesthetic agents may be injected into the spinal canal either intradurally or extradurally (epidural anaesthesia). In each type the sensory anaesthesia and paresis produced follows the level to which the local anaesthetic is instilled and is commonly intended to affect the thoracic cord so that the abdomen and lower thoracic area as well as the lower limbs will have sensory and motor loss.

The effect on bowel function resembles the acute stage of spinal cord injury since the distal sympathetic outflow is paralysed and the unopposed parasympathetic stimulation of the vagus produces hypermotility in both the small and proximal large intestine. The mean resting pressure in the anal canal falls as a result of paralysis of the external anal sphincter (Frenckner and Ihrre 1976b).

An advantage of epidural anaesthesia is that it may be used to produce restricted anaesthesia for lower abdominal procedures such as Caesarean section and some bowel and bladder operations. The motility effects of blockade of the sacral parasympathetic innervation include periods of ano y at suture lines during surgery and hypermotility on recovery.

Reversal of neuromuscular blocking agents by anticholinesterase drugs also requires careful consideration in relationship to colonic motility because of their effects on anastomoses. The normal intracolumic pressure is much higher than in the stomach, jejunum and ileum and may rise to as much as 30-90 cm H₂O. Anticholinesterase agents used to reverse neuromuscular blockade potentiate cholinergic activity in the gut and have been incriminated as a cause of anastomotic breakdown (Bell and Lewis 1968). Rises in colonic pressure may equal the diastolic blood pressure, rendering the anastomosis ischaemic for short periods. Atropine given prior to neostigmine does not reliably reverse the rise in intracolumic pressure (Wilkins et al. 1970).

Anticholinesterase agents have conversely been used for the stimulation of colonic motility, both in paralytic ileus (Marsden and Williamson 1939) and to relieve the faecal stasis and intractable constipation (Catchpole 1969) of pseudo-obstruction and idiopathic megacolon. The physiological effect on the colon in these patients is predominantly one of hypomotility. Marker studies show a very protracted slow transit form of constipation (Preston and Lennard-Jones 1986).

Spina bifida occulta must be excluded by radiology of the lumbosacral spine and other diseases of the spinal cord and neuropathies by appropriate clinical examination. Some of these patients have their symptoms improved by a combination of prostigmine anticholinesterase stimulation of the colon and a sympatholytic drug such as a beta blocker (Neely and Catchpole 1971).

Catecholamines secreted into the circulation are known to be inhibitory to colon motility since one of the rarer but accepted features of phaeochromocytoma is severe and intractable constipation.

Nerve Lesions

The commonest nerve lesions are to fibres from the S2, S3 and S4 roots which supply the pelvic floor and external anal sphincter muscle as well as the striated muscle of the urethral sphincter. The pudendal nerve is susceptible because its length and extrapelvic course effectively tether it at the ischial spine before returning to the pelvis to supply the external anal sphincter and the striated portion of the external urethral sphincter muscle. It is particularly susceptible to damage in its terminal portion where it supplies the external anal sphincters (Neill et al. 1981). The fibres to the urethral sphincter are even more susceptible due to their longer course. Early EMG studies and muscle biopsies suggested a neuropahtial type of denervation disorder (Parks and Swash 1979; Beersiek et al. 1979) of the pudendal nerve. The descending perineum results in damage to the fibres which supply the pelvic floor from S2, S3 and mainly S4 directly on its superior surface. This may follow lifelong straining at stool but in female patients the onset may be as a result of nerve traction at parturition (Kiff et al. 1983; Snoeks et al. 1984). In both aetiologies neurogenic faecal incontinence results. In the descending perineum syndrome, this follows a previous period of gross constipation associated with straining which in turn produces a descent of the pelvic floor (Fig. 9.6). This can be measured in centimetres by measuring the downward movement of the perineum during a Valsalva manoeuvre. As much as 4 cm of movement may be detected and a descent of more than 0.5 cm or a 13% increase imposes traction forces on the distal part of the pudendal nerve. This in turn leads to nerve damage, and denervation can be confirmed by single fibre density electromyography and also by delayed conduction in the terminal section of the pudendal nerve. The conduction of this portion of the nerve
may be tested by transrectal stimulation using a
ger-glove electrode devised by Brindley for
electro-ejaculation and adapted for this purpose
by Snooks and Swash (1985). Snooks and his co-
workers (1984) have shown that a stretch neuro-
pathy occurs in childbirth during the second stage
of labour. Serious nerve lesions of the pelvic floor
were strongly associated with such problems as
disproportion and forceps delivery. In the major-
ity spontaneous recovery was the rule, but the
more severe the lesion, the greater the chance of
faecal incontinence.

In others with multiparity and recurrent mild
damage, faecal incontinence may supervene a
decade or so later, perhaps because of a general
failure of pelvic floor function and continuing
denervation and muscle atrophy. The bowel
problem is often accompanied by a significant
incidence of genuine stress incontinence of urine.
These patients can be investigated by studying the
latency of pelvic floor reflexes such as the urethro-
sphincteric reflex and the pudendo-anal reflex
which are prolonged. The mean motor unit poten-
tial duration is also prolonged, which indicates
that there has been a denervation injury. There is
a diminution in the maximal resting pressure of the
external anal sphincter. Although the puborectalis
muscle is innervated separately from the external
anal sphincter, both are affected in neurogenic
incontinence of obstetric causation and by the
Clinical Measurement in Coloproctology

The pudendal nerve supplying the external anal sphincter is more often and more severely affected. Denervation of the puborectalis muscle alters the anorectal angle which becomes wider because of the weakness in the pull of the puborectalis sling (Fig. 9.6). The anorectal angle can be corrected by postanal repair. Since many of these patients are elderly, nonoperative methods have been explored. In our experience, physiotherapy produces minimal change (Varma 1987).

Another approach harnesses the pudendo-anal reflex arc and uses electrical stimulation to send trains of stimuli on the afferent side from the genital nerve to the conus medullaris and on the efferent side to puborectalis and the external anal sphincter muscle. Repeated electrical stimulation of the pudendal reflex arc results in reflex contraction of the puborectalis and external sphincter muscle. This reflex is not readily fatigued and repeated stimulation improves the maximum resting pressure, the position of the pelvic floor at rest and the voluntary squeeze and cough responses (Binnie et al. 1988c).

The descending perineum syndrome with its tendency to produce neuropathy of the pelvic floor may be accompanied by anismus which may explain why so many patients originally constipated because of anismus end with faecal incontinence. The continued straining may also lead to rectal prolapse which in turn causes further diminution of sphincter competence due to repeated anal dilatation.

Diabetes may cause a similar neuropathy of the pelvic floor (Henry and Swash 1985) with faecal incontinence. A co-existent intestinal autonomic neuropathy may contribute to slow transit constipation with other systemic aspects of autonomic degeneration such as postural hypotension and diminished afferent sensory conduction problems in the spinal cord. This may also be seen in tabes dorsalis and suspected in multiple sclerosis and degenerative diseases such as subacute combined degeneration of the cord associated with vitamin B12 deficiency.

A denervation injury of the parasympathetic nerve supply of the distal colon has been proposed for the dysfunction which may follow anterior resection of the rectum (Catchpole 1988). Hysterectomy is a common operation involving deep pelvic dissection known to have relatively few sequelae, but its urological consequences such as bladder dysfunction are well known (Green et al. 1973). Urologists accept that the motor nerves of the bladder are at risk in the presacral region, in the lateral wall of the pelvis and close to the bladder neck. The possibility of interruption of the parasympathetic innervation of the left colon and rectum which is derived from the same S2, S3 and S4 sacral segments as supply the bladder is less well known (Varma and Smith 1985). Parasympathetic fibres run from the sacral roots to the inferior hypogastric plexus and then pass forwards to inner- vate the bladder and rectum. Others run upwards and outwards from the pelvis to the left colon as far as the distal transverse colon. This innervation is thought to be of paramount importance in the coordinated contractions of the smooth muscle of the distal colon. The same fibres also carry sensory information from the bladder, which is conceivably considerable that damage during pelvic surgery could result in functional disorders of the evacuation of the distal colon. During hysterectomy the inferior hypogastric or pelvic plexus which in the female is placed on either side of the rectum, uterus, vaginal fornix and posterior aspect of the urinary bladder and extends into the base of the broad ligament of the uterus is susceptible to injury.

Thirty-four post-hysterectomy patients have been investigated in Edinburgh, all with severe constipation dating from the time of their operation. They were collected over a five-year period from many different clinicians during a time in which as many as 5000 women had hysterectomies performed in the hospitals of this medical centre.

The sigmoid colon motility exhibited hypomotility (Smith et al. 1990). Rectal compliance and sphincter function remained relatively normal, suggesting that the damage to the plexus and its distributing fibres is mainly at a higher level in the pelvis and that the fibres supplying the rectum at a lower level mainly escape (Fig. 9.7). This motor abnormality can be shown to follow both abdominal and transvaginal hysterectomy; in the latter case a traction injury is the most likely cause.

The parasympathetic motor fibres passing upwards from the pelvis to the left colon run close to the inferior mesenteric artery which is often tied in aortic aneurysm surgery. The ligation of this vascular bundle may result in an ileus further promoted by any extensive retroperitoneal dissection and haematoma accumulating postoperatively. Spinal ischaemia can result in severe ileus following aneurysm surgery. Somatic features such as lower limb paralysis and a sensory loss accompany functional disturbances such as bowel hypomotility and unawareness of bowel and bladder filling. This combination is due to spasm or damage to the exclusive blood supply to the lower thoracic and lumbar spinal cord which is derived from the arteria radicularis magna which
Neurological Disorders

Ganglion Cell Lesions

Infantile Hirschsprung's disease is considered elsewhere in this volume. When the condition presents in the adult slow transit constipation is always present and motility tests show little response to food and cholinergic stimulation. Patients who were undetected in the neonatal period sometimes reach adolescence or even adult life with minimal symptoms until an eventual decompensation of bowel motor function occurs. The features generally fit the hypothesis of a short segment of aganglionosis beyond which active bowel has managed to expel faecal contents but the local motility failure is difficult to prove. The proctosphincteric reflex is dependent on intact ganglion cells. The aganglionic defects of Hirschsprung's disease is confirmed by an absence of this recto-anal inhibitory reflex. Elicitation of this reflex is more valid than diagnosis by a mucosal biopsy to check cholinesterase activity in short segment Hirschsprung's cases as the site of the aganglionic anomaly may be easily missed on random biopsy. Many such patients have a gross secondary proximal dilatation of the colon and the preferred treatment in these late cases is a subtotal colectomy with ileosigmoid anastomosis, which leaves enough colonic reservoir function for water absorption to protect against faecal incontinence and removes the dilated, now inert, colon.

Similar aganglionic bowel with a gross mega-colon and hypomotility and a patchy dilatation in other areas of the gastrointestinal tract occurs in South America in the infective disorder known as Chagas' disease resulting from infection by Trypanosoma cruzi. Absence of the proctosphincteric reflex may be found as well as multiple motor defects culminating in pseudo-obstruction. An absent proctosphincteric reflex is not invariably indicative of the aganglionosis of Hirschsprung's disease and Chagas' disease. The reflex may be missing in patients with an irradiation anorectal injury which has destroyed ganglion cells. Damage to ganglion cells may also follow the use of chemotherapeutic agents such as vincristine, and some formerly used anthelmintic agents had a sinister reputation for producing a lasting pseudo-obstruction.

Ganglion cell function is very sensitive to hypoxia and ischaemia. Maturation arrest may affect wide areas of the myenteric plexus and it is now recognized that the gut may be affected widely by familial, sporadic and developmental abnormalities presenting as a visceral neuropathy. The familial group may be associated with mental retardation and calcification of basal ganglia. Sporadic cases are mainly degenerative and result from noninflammatory and inflammatory agents, among which Chagas' disease and cytomegalovirus are included. The most common representative of the developmental visceral neuropathies is undoubtedly Hirschsprung's disease but various less well known forms exist, often more severe in their expression, with mental retardation presenting with a myenteric plexus disorder in which some neurones exist but are few in number and are argyrophilic. Other forms exist and are associated with neurofibromatosis and the multiple endocrine adenoma syndrome MEA2 (for review see Schuffler 1988).
Table 9.2. Comparison of manometric and rectal motility parameters in control subjects and post colo-anal sleeve anastomosis cases showing lowered rectal sensory threshold, low maximal tolerable volume and a diminished amplitude of rectosphincteric reflex inhibition which combine to create increased frequency of defaecation and a sensation of obstruction.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=8)</th>
<th>Colo-anal sleeve anastomosis (n=8)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum resting anal pressure (cm H₂O, mean±s.e.m.)</td>
<td>104 ± 5.3</td>
<td>54 ± 7.7</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Maximum anal squeeze pressure (cm H₂O, mean±s.e.m.)</td>
<td>159 ±15.9</td>
<td>120 ±17.9</td>
<td>P&gt;0.1</td>
</tr>
<tr>
<td>Sphincter length (cm, mean±s.e.m.)</td>
<td>3.5± 0.25</td>
<td>2.4± 0.21</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>Amplitude of rectosphincteric reflex</td>
<td>47.5± 3.1</td>
<td>12.5± 5.6</td>
<td>P&lt;0.02</td>
</tr>
<tr>
<td>Rectal sensory threshold (ml air, mean±s.e.m.)</td>
<td>58 ±10.2</td>
<td>29 ± 3.8</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Maximal tolerable rectal volume (ml H₂O, mean±s.e.m.)</td>
<td>504 ±29</td>
<td>120 ±25</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Rectal pressure at maximal tolerable volume (cm H₂O, mean±s.e.m.)</td>
<td>73 ± 2.8</td>
<td>86 ± 6.5</td>
<td>P&gt;0.1</td>
</tr>
</tbody>
</table>

From Varma and Smith (1986a) with permission.

The ganglion cells of the bowel may be damaged by abuse of anthrane purgatives in the so-called cathartic colon syndrome. The typical brown staining of the mucosa is seen at sigmoidoscopy and there may be a dilatation of the lumen throughout the colon and rectum. These patients have mixed investigative details, the most outstanding of which is the slow transit form of constipation. They not uncommonly have other features among which are anismus, the descending perineum syndrome, a secondary megacolon or megarectum, an absent rectosphincteric reflex indicating damage to ganglion cells or nonpropulsive left colon and rectum as a result of colonic inertia.

Radiation damage is not only mucosal but may be accompanied by a visceral neuropathy, both of which contribute to frequent stools and dysmotility. The main physiological abnormality is a loss of internal anal sphincter function, with a significant reduction in the mean anal canal resting pressure and sphincter length (Varma and Smith 1986a). The rectosphincteric reflex may be absent with the maximal tolerable volume and the compliance severely reduced. The change in rectal compliance correlates well with the symptoms and the degree of mucosal abnormality seen at sigmoidoscopy. Excised specimens show marked abnormalities of the myenteric plexus (Varma et al. 1985). Chronic irradiation of the colon and rectum usually follows radiotherapy for carcinoma of the cervix, prostate or urinary bladder. The symptoms are distressing, with urgency of micturition, frequency of defaecation and faecal incontinence. Although the mucosal damage may be severe with haemorrhage, stricture of the rectum and sigmoid colon and fistulae (Hatcher et al. 1985), studies show an abnormality consistent with damage to smooth muscle and its innervation. These patients can be successfully treated by removal of the damaged segment of the colon and restoring intestinal continuity by anastomosing the healthy tissue of the transverse or descending colon to the anal canal.

Physiological studies several years after this operation show persistence of some of the preoperative abnormalities such as a low rectal capacity (Varma and Smith 1986b). The persistence of altered sensory awareness and reduced rectosphincteric reflex may follow mucosectomy of the anorectal junction (Table 9.2). This in turn promotes a failure of the normal reflex responses of the internal sphincter to rectal ampullary distension and may explain the rectal obstructive symptoms. This is in contrast to the reinnervation and return of rectosphincteric reflex following colo-anal anastomosis for nonirradiated tissue, and indicates that the functional abnormality caused by the addition of radiation to the surgical management of carcinoma of the rectum is a lesion of ganglion cells.

Miscellaneous

Anismus is the severe constipation resulting from an obstruction syndrome of the anorectum. This is due to paradoxical contraction of the pelvic muscle during defaecation straining, instead of the relaxation seen in normal subjects (Preston and Lennard-Jones 1985). The cell bodies of the neurons controlling the striated muscle of the pelvic floor lie in the S2, S3 and S4 ventral horns in neurons known as Onuf's nucleus. Percutaneous concentric needle EMG of the external anal sphincter and puborectalis muscle shows continuous electrical activity of these muscles at rest.

The diagnosis of anismus is established by the loss of inhibitory reaction to straining with pro-
nounced increase in motor activity in the pelvic floor, delayed left colonic transit and poor rectal filling with a high intrarectal pressure.

Severe anismus acts as a block to defaecation and straining against the obstruction may cause secondary pathological changes and damage to the anterior rectal wall. In mild cases the anterior rectal wall trauma results in mucoid discharge and abdominal pain but in severe forms rectal intussusception, external prolapse or solitary rectal ulcer result (Womack et al. 1987; Alexander-Williams 1977).

The phenomenon appears to be due to the loss of the normal inhibitory effect on the pelvic floor which follows straining by a pathway as yet unknown (Whitehead and Schuster 1981). This may be central, because EMG-induced biofeedback training (Binnie et al. 1989) can reverse the abnormal phenomenon and correct symptoms. For intractable cases, the alternative of partial muscle division of puborectal has been practised (Keighley 1988) but could have the danger of inducing prolapse or incontinence. A recently reported method is the use of locally injected Botulinum A toxin (Hallan et al. 1988) which produces local paralysis of the puborectalis muscle of the pelvic floor.

Neural mechanisms are involved in the pain of proctalgia fugax, inflammatory lesions and advanced tumours; while the effects of tumours are mainly local, these are occasionally due to metastatic involvement of central nerve pathways or of the spinal cord.

References


Barnes PRH, Lennard-Jones JE (1985) Balloon expulsion from the rectum in constipation of different types. Gut 26:1049


Connell AM, Frankel H, Gutman L (1963) The motility of the pelvic colon following complete lesions of the spinal cord. Paraplegia 1:92-115


Read NW, Abouzeyry L (1986) Why do patients with faecal impaction have faecal incontinence? Gut 27:283–287

Read NW, Abouzeyry L, Read MG et al. (1985) Anorectal function in elderly patients with faecal impaction. Gastroenterology 89:959–966

Riddoch G (1917) The reflex function of the divided spinal cord in man, compared with those associated with less severe lesions. Brain 40:264–402


Anal reflexes

J. S. Varma and A. N. Smith

The classical anal reflex (or cutaneo-anal reflex), described originally by Rossolimo (1911), is elicited by pricking the anal mucosa or the perianal skin and observing the contraction of the external anal sphincter as dimpling of the perianal skin. The reflex appeared to be present in all normal subjects. By transection of the spinal cord and the sacral nerve roots in dogs, he was able to localize the anatomical centre for the reflex in the sacral part of the cord, the reflex persisting until the fourth posterior sacral nerve roots were cut.

This original description thus recognized a spinal reflex connection between the skin around the anus and the external anal sphincter. Stimulation of the perianal skin, however, also gives rise to simultaneous reflex reactions elsewhere, particularly in the external urethral sphincter and in the bulbocavernosus muscle (Aller and Jelasic, 1974; Pedersen, 1978; Volusek, Janko and Lokar, 1983). This parallelism in the response characteristics of the external anal sphincter, external urethral sphincter and the bulbocavernosus muscles may allow conclusions about the reflex activity in one of the muscle groups to be applied by analogy to the others because of their common segmental innervation. Such conclusions are, of course, not valid in the case of localized peripheral neuromuscular lesions, since in such cases differences in responses in these muscles can be informative about the site of the lesion.

Reflex reaction in the external anal and urethral sphincter can also be provoked by stimulating the dorsal nerve of the glans penis (Bors and Blinn, 1959; Vereecken et al., 1982; Bilkey, Awad and Smith, 1983; Volusek, Janko and Lokar, 1983; Smith and Varma, 1984; Varma and Smith, 1988), the mucosa of the rectum, urethra and bladder (Bradley, 1972, 1978; Godec, Ayala and Cass, 1977; Rockswold and Bradley, 1977; Vereecken et al., 1982), and the skin of the distal parts of the leg, as used for elicitation of the flexor reflex (Pedersen, 1954; Mai and Pedersen, 1976; Booth, Harrison and Green, 1984). Reflex reactions from the rectum, colon and the bladder can, however, also inhibit activity in the anal sphincters, e.g. distension or contraction of visceral smooth muscle may initiate evacuation of the rectum (Parks, Porter and Melzack, 1962).

Reflex reactions can also be found in the ischiocavernosus (Dick et al., 1974; Lavoisier, Proulx and Courtois, 1988), puborectalis and part of the levator ani muscles, but systematic investigations of these muscles in humans are not available.

Elicitation by electrical stimulation and electromyography (EMG) of reflexes involving the striated muscles of the pelvic floor is a useful supplement to mechanical stimulation and visual observation. Such techniques are necessary for accurate measurement of threshold and latency and have stimulated much interest in the neurological evaluation of the conus medullaris and its sensory and motor connections. Such studies are of particular value in the assessment of functional disorders of the anorectum and the lower urinary tract and possibly of sexual dysfunction (Ertekin and Reel, 1976; Rockswold and Bradley, 1977; Krane and Siroky, 1980; Blaivas, Zayed and Labib, 1981; Haldeman, Bradley and Bhatia, 1982; Haldeman et al., 1982; Vereecken et al., 1982; Bilkey, Awad and Smith, 1983;
Electrophysiological techniques

Perianal stimulation

Elicitation of the classical anal reflex can be performed by single or repetitive pin-pricks or scratching of the perianal skin. In normal subjects, contraction of the stimulated side is normally accompanied by a reaction on the opposite side, often to a lesser degree. Electrical stimulation can be achieved by surface electrodes fixed to the perianal skin or by specially designed ‘prongs’ (Pedersen et al., 1978). Single electrical shocks or train stimuli can be used. A train of pulses is the most effective for eliciting polysynaptic reflexes, as exemplified by studies of the flexor reflex (Torrning, Pedersen and Klemar, 1981). However, due to the short distance between stimulating and recording electrodes in studies of the anal reflex, the time covered by the stimulus train will exclude observation of the early reaction and, in addition, the amplifier will often be saturated for even longer periods. Single or twin shocks are therefore most appropriate in studies of early and late reactions, pulses of 0.1–0.2 ms duration being most commonly used (Pedersen et al., 1978; Wright et al., 1985).

Dorsal nerve stimulation

The dorsal nerve of the glans or clitoris is best stimulated with a small bipolar felt surface electrode (type LBS 5301, Medelec, UK). A saline-soaked felt strap wrapped around the thigh is used as a ground electrode, with the patient in the left lateral or supine position. Sensory threshold is defined as the first sensation of ‘tapping’ perceived by the patient as the stimulating current is slowly increased via the constant-current generator (Fidas et al., 1987). Electrosensitivity should be measured in milliamperes (mA), voltage being an inaccurate unit of sensory measurement due to variations in skin resistance. The stimulation current is further increased to approximately three times its threshold value, which the patient should be able to tolerate without discomfort. Approximately 100 square-wave stimuli (duration 0.1 ms, frequency 2 Hz) are applied until a reproducible motor response (at the anal or urethral sphincters or bulbocavernosus muscle) is obtained on digital averaging (Smith and Varma, 1984; Galloway, Chisholm and McInnes, 1985; Varma, Smith and McInnes, 1986).

In the male patient, adjustable ring electrodes around the penis have also been used (Ertekin and Reel, 1976; Yalla et al., 1978; Vereecken et al., 1982) to deliver single or train stimuli.

Urethral stimulation

A catheter-mounted platinum urethral ring electrode (DISA, Copenhagen, 21L 10/11), inserted under sterile conditions, is used to stimulate the urethral mucosa. The same electrode can be used for recording the EMG from the external urethral sphincter. The electrode is mounted on a 14 FG Foley catheter and usually placed at the level of the external urethral sphincter in order to monitor external urethral sphincter EMG if necessary. Urethral mucosal electrosensitivity can be determined in the same way as dorsal nerve electrosensitivity described above, using similar stimulation parameters. Further details of the methodology are described by Galloway, Chisholm and McInnes (1985) and Fidas et al. (1987) The principle is based on the method described by Kieswetter (1977) and Powell and Feneley (1980). Train stimuli are used and the digitally averaged response from the external anal sphincter recorded.

External anal sphincter EMG recording

Several methods of recording striated anal sphincter EMG are available, e.g. surface...
stick-on' perianal electrodes, anal plug electrodes and intramuscular electrodes. Anal plug electrodes (DISA, Copenhagen, 13K 78/79) are preferred for the study of somatosensory reflexes as they enable collection of signals from a much larger area of the anal sphincter but have the disadvantage of movement artefacts within the anal canal, especially in patients with lax sphincters such as those encountered in faecal incontinence. The mere presence of an object within the anal canal may be considered unphysiological in certain studies. Newer designs of anal plug electrodes utilizing vertical linear strips instead of rings may alleviate some of these problems (Binnie, et al., 1991).

Needle electrodes are more appropriate when studying the classical anal reflex (Pedersen et al., 1978) or reflex responses of the anal sphincter to rectal distension or straining (Varma and Smith, 1986). The lateral or posterior midline anal position is most appropriate for needle insertion, which may be facilitated by a finger in the rectum. The patient is usually placed in the left lateral position for electrode insertion.

There is a renewed interest in the use of fine wire electrodes inserted percutaneously into the external anal sphincter for anorectal physiological studies. They are considered to constitute a more 'physiological' investigative tool than concentric needle or anal plug electrodes as their presence is not perceptible to the patient after insertion and they can be left in situ for much longer periods for dynamic studies (Womack et al., 1985a). Insertion is via a fine hypodermic type of needle. Once the correct location has been electromyographically ascertained, the needle is withdrawn over the wire, which then is kept in place by a terminal 'hook'.

External urethral sphincter EMG recording

For the recording of somatosensory reflexes in both sexes the recommended method is by the placement of a catheter-mounted platinum ring electrode (DISA, Copenhagen, 21L 10/11) at the level of the urethral sphincter. The electrode is mounted on a 14 FG Foley catheter and placed 1 cm below the balloon for females, and approximately 2.5 cm below the balloon for men, depending on the length of the prostatic urethra (Galloway, Chisholm and McInnes, 1985). This non-traumatic method may initially activate mucosal reflexes, which can be minimized by the application of sterile lignocaine jelly if mucosal electrosensitivity is not to be measured at the same study. As in the anal sphincter, EMG signals can be gathered from a larger area of the urethral sphincter if a surface ring electrode rather than a needle electrode is used. This method also has the added advantage of enabling emptying of the bladder to optimize the EMG studies (Bradley, 1972; Rockswold and Bradley, 1977).

Concentric needle insertion into the external urethral sphincter is usually very uncomfortable, and often painful, for the patient. In men, this is best performed in the left lateral position. A 50–90 mm needle is introduced through the perineum 2 cm in front of the anus and approximately 0.5 cm above the midline and, guided by the operator's index finger in the rectum, is inserted and placed on the middle lobe of the prostate. A slight resistance is usually felt when the needle penetrates the muscle. This coincides with the appearance of EMG activity on the oscilloscope and in the loudspeaker of the EMG equipment. In women, the dorsal position is the most convenient for this investigation. A 42 mm needle is introduced through the vaginal mucosa next to the external urethral orifice. The urethral sphincter is located at a depth of approximately 1.5 cm. The introduction of the electrode can be facilitated by a urethral catheter (Jesel, Isch-Treussard and Isch, 1973; Allert and Jelasic, 1974).

Bulbocavernosus EMG recording

The classical way of testing the bulbocavernosus reflex is by palpation of the bulbocavernosus and ischiocavernosus muscles, with the patient in the supine position. A response should be felt by stimulation of the glans penis or clitoris. This muscle contraction can facilitate the placing of surface electrodes or the introduction of a needle into the muscle. The muscles are located under the skin immediately to either side of the midpoint of a line drawn between the anus and the base of the scrotum or vagina (Dick et al., 1974; Krane and Siroky, 1980; Lavoisier, Proulx and Courtois, 1988). The ischiocavernosus muscles are located lateral to the bulbocavernosus muscles, just medial to the ischiopubic bone, at a depth of approximately 1–2 cm.
Concentric needle electrodes are most commonly used to record bulbocavernosus EMG (Dick et al., 1974; Krane and Siroky, 1980; Lavoisier, Proulx and Courtois, 1988; Porst, Tackmann and van Ahlen, 1988). Due to the small muscle mass, movement of the needle electrode may alter EMG activity as electrical activity from neighbouring muscles is picked up. This can disturb quantitative measurements of the activity of the striated muscles. A special amplifier recording a number of units firing over a certain threshold may overcome this problem (Klemar, Pedersen and Torring, 1981).

Haldeman, Bradley and Bhatia (1982) recorded reflex activity from the bulbocavernosus muscles using surface electrodes. The response with the highest amplitude was obtained from the electrode placed mid-way between the base of the penis and the anus.

**The classical anal reflex (cutaneo-anal reflex)**

The visible contraction of the anus on mechanical stimulation of the perianal skin can be analysed by EMG from the anal sphincter. The analysis may be further improved by replacing the mechanical stimulation by electrical stimulation and such an analysis will generally reveal a complex response, including early responses of short duration and later responses of longer duration. The latter responses form the electrophysiological basis of the visible response and for the mechanically elicited reflex.

Pedersen et al. (1978) demonstrated that the latency of the late response is, within certain limits, dependent on the intensity of stimulation. A latency at threshold stimulation of 200 ms (SD 80) and could be reduced to 50 ms (SD 10.5) by increasing the stimulus intensity (Figure 15.1). This was confirmed by Vodusek. Janko and Lokar (1983). With increasing stimulation intensity, the duration and voltage of the reflex response is increased, often with a tendency to rhythmicity, and it can have a duration of up to several hundred milliseconds.

This reflex has its afferent and efferent pathway in the pudendal nerve and uses the sacral segments S1–S4 (conus medullaris), the contribution from S1 being small. This is in accordance with the original demonstration in dogs and with the finding that efferent fibres from S1–S4 control the external anal sphincter (Torrin et al., 1983). The behaviour of the reflex, with long and stimulus-dependent latency and response characteristics, and with some tendency to habituation, indicates a polysynaptic reflex.

In suprasegmental lesions of the central nervous system, particularly of the spinal cord, the minimum latency of the reflex did not differ from that observed in normal subjects. The reaction was, however, usually more pronounced, sometimes with a duration of up to a few seconds, a behaviour similar to that of the flexor withdrawal reflex (Pedersen, 1954; Pedersen et al., 1978; Torring, Pedersen and Klemar, 1981).

By perianal electrical stimulation, Henry and Swash described a latency for this reflex of 8.3 ± 1.7 ms (mean ± SD) in 13 normal subjects and suggested that it was prolonged in faecal incontinence and rectal prolapse (Henry and Swash, 1978; Neil, Parks and Swash, 1981; Swash, 1982a, 1982b). The presence of these short-latency responses has been observed by other workers, who also noted later responses of longer duration (Haldeman et al., 1982; Pedersen et al., 1982; Vodusek, Janko and...
The classical anal reflex (cutaneous-anal reflex)

The early reactions have a very constant latency (Figure 15.2), uniform electrical pattern and generally show no sign of fatigue. They are not abolished by spinal anaesthesia (Pedersen et al., 1982; Wright et al., 1985) and their latencies are too short for a spinal reflex (Haldeman et al., 1982; Pedersen et al., 1982; Vodusek, Janko and Lokar, 1983). They have therefore been attributed to direct activation of the terminal innervation of the external anal sphincter (Pedersen et al., 1982; Swash, 1982b; Bartolo, Jarratt and Read, 1983; Vodusek, Janko and Lokar, 1983; Wright et al., 1985) but the latency is such that very slow conducting fibres should be in operation. However, Marsden. Merton and Morton (1982) were able to demonstrate different nerves with a conduction velocity of approximately 60 m/s following electrical stimulation of the conus medullaris. The short latency reaction is therefore more likely to be due to direct nerve stimulation, causing an antidromic volley in the efferent nerve travelling to a point of branching, then travelling anterogradely in the collateral division of the pudendal nerve. This would be in accordance with both the high threshold level and the very constant latency and uniformity of electrical pattern when a certain placement of stimulating and recording electrodes is used. It would also be consistent with the lack of habituation, the strictly ipsilateral response and the persistence of the response following epidural or spinal anaesthesia. Some of the intermediate responses may be due to antidromic stimulation with interaction between neighbouring a motor neurons in Onuf's nucleus (Onuf, 1901), hence resulting in 'oligosynaptic' latencies (Pedersen et al., 1982; Bartolo, Jarratt and Read, 1983a; Wright et al., 1985). Such a transmission of impulses has been observed between a motor neurons in the cat (Gogan et al., 1977) (Figure 15.3). These variable factors

![Figure 15.2 Electromyographic recording from the anal sphincter after perianal electrical stimulation with one pulse of 0.2 ms duration. The reflex in the upper trace is elicited by stimulus intensity near the threshold; the reflex in the lower trace by higher stimulation. S, stimulation.

![Figure 15.3 Arrows indicating the possible route of impulses in the first (a) and second (b) fast response. In (a) the impulse travels antidromically to the point of branching and then down the other collateral to the muscle; in (b) the impulse reaches the spinal cord antidromically through the efferent fibre and can then pass from the first to the second motor neurons either at sites of direct apposition or by spinal collaterals.](image-url)
have made the precise determination of the latency of the anal reflex difficult and limited its usefulness for studying the neurophysiology of the pelvic floor (Bartolo, Jarratt and Read, 1983a, 1983b). The classical (polysynaptic) anal reflex is now recognized to have a latency of $50 \pm 10.5$ ms (Pedersen et al., 1978).

The pudendoanal reflex

Stimulation of the dorsal nerve of the penis or clitoris evokes a reflex contraction of the external anal sphincter amongst other muscles (Bors and Blinn, 1959) (Figure 15.4). This has been variously termed the 'sacral evoked potential' (Krane and Siroky, 1980), 'sacral evoked response' (Galloway et al., 1985), 'sacral reflex' (Bilkey, Awad and Smith, 1983; Fidas et al., 1985), 'pudendal evoked response' (Haldeman et al., 1982) and 'pudendal sexual reflex' (Dick et al., 1974). However, the terminology of 'pudendo-anal reflex' was finally adopted at a meeting of the Physiological Society in London (Smith and Varma, 1984).

The latency of this response appears to be dependent on the intensity of stimulation (Bilkey, Awad and Smith, 1983) and it behaves much like the classical anal reflex (Pedersen et al., 1982) but with a shorter latency. The most appropriate electrophysiological method for investigating this reflex is to use a train of submaximal stimulus impulses and to digitally average the anal sphincter response (Torrings, Pedersen and Klemar, 1981). The averaging technique usually helps to obtain a clearly defined response by reducing background activity (Figure 15.5). The relatively greater distance between recording and stimulating electrodes diminishes the stimulus artefact and, more importantly, eliminates the 'direct' short-latency responses, such as those observed with the classical anal reflex. The use of the surface anal plug electrode is preferred because a much larger bulk of the sphincter can be sampled (Varma, Smith and McInnes,
(86). Modifications of the anal plug electrode using axial electrode strips instead of the conventional concentric rings may increase sensitivity (Binnie et al., 1991).

Varma, Smith and McInnes (1986) studied the latency of this reflex extensively in health and incontinence. Their findings in asymptomatic 'normal' subjects are summarized in Table 15.1. The latency of the reflex (38.5 ± 5.8 ms) appeared to be unaffected by age or sex within their study group. However, it was significantly prolonged in neurogenic faecal incontinence and the amplitude reduced (Table 15.2). Furthermore, the significant relationship of the latency of this reflex to mean motor unit potential duration of the external anal sphincter indicates it to be valuable as an index of neuropathy of this muscle (Figure 15.6).

Haldeman et al. (1982) were able to demonstrate a conduction time of approximately 8 ms in the afferent limb of the pudendoanal reflex by recording evoked potentials over the sacral

Table 15.1 Normal range and variations with sex and age of the latency of the pudendoanal reflex

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age range (years)</th>
<th>Latency range (ms)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 female, 13 male</td>
<td>23–75 (45 ± 14.6)</td>
<td>27.2–46.8 (38.5 ± 5.8)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>31 female (age-matched)</td>
<td>28–57 (46.4 ± 12.6)</td>
<td>33–46 (40.7 ± 4.4)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>13 male</td>
<td>28–59 (47 ± 12.7)</td>
<td>27.2–46.8 (38.5 ± 6.6)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>8 female ('young')</td>
<td>23–49 (33.6 ± 9.2)</td>
<td>33–44.8 (39.6 ± 4.3)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>8 female ('old')</td>
<td>55–75 (62 ± 6)</td>
<td>29.2–46 (36.6 ± 6.6)</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

Values in parentheses are mean ± sd.

Table 15.2 Electrophysiological external anal sphincter data in health and neurogenic faecal incontinence

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Incontinent</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency of pudendoanal reflex (ms)</td>
<td>(n = 25)</td>
<td>(n = 20)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Amplitude of pudendoanal reflex (uV)</td>
<td>39 ± 5.8</td>
<td>56 ± 12.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration of pudendoanal reflex (ms)</td>
<td>(3 absent)</td>
<td>1.95 ± 1.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean motor unit potential duration (ms)</td>
<td>16.9 ± 7</td>
<td>15.4 ± 5.4</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td></td>
<td>(n = 15)</td>
<td>(n = 20)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Measurements are mean ± sd.
The pudendoanal reflex latencies observed in normal subjects were measured as approximately 8 ms in the efferent limb of the reflex in normal subjects. This observation was confirmed by Squires, Henry and Swash (1985) who also showed prolongation of its latency in neurogenic faecal incontinence, thus demonstrating a lesion in the efferent pathway. Hence, assuming a normal latency range of 15–48 ms, the central conduction time for the pudendoanal reflex has a range of 15–33 ms, thus confirming its polysynaptic nature.

The rather startling prolongation of pudendoanal reflex latencies observed in neurogenic faecal incontinence (that is, more than expected by a delay in the efferent limb only), and the reduction in the amplitude of the response, suggest that in these patients the afferent impulse has some difficulty in stimulating the spinal α motor neurons to generate a potential and hence evoke a response from the external anal sphincter. This may be due to a reduction in the number of such neurons innervating the sphincter, as is suggested by the larger size of the motor units in these patients, suggesting reinnervation (Bartolo, Jarrett and Read, 1983b; Varma, Smith and McInnes, 1986). A smaller motor neuron pool must also result in less interaction between them (Gogan et al., 1977), further magnifying the latency differences between normal subjects and patients with defects of sphincter innervation. The analogy is clearly with multiple sclerosis, in which the latency of the visual evoked response at the cortex is far longer than that expected for any delay in conduction in the optic nerves, thus indicating that the nervous system experiences difficulty in generating the potential. Furthermore, there is now increasing evidence of a sensory neuropathy in some forms of faecal and urinary incontinence (Roie, Bartolo and Mortensen, 1985; Varma et al., 1988).

Binme et al. (1990) have reported encouraging early results in restoring faecal continence by therapeutic use of the pudendoanal reflex in patients with prolonged latencies. Seven out of eight patients benefited from a 2-month course of self-treatment utilizing an electrical stimulator at home. Following this treatment there was a significant increase in both the resting and squeeze anal canal pressures, but not in the sphincter length. There was also a significant increase in the amplitude of the pudendoanal reflex and in the integrated external sphincter EMG.

The polysynaptic nature of the pudendoanal reflex and its reproducibility also prove it a suitable tool for the electrophysiological exploration of the sacral spinal cord in the absence of neuropathic changes in the external anal sphincter. Hence, it has been used in the investigation of patients with possible neurogenic disorders of the urinary bladder and sexual function (Ertekin and Reel, 1976; Rockswood and Bradley, 1977; Krane and Siroky, 1980; Blaivas, Zayed and Labib, 1981; Haldeman, Bradley and Bhatia, 1982; Haldeman et al., 1982; Vereecken et al., 1982; Bilkey, Awad and Smith, 1983; Vedosek, Janko and Lokar, 1983; Fidas et al., 1985, 1987; Galloway, Chisholm and McInnes, 1985; Porst, Tackmann and van Ahlen, 1988; Varma et al., 1988). These patients often have radiological evidence of spinal dysraphism (Galloway and Tainsh, 1985; Fidas et al., 1989). Similar observations have been made in some young women with intractable constipation of idiopathic origin (Varma and Smith, 1988; Kerrigan et al., 1989). In these patients the latency of the reflex may be quite prolonged or even absent, and appears to be due to a defect of central conduction.

**Anal sphincter response to urethral stimulation**

A contractile response of the external anal sphincter may be observed in response to electrical stimulation of the vesical neck or urethral mucosa. The technique of eliciting and measuring this response was termed ‘urethral electromyography’ by Bradley (1972). A caudal block at the L4 level obliterated this response, as did pudendal nerve block (Rockswood and Bradley, 1977). In a study involving 29 normal subjects they reported a latency of 60–80 ms. Vereeeken et al. (1982) reported a range of 55–80 ms in 50 normal subjects for this response. Varma et al. (1988) observed a latency range of 54.5–80.5 ms, mean 69.6 ± 8.8 ms in 16 control subjects. This reflex has also been found useful in the investigation of bladder function (Fidas et al., 1985, 1987; Varma et al., 1988). Urethral electrosensitivity can also be measured during this investigation and provides further useful information.
Lesions of the segmental pathways

The normal demonstration of the somatosensory reflexes described above is dependent on the integrity of segmental pathways, including afferent and efferent peripheral nerves and their connections in the conus medullaris. These reflexes are always present in normal subjects, the classical anal reflex typically recorded with a minimum latency around 50 ms (Pedersen et al., 1982), and the pudendoanal reflex with a minimum latency around 38 ms (Varma, Smith and McInnes, 1986). Prolongation or absence of these reflexes is therefore an indicator of a defect in the reflex pathway, as is a reduction in their amplitude (Varma, Smith and McInnes, 1986).

The short latency reactions seen during the electrophysiological elicitation of the classical anal reflex, typically with a latency of 5–8 ms, most probably reflect activity in the efferent peripheral nerves and not in the nerve roots or the spinal segment, as demonstrated in their

Other useful pelvic floor reflexes

By electrical stimulation of the glans penis or clitoris, a reflex reaction is provoked in the bulbocavernosus muscle with a latency in the range of 27–42 ms: this is the classical bulbocavernosus reflex (Lapides and Bobbitt, 1956; Rashworth, 1967; Dick et al., 1974; Ertek and Reel, 1976; Siroky, Sax and Krane, 1979; Krane and Siroky, 1980; Haldeman, Bradley and Bhatia, 1982; Haldeman et al., 1982). In a comprehensive study of 39 normal men, Porst, Teckmann and van Ahlen (1988) described minimal latencies ranging from 22 to 38 ms (mean 31.4 ± 3.4 ms). In most patients no side differences were detected. Krane and Siroky (1980) described early and late components in their recordings, the origin of the late component being speculative. They found the use of lateral stimulation and recording techniques more effective in localizing neurological lesions. This reflex has been most commonly used in the neurophysiological investigation of bladder and sexual dysfunction. Lavoisier et al. (1989), however, have cast doubt about its validity as a diagnostic test of neurogenic impotence and have suggested that the ischiocavernosus reflex (Lavoisier et al., 1988) may be a more appropriate reflex to study this disorder.

Electrical stimulation of the dorsal nerve also provokes a reflex contraction of the external urethral sphincter, which has been found useful in the investigation of bladder function (Fidas et al., 1985, 1987; Varma et al., 1988). Normal latencies are usually within 30–50 ms, mean 40.5 ± 5.2 ms (Varma et al., 1988). These latencies are similar to those of the pudendoanal reflex in health, and may be measured simultaneously (Figure 15.7). Delayed latencies and blunted electrosensitivities were recorded in genuine stress urinary incontinence (Figures 15.8 and 15.9).

The qualitative assessment of anal sphincter reflexes in response to rectal distension and straining at defaecation are also becoming increasingly important in the evaluation of various organic and functional disorders of the ano rectum, e.g. idiopathic constipation, faecal incontinence, solitary rectal ulcer syndrome and radiation rectal injury (Womack et al., 1985a; Varma and Smith, 1986).
Anal reflexes

Figure 15.8 Scattergram depicting three different somatosensory pelvic floor reflex latencies in genuine stress urinary incontinence. Numbers in brackets denote numbers of patients and controls studied. DN, dorsal nerve; EAS, external anal sphincter; US, urethral sphincter; UM, urethral mucosa. X indicates absent response.

Figure 15.9 Scattergram depicting cutaneous sensitivities in genuine stress urinary incontinence. Numbers in brackets denote numbers of patients and controls studied. X indicates sensitive (>70 mA).

survival during sacral anaesthesia. A significant increase in the latency of these responses is therefore assumed to indicate impairment of the efferent nerves in their terminal portion. However, the short latency responses are not constantly present and their absence is therefore of dubious significance (Bartolo, Jarratt and Read, 1983a; Wright et al., 1985).

Absence or depression of the long-latency reflexes can be caused by a central lesion in the conus medullaris (Varma and Smith, 1988), by congenital lesions such as spina bifida, or by acquired, infectious, traumatic or expanding lesions. Multiple sclerosis only depresses the reflexes in those unusual cases with conus lesions. The anal reflex can be absent in spinal shock but is usually the first to return after this insult (Riddoch, 1917; Pedersen et al., 1978). In some patients with absence of reflex anal reactions after perianal stimulation, peripheral stimulation over the posterior tibial nerve can result in an anal response. In such cases a lesion in the afferent sacral nerves may be present.

Causes of nerve damage, other than a stretch injury of the terminal innervation of the
sphincter musculature, can result in increased latencies. Thus, following glans stimulation, Rushworth (1967) found reflexes with a latency of 120 ms in a patient with polyneuritis, and Vereecken et al. (1982) recorded a latency of 630 ms in a patient with a T12 fracture. Federsen et al. (1978) described latencies of up to 200 ms after perianal stimulation in cases where disc protrusion had caused a cauda equina syndrome. Ertekin et al. (1979) described abnormalities of the bulbocavernosus reflex in 40 patients with traumatic or compressive lesions of the cauda equina. Similar observations were made by Rockswold and Bradley (1977).

Traumatic lesions caused by stretch injury of the pudendal nerve are now recognized as the case of ‘idiopathic’ faecal incontinence in which denervation of the external anal sphincter has been confirmed by histological and electrophysiological data. Henry and Swash (1978) found a delay in the early reactions of the classical anal reflex in such cases, whereas Bartolo, Jarratt and Read (1983a, 1983b) did not. The latter authors did not find any difference for the late component either, but this may have been due to difficulties in recording distinct reactions. Varma, Smith and McIntnes (1986) found the pudendanal reflex value in evaluating neurogenic faecal incontinence and correlated their findings to mean motor unit potential measured from the external anal sphincter. Furthermore, this reflex has been found of value in evaluating stress urinary incontinence (Varma et al., 1988) and in certain patients with ‘idiopathic’ constipation in which a central defect may be postulated (Varma and Smith, 1988; Kerrigan et al., 1989). Reflexes involving the bulbocavernosus and external urethral sphincter muscles may also be of value in the assessment of other bladder and sexual functional disorders (Ertekin and Reel, 1976; Rockswold and Bradley, 1977; Krane and Siroky, 1980; Blaivas, Zayed and Labib, 1981; Haldeman et al., 1982; Vereecken et al., 1982; Bilkey, Awad and Smith, 1983; Vodusek, Janko and Lokar, 1983; Fidas et al., 1985, 1987; Golloway, Ashman and McIntnes, 1985; Porst, Taekman and van Ahlen, 1988).

The diagnostic value of latency measurement of somatosensory pelvic floor reflexes is increased when supplemented by other functional investigations. These include anorectal manometry, videoproctography, urodynamics and videocystometry, EMG (duration of motor units, number of polyphasic potentials, fibre density) and measurement of conduction velocity in the motor innervation of the pelvic floor (Snooks, Barnes and Swash, 1984).

References

Electrical stimulation of the rectal ampulla causing reflex dysfunction.

Bulbocavernosus reflex: its validity as a diagnostic test of neurogenic impotence.

The latency of the anal reflex.

Physiological studies on the anal sphincter muscle in faecal incontinence and rectal prolapse.


Human anal reflexes. Journal of Neurology, Neurosurgery and Psychiatry, 9, 813–818


The reflex functions of the
References

219

completely divided spinal cord in man, compared with those associated with less severe lesions. Brain, 40, 264–402.


Solitary Rectal Ulcer: The Place of Biofeedback and Surgery in the Treatment of the Syndrome

N.R. Binnie, M.D., F.R.C.S.Ed., Maria Papachrysostomou, M.D., Nicola Clare, and A.N. Smith, M.D., F.R.C.S.Ed.

University Department of Surgery, Western General Hospital, Edinburgh, Scotland

Thirty-one patients with the solitary rectal ulcer syndrome were studied, the majority of whom presented with fresh blood per rectum and a rectal ulcer, mucorrhoea, or a varying degree of rectal prolapse. Fourteen patients were treated conservatively or with surgery and had a high rate of recurrence of the solitary rectal ulcer syndrome. Seventeen patients were treated with biofeedback for the associated obstructed defecation (anismus) either before or immediately after surgery with a lower recurrence rate. The final symptomatic cure rate was similar in both groups but 15 episodes of recurrence requiring further surgery were encountered in the non-biofeedback group compared to 4 recurrences in the biofeedback group.

The solitary rectal ulcer (SRU) syndrome is most commonly associated with chronic straining at stool with a limited, mostly concealed, degree of rectal mucosal prolapse and the passage of blood and mucus per rectum [1,2]. There are several synonyms for the syndrome including localized colitis cystica profunda [3], inverted hamartomatous polyp [4], and mucosal prolapse syndrome [5] which can now be grouped under the term SRU syndrome. The diagnosis of the SRU syndrome should be considered particularly in young patients with atypical ano-rectal lesions. The solitary rectal ulcer is typically 4 cm to 12 cm from the anal verge and anteriorly at the ano-rectal junction. The ulcer may vary from several mm to several cm in diameter and, despite the term solitary, there may be several ulcers. The shallow ulcers have a characteristic white fibrinous polymorph exudate in the base and a hyperaemic halo of several mm resembling the results of trauma before merging with normal mucosa (Fig. 1).

The clinical appearance of the solitary rectal ulcer has suggested a functional disturbance of the puborectalis muscle and the site of the ulcer at the level of the pelvic floor has helped advance the idea that it may be caused by the trauma of pressure on the mucosa which in turn may have followed a "concealed" rectal prolapse [6]. Ano-rectal manometric, electrophysiological, and radiological investigations have therefore been directed to possible pathophysiology of the pelvic floor in addition to the identification of the well defined histological appearances on biopsy. Until recently the mainstay of treatment has been the correction of the rectal mucosal prolapse by surgery or the excision of the ulcerated area. The recognition of damage from inappropriate contraction of the puborectalis muscle with obstructed defecation (anismus) contributing to the occlusion of the ano-rectal junction, while straining at stool, has led to the use of electromyography (EMG) biofeedback therapy. This therapy aims to correct the functional "spastic" disorder of anismus [7] which underlies the SRU syndrome. Thus further trauma is avoided to the anterior rectal mucosa which is being forced into a closed upper anal canal. This paper is based on a series of patients with histologically confirmed SRU syndrome, some of whom were treated by conventional surgery in the early part of the series while in the latter part the same surgical therapy was preceded by EMG biofeedback.

Patients

A group of 31 patients with SRU syndrome were studied over the past decade. There were 20 women with a mean age of 34.8 yrs (range 19 to 66 years) and 11 men with a mean age of 28.2 yrs (range 14 to 52 years). The mean duration of symptoms prior to presentation was 3.8 years with considerable variation from 4 months in the youngest male to 17 years in the oldest female.

The patients were divided into two groups, the first 14 patients were treated before the introduction of EMG biofeedback. The second group of 17 patients was treated by the same surgical measures and by biofeedback to reduce the anismus, after this therapy became available.

Methods

All patients underwent rectal examination and rigid sigmoidoscopy followed by a double-contrast barium enema to exclude more proximal colonic mucosal lesions. Biopsies were done at the edge of any rectal ulcer seen or from areas of abnormal anterior rectal mucosa. In some cases the biopsies were taken during an examination under anesthesia.

As part of the diagnostic work-up the patients underwent
standard ano-rectal manometric investigation to assess anal canal resting pressure plus reflex cough and voluntary squeeze pressures [8]. The presence of the recto-sphincteric reflex was also confirmed to exclude Hirschprung’s disease. The rectal compliance with volume of sensation and overall rectal capacity were assessed by the continuous infusion proctometrogram method [9]. A rectal balloon expulsion test was performed in all patients as a means of confirming obstructive defecation [10].

The demonstration of an abnormal increase in EMG activity in the puborectalis muscle was sought in the patients in the latter half of this study. The methods used were the same as those used to diagnose anismus in patients who have ano-rectal outlet obstruction but no SRU syndrome. Similarly the EMG biofeedback techniques used to retrain the non-relaxing pelvic floor in this study were the same as those used for anismus patients [11]. The EMG abnormality of anismus was detected with an anal plug surface electrode [12] and is illustrated in Figure 2. An index was used to calculate the degree of anismus present [13]. The anismus index is calculated by \((\text{Strain EMG} - \text{Rest EMG}) / (\text{Squeeze EMG} - \text{Rest EMG})) \times 100\). An index of 20% or less is unlikely to be symptomatic in our experience.

The histological features which permitted the diagnosis of solitary rectal ulcer were best seen in biopsies from the edge of the ulcer or from the erythematous mucosa in non-ulcerative cases [14]. Microscopically there was replacement of the lamina propria by muscle fibers from the muscularis mucosae which passed between the glandular tubules. There was a similar excess of fibroblasts with thickening of the muscularis mucosae (Fig. 3). There were localized areas of colitis cystica profunda with submucosal mucous lakes lined by colonic epithelium (Fig. 4).

Results

Presenting Features

The predominant symptoms at the time of presentation are shown in Table 1. All patients described some problems with defecation, the most common of which was excessive straining with the feeling of ano-rectal blockage and the feeling of incomplete evacuation with the need for repeat visits to the toilet, on occasion with urgency. A total of 15 (48%) patients admitted to self anal digitation to achieve satisfactory ano-rectal evacuation. All patients had some degree of anterior rectal mucosal prolapse. Other significant clinical and pathological findings on presentation are shown in Table 2.

Manometric Features

The results of the manometric investigations are shown in Table 3. The resting pressure in the anal canal was at the lower end of the accepted normal range with cough and squeeze pressures within normal limits. The recto-sphincteric reflex was present in all patients although the activity of the internal sphincter appeared to be somewhat reduced. The maximum tolerable volume and rectal compliance were reduced and resembled the results seen in patients with irritable bowel syndrome. No patient was able to expel the rectal balloon on testing for obstructive defecation.

Results of Treatment

These patients with the SRU syndrome were seen at the Gastrointestinal and General Surgery Units at the Western
Table 1. Presenting symptoms in patients with solitary ulcer syndrome.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percent of pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh blood per rectum</td>
<td>91</td>
</tr>
<tr>
<td>Mucorrhoea</td>
<td>76</td>
</tr>
<tr>
<td>Rectal prolapse</td>
<td>70</td>
</tr>
<tr>
<td>Self digitation</td>
<td>48</td>
</tr>
<tr>
<td>Ano-rectal pain</td>
<td>48</td>
</tr>
<tr>
<td>Constipation</td>
<td>31</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19</td>
</tr>
</tbody>
</table>

General Hospital, Edinburgh, from 1977 to 1990. The patients were grouped into an early series managed conservatively followed by surgery and a later series in which biofeedback therapy was incorporated as part of the management. Conservative measures relied on the usage of an anal dilator, steroid suppositories, and local diathermy applied to the ulcer to lessen bleeding. Surgical measures adopted were excision of the prominent anterior mucosal fold or the ulcer itself, and when that failed, a rectopexy. The cumulative results of this policy of serial treatments, whereby patients progressed from one form of management to another, are given in Table 4. Of the 14 patients treated in the non-biofeedback group there were 15 episodes of recurrence (5 patients had more than one recurrence) of the SRU syndrome with finally 3 patients remaining with persistent recurrence. In the biofeedback group there was a total of 4 recurrences (no patient had more than one recurrence) in 17 patients treated, with 2 patients remaining with persistent recurrence. Using Fisher's exact test for small numbers with the Armitage factor [15] the difference in episodes of recurrence was significant (p < 0.01) while there was no difference in the final cure rate.

Discussion

The solitary rectal ulcer has been recognized since first described by Cruveilhier in 1870 [16]. The syndrome may present...
in a variety of ways although classically there is excessive straining at stool with a feeling of obstructed defecation together with a history of some degree of rectal prolapse and fresh blood and mucus per rectum. In this study 91% of patients had fresh blood per rectum and 76% of patients had excessive mucus per rectum. The macroscopic appearance of resected specimens in the early part of this series showed defects in the mucosa (Fig. 5a) which the pathologists at that time believed to be the site of inverted hamartomatous polyps and suggested wider, deeper excisions to avoid recurrences (Fig. 5b). In many patients the lesions recurred at about 3 months postoperatively, having apparently healed initially.

The association between rectal prolapse and the SRU syndrome is well established [6, 17-20]. The patients in this study all had some degree of rectal prolapse with 22% having anterior mucosal fold prolapse, 24% with full thickness prolapse, and 51% had rectal intussusception. Womack and coauthors [6] found a higher rate of rectal intussusception (84%) in their study of the SRU syndrome. There are several methods described for treating rectal prolapse and all have their proponents. In this series 7 patients underwent excision of the redundant anterior mucosa while 17 patients underwent an ileal sponge resection using the transabdominal retro-rectal approach of Wells [21] with the addition of an anterior T-shaped extension to stabilize the site where the mucosal prolapse most commonly occurs.

Ano-rectal outlet obstruction due to inappropriate contraction of the puborectalis muscle has been called "anismus" [22]. The excessive straining at stool with the feeling of ano-rectal obstruction requiring self anal digitation to allow defecation is now recognized in the SRU syndrome [6, 17, 23]. Other authors have found anismus in only 50% of patients with the SRU syndrome while finding anismus present in up to 76% of patients with simple constipation, thus concluding that anismus was a non-specific finding [24]. However the high pressures associated with the obstruction of anismus may be related to the mucosal ulceration seen [6]. The functional abnormality of anismus has been treated with varying success by several methods including division of the puborectalis muscle [25] and local injection of Botulinum A toxin to paralyze the puborectalis [26]. Anismus has also been treated by EMG biofeedback to good effect by several groups [7, 10]. All the patients treated by biofeedback in this study had EMG proven anismus further demonstrated by a failure to expel a rectal balloon. Several patients also had dynamic video-proctography confirmation of obstructive defecation. The anismus was corrected as far as possible by EMG biofeedback before any surgical procedures were undertaken although in 3 patients the EMG biofeedback was performed immediately postoperatively.

From recent reports it seems likely that the combination of high pressure in the anal canal with anismus [6] and rectal prolapse [27] are linked in the development of the SRU syndrome. However, not all patients present with high intra-anal canal pressures. The duration of symptoms, such as chronic straining in obstructive defecation, often leads to neurogenic damage to the sphincters paradoxically giving low resting pressure.

The problem of those patients who do not respond to combined biofeedback and surgery has still to be addressed. In this series we noted that 3 such patients (2 female and 1 male) were found to have spina bifida occulta of L5 with associated cauda equina conduction defects and altered somatosensory evoked potential studies. The remaining 2 patients were both young males in their teenage years who admitted to an aversion to defecation. We suspect that these young men may have suffered some form of sexual abuse but have not as yet been able to substantiate this.

Résumé

Trente et un patients ayant un ulcère solitaire du rectum font l'objet de cette étude; la plupart d'entre eux présentaient, associés à des rectorragies et un ulcère, des glaires rectales ou un prolapsus rectal plus ou moins important. Quatorze d'entre eux ont été traités de façon conservative ou par la chirurgie seule: le taux de récidive était élevé. Dix-sept patients ont été traités par biofeedback pour leur anisme soit avant soit après l'acte chirurgical: le taux de récidive était bien moindre. Le taux final de cure symptomatique était similaire dans les deux groupes mais quinze patients ayant une récidive et n'ayant pas eu de biofeedback ont nécessité un acte chirurgical supplémentaire, alors que seulement quatre patients parmi ceux qui avaient eu une thérapie par biofeedback ont récidivé.
Resumen

El síndrome de úlcera rectal solitaria (URS) está comúnmente asociado con estreñimiento crónico y con un grado limitado, y generalmente oculto, de prolapso rectal y la secreción de sangre y moco por el recto. La presentación clínica del síndrome de URS sugiere que se trata de una alteración del músculo puborrectal y la ubicación de la URS al nivel del piso pélvico sugiere que la URS puede ser causada por trauma o presión sobre la mucosa. El reconocimiento del daño causado por una contracción inapropiada del músculo puborrectal en el síndrome de URS sugiere que se trata de una alteración del músculo puborrectal en el síndrome de prolapso rectal, y la ubicación de la URS al nivel del piso pélvico sugiere que se trata de una alteración del músculo puborrectal en el síndrome de URS.

La mayoría de los pacientes con el síndrome de URS presentan sangrado fresco por el recto y una úlcera rectal, mucorrea o un prolapso rectal de grado variable. Catorce pacientes fueron tratados en forma conservadora o con cirugía. Diecisiete pacientes fueron tratados con bioretroalimentación EMG. Esta persigue corregir la alteración funcional “espástica” del anísmus que está presente como subfondo de este síndrome. Se estudiaron treinta y un pacientes con el síndrome de URS. La mayoría presentaba sangrado fresco por el recto y una úlcera rectal, mucorrea o un prolapso rectal de grado variable. Catorce pacientes fueron tratados en forma conservadora o con cirugía y exhibieron una elevada tasa de recurrencia del síndrome de URS. Diecisiete pacientes fueron tratados con bioretroalimentación para el cuadro de defecación obstruida antes o inmediatamente después de la cirugía, con una menor tasa de recurrencia. La tasa final de curación sintomática resultó similar en ambos grupos, pero hubo 15 episodios de recurrencia que requirieron cirugía adicional en el grupo en que no se hizo bioretroalimentación, contra cuatro recurrencias en el grupo de bioretroalimentación.

Aknowledgments

The authors thank Dr. W. Sircus, formerly Consultant Physician, Gastrointestinal Unit, Western General Hospital, Edinburgh for access to information on some of the patients in this study. N.R. Binnie was supported by a Scottish Hospital Endowment Research Trust Grant, No. 720 and Maria Papachrysostomou was supported by a Scottish Home and Health Department Chief Scientist Organisation Grant, No.K/MRS/50C1202.

References

Anal endosonography is a simple, minimally invasive technique that can be used to visualize the anal sphincters and can be advantageous in evaluating the anorectum. The first ultrasonographic studies of the human intestinal wall thickness were made many years ago (Wild, 1950). Until recently, technical shortcomings of the equipment have prevented the clinical use of ultrasound as a means of imaging the anal sphincters; so disruption of a sphincter was determined from clinical examination, pressure studies and by concentric electromyogram mapping. Modern endoprobes give high-resolution ultrasound images of the separate sphincter muscles (Law & Bartram, 1989).

When an endoprobe is introduced into the anal canal, it is bound to distend the canal to some extent. Different groups of investigators have used different sizes of endoprobes. We were interested to discover if the larger sizes of probes would have any stretching effect on the sphincters, altering their thicknesses. For this reason, two ultrasound endoprobes of different tip diameter were used in evaluating how the thickness of the anal sphincters might respond to the stretching effects of the probe size.

Materials and methods

Anal endosonography was conducted on 38 patients using two probes: (1) a Bruel & Kjaer 6.5 MHz radial rotating endoprobe of maximum tip diameter 1 cm, and (2) a 7 MHz radial rotating endoprobe of maximum tip diameter 2 cm (Fig. 1). The 1 cm probe tip was fitted with a rigid plastic cone filled with degassed water to provide protection for the rotating probe and effective acoustic coupling within the anal canal. The 2 cm probe tip was protected by a disposable latex tube containing degassed water. Both endoprobes were used in each patient, at the same visit to the hospital.

Each lubricated endoprobe was inserted into the rectum with the patient in the left lateral position and serial images were obtained on slow withdrawal of the endoprobe from the rectum through the anal canal. Video-recordings of the ultrasonic scanning were obtained for all patients and were stored for further analysis and study. Hard copy was acquired on single-sided emulsion film and measurements of sphincter thickness were made to ±0.2 mm. The smooth muscle of the internal anal sphincter (IAS) was clearly identifiable as a homogeneous hypoechoic circular band extending caudally to a level just proximal to the anal verge. The striated muscle of the external anal sphincter (EAS) had a different acoustic texture, with mixed echogenicity and linear pattern, giving a "streaky" appearance. Between the two sphincters there was a narrow echogenic band that represented the intersphincteric plane. Immediately adjacent to the endoprobe tip was a hypoechoic layer of mucosa, continuous with the rectal mucosa. Between the mucosa and the IAS was the more echogenic submucosa, which became progressively denser and thicker caudally (Fig. 2). It was possible to identify clearly the hypoechoic layer of the IAS lying

Figure 1. The 7 MHz radial rotating endoprobe, maximum tip diameter 2 cm. The 6.5 MHz endoprobe had a similar appearance, but with a 1 cm diameter.
between the two more echogenic structures of the submucosa and the intersphincteric plane. Measurements of the IAS thickness were thus simple and accurate (Fig. 3). On the other hand, the EAS thickness measurements were not as easy to acquire since the EAS was adjacent to the hyperechoic intersphincteric plane, and therefore there is hardly a distinctive line between the two layers of muscle. The solution to this was to measure the thickness of the EAS at the very distal part of the anal canal and to relate its outer border to the anterior border of the coccyx. The thickness of the muscle measured in that way is subjective and depended on individual anatomical considerations. The thickest terminal portion of the internal sphincter was measured at the mid-anal canal. In the lowermost part of the anal canal, the thickness of the EAS was measured using the boundaries of the coccyx shadow.

Results
With the 1 cm endprobe, results (mean ± SD) were IAS thickness = 0.29 ± 0.11 cm, and EAS thickness = 0.81 ± 0.15 cm. With the 2 cm endprobe, results (mean ± SD) were IAS thickness = 0.22 ± 0.07 cm, and EAS thickness = 0.83 ± 0.24 cm.

A paired t-test was used for comparing the thicknesses of the anal sphincters in the 38 patients using both endoprobes. This showed no difference in the measurements of EAS thickness using either endprobe (p > 0.5), whereas the IAS was found to be thinner in appearance when measured using the 2 cm diameter endprobe (p = 0.0003).

Discussion
We have used ultrasonicographic demonstration of the sphincters in patients with various disease states and have measured the thicknesses of both the IAS and EAS using two endoprobes.

The larger 2 cm endprobe alters the thickness of the IAS by about 30%, but had no measurable effect on the EAS. We would expect the IAS to be more susceptible to stretching than the EAS because of its small size. This is approximately 20 times less than the diameter of the larger probe used. In addition, the difference resulting from stretching may also depend on the IAS smooth muscle "elastance" property. On the contrary, the EAS striated muscle may be less subject to distension effects because of its tonic control, which allows adaptation.

Our conclusion is that a 1 cm diameter endprobe is preferable for imaging the anal sphincters and for measuring their thickness, since it causes less disturbance than the 2 cm probe.

As various rectal endoprobes with tip diameters ranging from 1 cm to over 2 cm are in common use, it is...
Technical notes

Important that the size of the probe used should be recorded when reporting anal sphincter measurements.

Acknowledgements

Dr M. Papachrysoomou was supported by the Scottish Home and Health Department Clinical and Biomedical Research Grant (K/MRS/5001202). Miss N. Clare is thanked for her technical assistance.

Virtual source distances and field geometry independent output factors for 5–14 MeV electron beams from a Siemens Mevatron M7145

By J. H. Plane, BA, MSc and M. M. Trevor, BSc, MSc

Regional Medical Physics Department, South Cleveland Hospital, Marton Road, Middlesbrough, Cleveland TS4 3BW, UK

(Received 30 October 1991 and in revised form 16 March 1992, accepted 7 April 1992)

Keywords: Virtual source distances, Output factors, Electron beams

It is well established that an inverse square factor based on virtual source distance (VSD) corrects for an air space between the electron applicator and the skin surface (ICRU, 1972; Almond, 1976). Values of VSD have been measured for electron fields of a Siemens Mevatron M7145. Double scattering foils and collimators above the applicator reduce scatter from the applicator walls. As a result some virtual sources are near to the electron window. However, there is some variation with energy and field size.

Output factors for open applicators and those containing irregular shaped fields have been measured for a range of applicators and irregular areas. The output factor for the open applicator is valid for any irregular shape within a given range. Possible reasons for this effect are discussed.

Method

Electrons from a Siemens Mevatron M7145 linear accelerator at South Cleveland Hospital were investigated. The energies of electrons as measured using the HPA protocol (HPA, 1985) were 5.0, 7.2, 9.2, 12.0 and 14.0 MeV. Applicators ranged in size from a 5 cm diameter circle to 10×10 cm, 15×15 cm, 20×20 cm and 25×25 cm.

The method used to measure VSD was described by Almond (1976). Ionization readings were made in air using a thimble ionization chamber (Type 2571, NE Ltd) connected to an electrometer (Type 2570, NE Ltd). The chamber was moved using a custom made lead screw driven by a stepper motor. The distances from the end of the applicator were 0, 5, 10, 15, 20, 25 and 30 cm. The transmission ionization chamber of the linear accelerator was used as a reference. The radiation beam was on continuously. Readings were taken by switching the dose meter on for 6 s in each position. This gave adequate ionization readings up to and including 30 cm. The automatic frequency control of the linear accelerator stabilized the output and helped maintain precision. A graph of reciprocal square root of ionization readings against distance from the end of the applicator gave a straight line using linear regression (Klevenhagen, 1985). The intercept on the distance axis gave the value of VSD.

The method used to measure the output factor was that described by HPA (1985). An ionization chamber in a multilayer polystyrene phantom was irradiated. Open applicators in contact with the phantom were used. Regular and irregular fields were produced using the method of Plane and Usher (1990).

Results

The values of VSD are shown in Fig. 1. For high energies at large field sizes the virtual source approaches the electron window. At lower energies and smaller field sizes the VSD was reduced.

The relative outputs of electron fields are shown in Fig. 2. Each output factor is normalized to the 10 cm square open applicator. Fig. 2 shows output factors for regular and irregular shaped fields. Irregular shaped fields may include or exclude the central axis of the applicator. In both cases the output factors are remarkably close to the open applicator.

Application

The absence of significant field geometry dependence permits considerable simplification of irregular field dosimetry. This simplification applies to a Siemens Mevatron M7145. An output factor, OF, can be used depending only on the size of the applicator and the

References


Figure 1. Virtual source distance against area for different applicators and electron energy. ■ 5 MeV, ▲ 7 MeV, ▼ 9 MeV, ♦ 12 MeV, * 14 MeV.

Figure 2. Relative output factors of electron fields for a 15 cm applicator at 9 MeV. * regular, ○ irregular.

electron energy. The mean and standard deviation from the data in Fig. 2 is $1.033 \pm 0.005$. This compares with 1.030 for the open applicator. The close agreement is typical of all data collected in this study. The number of monitor units (MU) to be set on the dosimetry system is calculated from

$$MU = \frac{D \times 100 \times (VSD + s)^2 \times 1}{n \times p \times (VSD)^2 \times OF}$$

At this centre the radiotherapy prescription defines the total dose ($D$) the number of fractions ($n$) and therapeutic range. The last parameter is used to select electron energy, depth of bolus material and the prescribed percentage ($p$). At the attendance of the patient for the first fraction the stand off ($s$) between the end of the applicator and the surface of the entry surface is measured.

Output factors are measured to three decimal places but quoted to two decimal places. This does not compromise the tolerance level of 2% required by WHO (1988).

Discussion

In this centre all radiotherapy with electrons comprises single straight on fields. Without the pre-
A method of computerised isotope dynamic proctography

M. Papachrysostomou1, T.M.J. Griffin2, C. Ferrington3, M.V. Merrick2, and A.N. Smith1

Departments of Surgery, Nuclear Medicine and Medical Physics, Western General Hospital, Edinburgh EH4 2XU, UK

Received 20 August 1991 and in revised form 28 January 1992

Abstract. Patients with long-standing constipation were examined by radioisotope proctography. A radiolabelled synthetic potato mash was inserted intrarectally and the dynamic changes during simulated defaecation recorded using a gamma-camera. Computer images from the stored data illustrate changes in the anorectal angle and pelvic floor. The median (and 95% confidence intervals) of the anorectal angles were: at rest 105° (101°, 116°), on voluntary contraction of the pelvic floor by 'squeezing' 91° (81°, 98°), on straining 120° (107°, 137°) and during evacuation 126° (116°, 153°). The pelvic floor movements were: pelvic floor ascent on voluntary contraction 28 mm (9, 34 mm), pelvic floor descent on straining −8 mm (−14, −4 mm) and descent during evacuation −27 mm (−34, −11 mm). Useful additions to previous methods are measurement of the completeness of rectal evacuation 58% (42, 77%), the defaecation time 64 s (50, 138 s) and the defaecation rate 0.9%/s (0.4, 1.4%/s).

Key words: Constipation - Evacuation - Isotope proctography - Anorectal angle - Pelvic floor


Introduction

The most commonly available examination at the present for the investigation of the physiology of defaecation is defaecating radiological videoprostography (Mahieu et al. 1984). The primary use of this is in determining the presence of structural defects such as rectal intussusception or occult rectal prolapse (Finlay 1988). Radiological proctograms have also been used to calculate resting and straining anorectal angles (Mahieu et al. 1984; Ekberg et al. 1985; Skomorowska et al. 1987; Shorvon et al. 1989), but none of these measures the ability of the rectum to evacuate. This is valuable information in patients with constipation, or those who find defaecation difficult.

Scintigraphic techniques have been used by several investigators to outline the 'neo-rectum' following ileoanal pouch anastomosis and the efficiency of its evacuation (O'Connell et al. 1986). Another method assesses the anorectal angle scintigraphically (Barkel et al. 1988) by a balloon inserted intrarectally and filled with water containing technetium-99m to outline the rectum. Scintigraphic assessment of 'faecal' bolus expulsion (O'Connell et al. 1986) has also been performed using an artificial radiolabelled 'stool' by inserting a 7.5% coloidal dispersion of aluminium magnesium silicate, technetium-99m and aluminium powder to make a thick paste. They found that about 70% of the artificial 'stool' was usually evacuated.

A new method of illustrating changes in the anorectal angle and pelvic floor in constipated patients is presented which combines elements of both the foregoing techniques (O'Connell et al. 1986; Barkel et al. 1988). The aims were to outline the anorectum and to simulate the passage of a 'faecal' bolus during certain manoeuvres which may occur in normal and/or abnormal defaecation.

Materials and methods

The clinical protocol was approved by the Ethical Committee of Lothian Health Board and by ARSAC (Administration of Radioactive Substances Advisory Committee). Twelve constipated subjects (3 men, 9 women), median age 48 years (age range 18-60 years) were recruited to the study. The patients had been suffering from constipation for 3–30 years. There were four women of childbearing age in the study, all of whom had the possibility of pregnancy excluded prior to the study.

The radiopharmaceutical used was rehydrated potato labelled with 99mTc-methylene diphosphonate (99mTc-MDP). The volume of the potato paste used in each subject was determined by prior balloon proctometrogram studies, which measured the maximum rectal capacity. This simulates the usual state of filling of the rectum at the time of defaecation (Mahieu 1989). The radiopharmaceutical was prepared by adding approximately 200 MBq of 99mTc-MDP to a volume of warm water determined by the proctometrogram, thus allowing for each patient's individual rectal capacity. The dehydrated potato powder was slowly added while constantly stirring to produce a smooth thick paste (30 ml of warm water to 1 tablespoon of potato powder). A Foley catheter (12 CH) filled...
with approximately 20 MBq 99mTc-MDP was used as the anal canal marker.

The patients were given prior bowel preparation in the form of suppositories (Carbalax containing 1.72 g sodium acid phosphate) to ensure an empty rectum before the insertion of the isotope-labelled paste and to avoid dilution of the isotope activity with any residual faecal matter. For introduction of the paste into the distal bowel, the subjects lay on their left side with hips fully flexed. A 15-cm-long tube (E-Z-EM) was inserted 10 cm per anum and the labelled potato paste introduced using 50-ml syringes. The volume introduced approximated to the maximum tolerable capacity.

Thereafter, the patient was seated upright on a commode with a plastic bag lining the collection pan. The computer was then set for the dynamic acquisition of 2-s images over 5 min per session. Further sessions were allowed when required. Recordings of rectal images were performed using a small field (Ohio Nuclear Series 100 or Elscint Dymax) gamma-camera equipped with a GAP (general all-purpose) collimator connected to a computer, in the left lateral seated position at rest and during various expulsive manoeuvres following commands for activities such as 'squeezing' (and/or coughing) for maximal voluntary contraction of the anal sphincter and straining at stool. Each subject was then asked to defaecate at will. At the termination of the study, if the evacuation of the paste was not complete, the residue was washed out. It is known that little of the radioactivity is absorbed by the rectal mucosa; moreover, it remains in situ for less than 15 min. Thus, the effective dose equivalent (EDE) is extremely low (EDE < 0.3 mSv), irrespective of the duration of observation. In contrast, fluoroscopy in the lateral projection is associated with an EDE of approximately 1 mSv/min (Padovani et al. 1987). Additional information in the case of incomplete defaecation could be obtained by screening and calculating the activity in the plastic liner containing the excreted 99mTc-MDP-labelled paste.

The statistical analysis used the median value and its 95% confidence intervals and the sign test for paired comparisons.

Data analysis. The data were stored for processing. Specially written software allowed the anorectal angles and changes in the pelvic floor level to be graphically displayed and measured as well as the percentage of activity evacuated within the defaecation time.

The stored data were then analysed by comparing the pre- and post-evacuation counts. The percentage of evacuation obtained from the scintigraphic data was calculated for the period of time during which the evacuation had taken place. On the lateral pre- and post-evacuation images, radioactivity clearly outlined the rectum and the anal canal. Using the 'regions of interest' (ROI) programme on the computer, radioactivity in the rectum could be separated from that in the anal canal. A third ROI included the overall radioactivity in the anorectum taken as a whole. The ROIs thus defined were applied to the dynamic emptying data, and separate emptying curves for the areas of interest were obtained (Fig. 1).

The time taken for evacuation was determined visually on the emptying curves, from the time at which defaecation commenced. Completion of defaecation was indicated by the evacuation curves as the point at which the isotope activity had dropped to a plateau level. A patient was considered to have an adequate rectal emptying when 60% or more of the isotope 'faecal' bolus was expelled. A further criterion of adequate rectal emptying was the duration of defaecation, which was expected to be 40 s or less. This is in agreement with measurements obtained from normal controls (O'Connell et al. 1986). The defaecation rate was derived by dividing the percentage of the activity evacuated by the time taken for evacuation.

The anal canal was outlined using a fine Foley (WSD' 7L31, 12CH) catheter containing isotope material (approximately 20 MBq of 99mTc-MDP). From the lateral position, it was possible to mark the theoretical line of the muscular pelvic floor by projecting a horizontal line through the anorectal junction at rest. The computer 'memorised' this level. Thereafter, measurements were made of the degree of pelvic floor descent on maximally contracting it during squeezing and coughing, relating this line at rest to the upward movement of the anorectal junction. Similar measurements were obtained of the degree of pelvic floor descent on straining and evacuation in relationship to the downward movement of the anorectal junction, again compared with the pelvic floor level at rest.

The anorectal angles (ARA) were recorded as upper and lower. The upper ARA was formed by the intersection of the axis of the rectum with that of the anal canal. The lower ARA was defined as the angle between the posterior rectal wall and the axis of the anal canal as they intersected at the level of the anorectal ring. The computer programme allowed objective measurements to be made of the anorectal angles imaged by the method described: during resting (Fig. 2), coughing, squeezing (Fig. 3), straining and evacuation (Fig. 4).

Results

The measurements obtained are summarised in Table 1. The changes recorded during the various manoeuvres are discussed below.

Lower anorectal angle

In the constipated patients studied, the resting anorectal angle was 105° (101°, 116°), decreasing by 14° (10°, 27°) during 'squeezing' and by 5° (1°, 8°) on coughing. During straining it was increased by 15° (1°, 24°), and on evacuation it was increased by 16° (11°, 38°).

Upper anorectal angle

The resting upper anorectal angle was 122° (105°, 131°) in the constipated patients studied; it decreased by 20° (13°, 30°) during 'squeezing' and by 5° (—4°, 7°) on coughing. It was increased on straining by 8° (5°, 18°), and again it was increased during evacuation by 22° (13°, 37°).

Pelvic floor movement

The pelvic floor movements were upwards on 'squeezing' by 28 mm (9, 34) and were upwards in most cases on coughing by 4 mm (—1, 9) compared with the pelvic floor level at rest. The pelvic floor movements were downwards on straining by —8 mm (—14, —4) and on evacuation by —27 mm (—34, —11). (The negative sign signifies a downward movement as compared with the level at rest.)
Fig. 1. Curves obtained during proctography. Vertical axis represents the count rate and horizontal axis, the time in 2-s frames. Middle curve depicts the activity in the rectum, lower one the anal canal and uppermost one the anorectum. The patient was asked to evacuate at will at the point indicated by an arrow. The slight increase followed by the decrease in activity, as demonstrated in the tracings, results from the passage of the bolus through the anal canal before its expulsion. End of defaecation is considered the time when the curve reaches a plateau level.

Fig. 2. Silhouette of the anorectum at rest. Horizontal line represents the level of the pelvic floor, vertical line the anal canal, lower oblique line the posterior lower rectal wall and upper oblique line the midline of the rectum. The lower ARA is formed by the line of the mid-anal canal and the lower oblique line, and the upper ARA is formed by the midline of the anal canal and the midline of the rectum (see text).

Fig. 3. Silhouette of the anorectum during 'squeezing' on voluntary maximal contraction of the pelvic floor muscles. Pelvic floor ascends. For details, see Fig. 2.

Fig. 4. Silhouette of the anorectum during evacuation. Pelvic floor descends. For details, see Fig. 2.

(Fig. 1-4 are taken from the same study of one patient)
Table 1. Anorectal angles (both upper and lower) measured by isotope proctography at rest, during voluntary contraction of the external sphincter on ‘squeezing’ and coughing, straining and evacuation. Pelvic floor ascent (positive sign omitted) and descent (negative sign) are shown. Defaecation time and rate and the percentage of the evacuated activity are derived.

<table>
<thead>
<tr>
<th></th>
<th>LARA</th>
<th>UARA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>105° (101°, 116°)</td>
<td>122° (105°, 131°)</td>
</tr>
<tr>
<td>Squeezing</td>
<td>91° (81°, 98°)</td>
<td>103° (88°, 112°)</td>
</tr>
<tr>
<td>Coughing</td>
<td>105° (92°, 118°)</td>
<td>121° (103°, 132°)</td>
</tr>
<tr>
<td>Straining</td>
<td>120° (107°, 137°)</td>
<td>136° (115°, 149°)</td>
</tr>
<tr>
<td>Evacuation</td>
<td>126° (116°, 153°)</td>
<td>139° (133°, 156°)</td>
</tr>
</tbody>
</table>

PF ascent on squeezing | 28 mm (9, 34)
PF ascent on coughing  | 4 mm (1.9)
PF descent on straining| -8 mm (-14, -4)
PF descent on evacuation| -27 mm (-34, -11)

Evacuation % | 58 (42, 77)
Defaecation time (s) | 64 (50, 138)
Defaecation rate %/s | 0.9 (0.4, 1.4)

LARA, lower anorectal angle; UARA, upper anorectal angle; PF ascent, pelvic floor ascent; PF descent, pelvic floor descent; Evacuation %, percentage of evacuated activity. The percentage of the activity evacuated, the defaecation time and rate are derived from 9 patients who evacuated during a single session of 5 min duration.

Defaecation assessment

The percentage of the evacuated activity achieved in this group as well as the defaecation time and rate are given in Table 1. Three patients (25%) were not able to evacuate during the procedure, and they had to use suppositories to empty the isotope paste. Nine patients (75%), however, evacuated the isotope paste, and 7 of them (78%) did so in less than 70 s.

Discussion

The rectum acts as a reservoir for faecal matter until evacuation is socially convenient. The rectum must, therefore, empty efficiently and completely when required. A patient is defined as constipated if straining at stool occupies more than 25% of the defaecating time or, alternatively, passes 2 or fewer stools per week (DeVroede 1988). A definition of constipation must include, notionally, the ideas of delay in colonic emptying as well as of problems in evacuating a full rectum, namely, straining. The implication from the above definition is that this disorder may be the consequence either of pelvic floor dysfunction or of delay in transit of faecal material through the colon.

Evacuation depends on complex interactions between the rectum, the pelvic floor and the anal sphincters (Parks et al. 1966). These interactions are part of a dynamic process; thus, the dynamic study of defaecation (Bartram et al. 1988) is considered more informative than studying static situations (Brown 1965; Kerremans 1969). The mechanisms which facilitate defaecation are interrelated and complex (Phillips and Edwards 1965). A more sophisticated understanding of anorectal physiology has been made possible by the introduction of methods designed to give quantitative as well as qualitative information about the dynamics of anorectal motility (Brown 1965; Kerremans 1969).

Isotope proctograms were obtained using radiolabelled rehydrated potato mash and recording a series of consecutive images to outline changes in the anorectal angle and movement of the pelvic floor on expulsion of the labelled simulated ‘faecal’ material. At the same time the capacity of constipated subjects to evacuate the simulated faecal bolus and any retrograde movement were studied. Observations on changes in the anorectal angle and pelvic floor have previously been made during radiological videoprocrocography, developed particularly to detect any anatomical and pathological changes upon defaecation (Poon et al. 1991), a method that has been considered unpleasant and has caused concern because of the high dose of radiation involved, especially to the pelvic organs (Womack and O'Connell 1991). Moreover, X-ray techniques involving the use of barium are not a very reliable means of estimating the ‘normal’ ability of patients to achieve defaecation, in view of the highly abnormal characteristics of the radiopaque barium used as a stool marker.

An assessment can also be made of the anorectal angles and the pelvic floor changes by our method. These are recorded simultaneously while assessing the adequacy of evacuation in a single dynamic study. This was simpler for patients who are thus exposed to one test only and one which minimises the amount of radiation exposure (EDE < 0.3 mSv). Although the method allows measurements of both UARA and LARA, the LARA measurement may be a more sensitive indicator of anorectal movements during the various expulsive manoeuvres (Bartram et al. 1988). The lower, or according to others the posterior, ARA reflects movements of the posterior wall of the rectum and does not depend on
the shape of the rectum, which may be altered with the position of the body, whether standing or sitting, as happens with the upper or central ARA (Shorvon et al. 1989).

The serial changes in the anorectum recorded in 2-s images can be analysed quantitatively. Preliminary comparisons with videoproctography have shown that isotope proctography gives comparable or possibly more sensitive results in detecting the angle changes upon defaecation (Papachrysostomou et al. 1991a).

Isotope proctography is thus a useful method of investigating constipation, providing information about evacuation, pelvic floor movement and the ARA as a means of assessing anorectal function. Finally, even the protracted defaecation associated with gross constipation can be studied safely because of the low dose of radiation involved. Potential applications for the isotope method include assessing various forms of abnormal defaecation, such as obstructive defaecation or anismus, compared with slow transit constipation. It may be of value to differentiate reduced movements of the pelvic floor or increased ARAs due to sphincter and pelvic floor laxity resulting from pudendal neuropathy associated with chronic straining in slow transit constipation, or to distinguish the more acute ARA of a non-relaxing pelvic floor in obstructive defaecation (Papachrysostomou et al. 1991b).

Acknowledgements. Dr. M. Papachrysostomou was supported by a Scottish Home and Health Department Clinical and Biomedical Research Grant (K/MRS/5001202). Current address: Gastrointestinal Unit, Department of Medicine, Western General Hospital, Edinburgh. Miss N. Clare is thanked for her technical assistance.

References


Brown BSJ (1965) Defecography or anorectal studies in children including cinefluorographic observations. J Can Assoc Radiol 16:66-76


Evaluation of isotope proctography in constipated subjects

M. Papachrysostomou, A. J. M. Stevenson, C. Ferrington, M. V. Merrick, A. N. Smith

Abstract. Twelve patients with longstanding constipation were examined by isotope proctography. Radio-labelled potato mash was inserted rectally to provoke the urge to defaecate and expulsive manoeuvres were recorded using a Gamma-camera. The method illustrated dynamic alterations in the anorectal angles (ARA) which became more acute on 'squeezing', less so on coughing and more obtuse on straining, and maximally so on evacuation. The pelvic floor (PF) movements were consistently upwards on squeezing, less so on coughing, downwards on straining, and maximally so on evacuation. A useful addition was the measurement of the completeness of evacuation and the time involved. The results were comparable to radiological videoproctography (P < 0.01), but the isotope method gave greater discrimination for both ARA and PF movement changes. It also allowed correlations to be made between the pelvic floor descent (P < 0.05) and anorectal angle changes (P < 0.01) with rectal evacuation.

Résumé. 12 patients avec une constipation au long court ont été examiné par proctographie isotopique. De la purée de pomme de terre marquée était introduite dans le rectum afin de provoquer un besoin de défécation et les manoeuvres d’expulsion étaient enregistrées par une gamma-caméra. Cette méthode illustre les altérations dynamiques de l’angle ano-rectal (ARA) qui devient plus aigu lors de la rétention ou de la toux et plus obtu à l’effort et maximal à l’évacuation. Les mouvements du plancher pelvien (PP) étaient ascendants lors de la rétention, mointre à la toux et descendant lors de l’effort avec un maximum pendant l’évacuation. Un ajout utile était la mesure de la totalité de l’évacuation et du temps mis à cela. Les résultats étaient comparables à la scintigraphie radiologique (P < 0.01), mais la méthode isotopique donnait une meilleure discrimination à la fois pour l’angle ano-rectal et les variations des mouvements du plancher pelvien. Ceci permettait aussi des correlations entre la descente du plancher pelvien (P < 0.05) et les variations de l’angle ano-rectal (P < 0.01) avec l’évacuation rectale.

Materials and methods

The clinical protocol was approved by the Ethical Committee of the Lothian Health Board and by ARSAC (Administration of Radioactive Substances Advisory Committee). Twelve constipated subjects (3 males; 9 females), median age 48 years (age range: 36, 53 years) were recruited to the isotope proctographic study. The patients had been suffering from constipation from 3 to 30 years, all had delayed bowel transit, with features of difficult, protracted, painful defaecation. Six patients with similar symptomatology were studied by radiological videoproctography, for a comparison of the 2 methods. These 6 'control' patients (1 male; 5 females) median age 50 years...
In the study, all of whom had the possibility of pregnancy excluded prior to the study.

Methods

Isotope proctography. The radiopharmaceutical used was rehydrated potato, labelled with approximately 200 MBq of 99m-Tc Methylene Diphosphonate (99mTc MDP). The volume of the bolus used in each subject was determined by prior balloon proctogram studies, thus allowing for each patient’s individual rectal capacity (for every 30 ml of warm water, 1 tablespoon of potato powder). A Foley catheter (12 CH) filled with approximately 20 MBq 99mTc MDP, was used as the anal canal marker.

Prior to insertion of the radiolabelled potato paste rectally, the patients were given bowel preparation in the form of suppositories. The method is described as by Papachryssostomou et al. (1992) [5]. Radiocal images were recorded in the left lateral projection with the patient seated upright on a commode using a Gamma camera. 2-second frames were acquired for five minutes per session (extended if required), during each manoeuvre: voluntary anal canal contraction during ‘squeezing’, on coughing, straining and evacuation. In the instance of incomplete evacuation residual isotopic material was washed out.

The stored data were analysed by comparing the pre- and post-evacuation counts. The percentage of evacuated activity was calculated from the change in the counts for the period during which the evacuation had taken place.

On the lateral anorectal images, radioactivity clearly outlined the rectum and the anal canal. The ARAs are recorded as upper and lower ARAs. The upper ARA is formed by the intersection of the axis of the rectum with that of the anal canal. The lower ARA is defined as the angle between the posterior rectal wall and the axis of the anal canal as they intersect at the level of the anorectal ring.

Although the method allows measurements of both UARA and LARA, the LARA measurement may be a more sensitive indicator of anorectal movements during the various expulsive manoeuvres, as it reflects movements of the posterior wall of the rectum and does not depend on the shape of the rectum, which may be altered with the position of the body [6, 7]. Because of this, the LARA has been therefore used for comparison throughout the study and will be referred thereafter in this text as the anorectal angle (ARA). With the use of a computer program it has been possible to measure changes in the ARAs during the various expulsive manoeuvres.

The PF ascent on ‘squeezing’ and coughing and descent on straining and during evacuation are recorded from the movement upwards or downwards of the anorectal junction away from its position at rest.

The defaecation time was calculated during the isotope method, as the time taken for evacuation, determined visually on the emptying curves, from the time at which defaecation commenced. The defaecation rate was derived by dividing the percentage of the activity evacuated by the time taken for evacuation.

Radiological videoproctography. Radiological proctography was done without bowel preparation. The composition and preparation of the contrast medium aimed at getting a radioopaque substance with a consistency similar to normal stools. A suspension of 50 ml barium sulphate (BaritopTM (100)) mixed with potato mash and hot water stirred into a smooth thick paste (1 tablespoon of potato powder for every 30 ml of hot water). The amount of contrast used depended upon each patient’s tolerance. The paste is introduced per rectum at body temperature via a wide tip syringe connected to a short wide anal catheter (Polibur ACR™). A fine Foley catheter with a guide wire placed within it was used as an anal canal marker. For improved coating and for a sharper outline of the rectal mucosa a concentrated suspension of barium is placed in the anal catheter and injected into the rectum prior to the paste. The anorectal images were videorecorded with the patient seated in the left lateral upright position on a commode (ELSANT™), and standard films were acquired at rest and during each expulsive manoeuvre. An allowed maximum screening time was set to keep within acceptable radiation dosage and the procedure was terminated at this point.

Statistical analysis. The statistical analysis of the results obtained by the ARAs were used the median and its 95% confidence intervals (CI). Statistical significance of the differences of data was assessed using the non-parametric Mann-Whitney test for paired comparison of observations. Correlations were assessed by the Pearson correlation coefficient and R-values.

Results

Anorectal angles

The measurements of ARAs studied by isotope proctography in 12 subjects with constipation are presented in Table 1. The ARAs measurements (Figure 1) altered during the various manoeuvres and evacuation, showing a significantly more acute ARA on ‘squeezing’ (Figure 2) but less so on coughing compared with the resting ARA and more obtuse on straining and significantly so on evacuation (Figure 3).

The ARA measurements, in the six patients studied by radiological videoproctography, showed similar dynamic changes on ‘squeezing’, straining and evacuation but with greater overlap than those studied by the isotope method (Table 1).

However, comparing the ARAs (median and its 95% CI) at rest, on ‘squeezing’ straining and evacuation obtained during isotope proctography with those on radiological videoproctography (Figure 4), a highly significant correlation was derived (P < 0.01).

Pelvic floor movements

The measurements of PF movements obtained during isotope proctography are also summarised in Table 1. These PF movements altered during the various expulsive

<table>
<thead>
<tr>
<th>Table 1. Anorectal angle (ARA) measurements (median and its 95% CI)</th>
<th>Isotope proctography</th>
<th>Radiological proctography</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>100° (101°, 116°)</td>
<td>88° (76°, 100°)</td>
</tr>
<tr>
<td>SQ</td>
<td>91° (81°, 98°)</td>
<td>75° (67°, 93°)</td>
</tr>
<tr>
<td>ST</td>
<td>120° (107°, 137°)</td>
<td>103° (92°, 120°)</td>
</tr>
<tr>
<td>EV</td>
<td>126° (116°, 135°)</td>
<td>115° (100°, 130°)</td>
</tr>
<tr>
<td></td>
<td>23 (4°, 50°)</td>
<td>PF mm (95% CI)</td>
</tr>
<tr>
<td>SQ</td>
<td>19 (9, 33)</td>
<td>PF mm (95% CI)</td>
</tr>
<tr>
<td>ST</td>
<td>-7 (-11, -3)</td>
<td>-30 (-51, -22)</td>
</tr>
<tr>
<td>EV</td>
<td>-24 (-26, -12)</td>
<td>-22 (-40, -5)</td>
</tr>
</tbody>
</table>

The negative sign in the pelvic floor movement represents downward movement compared to its position at rest.
anorectal image at rest

lower anorectal angle = 107.0
upper anorectal angle = 135.0

Fig. 1. Silhouette of the anorectum at rest obtained during isotope proctography. Horizontal line represents the level of the pelvic floor, vertical line the anal canal, lower oblique line the posterior lower rectal wall and upper oblique line the midline of the rectum. The lower ARA is formed by the line of the mid-anal canal and by the lower oblique line, and the upper ARA is formed by the midline of the anal canal and the midline in the rectum (see text).

anorectal image during squeezing

pelvic floor difference = 32.2 mm
lower anorectal angle = 102.0
upper anorectal angle = 115.0

Fig. 2. Silhouette of the anorectum during 'squeezing' on voluntary maximal contraction of the pelvic floor muscles. Pelvic floor ascends. For details see Fig. 1.

Fig. 3. Silhouette of the anorectum during rectal evacuation. Pelvic floor descends. For details see Fig. 1. (Figures 1–3 are taken from the same study of one patient)

Fig. 4. The comparison of the anorectal angle (ARA) measurements obtained during isotope proctography and the anorectal angle measurements obtained during radiological videoproctography, at rest, on maximal contraction of the anal sphincter during 'squeezing', on straining and evacuation. (The black spots and crossed lines represent the median values and its 95% confidence interval. Pearson correlation coefficient r = 0.990; P < 0.001)

Manoeuvres showing an upwards movement for 'squeezing' (Figure 2) and coughing, as compared to the resting position, indicated by a positive sign, and a downwards movement for straining and evacuation (Figure 3) indicated by a negative sign.

The radiological technique measured the PF ascent as the movement of the anorectal junction on squeezing and the descent as the position of the anorectal junction on straining and during evacuation, both relative to the pubococygeal line; whereas the isotope method reflected movement of the anorectal junction away from its resting position (see Figure 1). Comparison between the two methods (Table 1) for the PF ascent on squeezing and the PF descent on evacuation showed no significant difference (P > 0.05).

Defaecation assessment

9 constipated subjects evacuated approximately 58% of the isotope 'faecal' bolus (95% CI: 42, 77%). The defaecation time was 64 seconds (95% CI: 50, 138 s). The defaecation rate was calculated at 0.9%/sec (95% CI: 0.4, 1.4%/s). The other 3 patients emptied 10% or less of the evacuated activity and their performance was considered poor (see Figure 5).
The radiological method was confined to a subjective qualitative assessment of the rectal evacuation. Three patients were unable to empty the radiopaque paste and the defaecation was considered poor whereas the remaining 3 had a fair emptying of their rectum.

**Defaecation assessment and the anorectum**

The percentage of the activity evacuated, in the 12 constipated subjects, correlated with the ARA on straining ($P < 0.01$; Figure 6) and also correlated with the PF descent on evacuation ($P < 0.05$; Figure 7).

**Discussion**

In the investigation of the aetiology of constipation it becomes necessary to study the pelvic floor and anorectal changes as well as the ability of the subject to evacuate adequately a ‘full’ rectum [8]. Observations on changes in the ARA and PF have previously been made during radiological videoproctography, a method that has been developed particularly to detect anatomical and pathological changes at defaecation [9]. As a method it may be considered unpleasant for the patient and concern has been expressed because of the high dose of radiation involved [10], especially to the pelvic organs (EDE of approximately 1 mSv per minute of fluoroscopy). Moreover, radiological techniques involving the use of barium are not a reliable means of estimating the ‘normal’ ability of patients to achieve defaecation, in view of the highly abnormal characteristics of the radio-opaque barium used as a stool marker.

The information obtained by isotope proctography studying patients with constipation and those who find defaecation difficult is thus valuable as a tool of investigation and management. It quantitatively assesses the changes in the anorectum during simulated defaecation, such as widening the ARA and descent of the PF, as well as recording the adequacy of defaecation.

The widening of the ARA together with greater PF descent should facilitate more complete or adequate evacuation. Thus the quantitative measurement of the adequacy of defaecation would enable discrimination to be made from the incomplete evacuation associated with a non relaxing pelvic floor. In this series the patients were able to evacuate about 58% of the faecal bolus, which approximates that for normal controls, who evacuated about 60% [3]. The same normal controls also took less time (40 s) to accomplish defaecation, compared with the constipated subjects studied. The defaecation rate (3) was slower in the constipated patients when compared to the one quoted for normal controls (1.5%/s). All these
parameters can be recorded simultaneously in a single dynamic study which is simpler for patients, who are exposed to one test only that minimises the amount of radiation (EDE < 0.3 mSv independent of 'screening time') exposure. Moreover, the physical characteristics of the artificial stool used in isotope proctography closely mimic the natural substance.

The method gives comparable results of the ARA measurements to conventional radiological videoproc- tography. However, the changes of the ARA showed better discrimination with less overlap of the parameters measured for each performance with the isotope method as compared to the radiological one as can be inferred by the 95% confidence intervals in Table 1. The PF movements studied by isotope proctography reflected the true movement of the anorectal junction during the various manoeuvres, compared to its position at rest, with more effective movements upwards and downwards during the extremes of squeeze and evacuation. This is also a more accurate method of recording the PF movement than the one employed in radiological videoproc- tography, which records the PF ascent or descent as the anorectal junction position at squeezing or on evacuation respectively, relative to the pubococygeal line. One might assume that the pubococygeal line remains at the same position during the whole test; however one becomes aware that the slightest movement of the patient may change the reference line position. The radiological method is unable to depict the true movement of the anorectal junction during the contact of the various manoeuvres because superimposing the anorectal images on these manoeuvres is virtually a technical impossibility.

Isotope proctography is therefore a useful method of assessing anorectal function since it provides information about the relationship of rectal evacuation to the ARA and to PF descent. Even the most protracted forms of defaecation associated with gross constipation can be studied safely because of the low dose of radiation involved. Although it successfully demonstrates quantitative changes in the parameters described, isotope proctography lacks thus far the diagnostic applications which the radiological method has for making observations on structural changes such as rectocele and rectal intussusception [11]. The possibility exists however, that by isotope mucosal coating this may become a future development.

Acknowledgements: Dr. M. Papachrysostomou was supported by a Scottish Home and Health Department Clinical and Biomedical Research Grant (K/MRS.5001202). Current address: Gastrointestinal Unit, Department of Medicine, Western General Hospital, Edinburgh. Miss N. Clare is thanked for her technical assistance.

References


Prof. A. N. Smith
Department of Surgery/Urology
Western General Hospital
Crewe Road South
Edinburgh EH4 2XU
UK
The control of continence is vested in the responses of the anal sphincters and pelvic floor muscles, which maintain a tonic contraction under the influence of their innervation. Until recently there has been no means of imaging the anal sphincters, so that actual disruption of a sphincter was determined from clinical examination, from pressure studies, and by concentric needle electromyogram mapping (1). However, with the development of anal endosonography, high-resolution ultrasound images of the separate sphincter muscles may be obtained (2).

Rectal endosonography was first described in 1956 (3) but remained neglected for many years owing to the limitations of the technology then available. Over the past 10 years this technology has developed considerably, and rectal ultrasound now has an established role in the examination of the prostate (4) and has been used in staging rectal cancer (5).

The purpose of this paper was to examine age and gender change in both sphincters, internal and external, and correlate each sphincter with its dynamic activity. Faecal incontinence is more prevalent in females and the older population. We were interested to see any morphologic difference in the anal sphincters that might predispose these groups to disease. In man striated muscle bulk appears to decrease with age; however, animal work paradoxically has suggested that the external anal sphincter (EAS) increases its thickness with age (6). In the rat this process is influenced by oestrogen and ovariectomy (7), which may have a clinical significance in humans, as most women who are incontinent are at the menopause. Nonetheless, one must not underestimate the importance of the internal anal sphincter (IAS).

MATERIALS AND METHODS

Thirty subjects, 13 men aged from 20 to 51 years and 17 women aged from 20 to 75 years, were recruited to the study. Subjects were selected from asymptomatic normal volunteers and those attending the hospital (Western General Hospital) for conditions unrelated to anorectal dysfunction.

Anal endosonography has been conducted using a specially designed hard sonolucent plastic cone attachment to a 6.5-MHz radially rotating endprobe with a maximum diameter of 1 cm (Bruel & Kjaer, ultrasound scanner type 1846) so as to cause minimal disturbance to the anal sphincters. The plastic cone, filled with degassed water, provided protection for the rotating probe and effective acoustic coupling within the anal canal. The lubricated cone was inserted in the rectum with the patient in the left lateral position, and serial images were obtained on slow withdrawal of the endprobe from the rectum down the anal canal.

Anal manometry was performed in all the above subjects by using a station pull-through technique with a water-filled latex balloon 4 mm in diameter connected to a pressure transducer. The maximum anal canal pressures at rest (MRP) and during voluntary contraction on 'squeeze' (SOP) were determined in an attempt to examine whether sphincter...
thickness is related to the intraluminal anal canal pressure as a facet of the dynamic property of the muscle.

The statistical analysis was performed using the non-parametric Mann-Whitney ‘U’ test, the median and its 95% confidence interval (CI), the Pearson correlation coefficient, and p values.

Ethical permission for this protocol was given by the Ethics Committee of the Lothian Health Board, and all subjects gave written informed consent.

Data analysis

Video recordings of the ultrasound scans were obtained from all the subjects recruited and were stored for further analysis and study. Using the recorded information on the video tape, it was possible to study in detail any stage of the stored anorectal images. Film hard copies were acquired at different levels of the rectum and anal canal. After having studied the anatomic concepts (9) of the related structures, we created a diagrammatic representation of the sonographic anatomy of the normal anal canal layers (Fig. 1).

The sonographic anatomy of the anal canal was consistent in subjects of the same sex. The smooth muscle of the IAS was clearly identifiable as a homogeneous hypoechoic circular band extending caudally to a level just proximal to the anal verge. The striated muscle of the EAS had a different acoustic texture, with mixed echogenicity and linear pattern, giving a 'streaky' appearance (Fig. 2a). The EAS could be traced from the puborectalis component of the levator ani muscle to its cutaneous termination and was consistent in appearance for both sexes posterolaterally. Posteriorly in the distal anal canal, the close proximity of the coccyx produced a variable hypoechoic band, and the EAS was visible in front of it. The thickness of the EAS was measured at this point. Between the two sphincters there was a narrow echogenic band that represented the intersphincteric plane. Immediately adjacent to the endoprobe plastic cone was a hypoechoic layer of mucosa, continuous with the rectal mucosa. Between the mucosa and the IAS was the more echogenic submucosa, which became progressively denser and thicker caudally.

It was possible to identify clearly the hypoechoic structure of the IAS lying between the two more echogenic structures of the submucosa and the intersphincteric plane. Thus the measurements of the IAS thickness were made fairly simple and accurate, whereas the EAS thickness measurements were not as easy to acquire since the EAS was adjacent to the hyperechoic intersphincteric plane. On the other hand, the outer border of the EAS was not clearly outlined as this muscle is surrounded by other striated muscles. Therefore there is hardly a distinctive line between the two layers of muscle. Our solution to this was to measure the thickness of the subcutaneous portion of the EAS at the very distal part of the anal canal and to relate its outer border to the boundary of the coccyx. The video recording of the ultrasound scanning of the anal canal enabled us to acquire continuous imaging of the anal canal muscles, at the same time recording the movement of these muscles during voluntary contraction and any change in their thickness during
Fig. 2. Anal endosonography in middle anal canal of a healthy volunteer. 2a. The hypoechoic band of the internal anal sphincter (I), the hyperechoic external anal sphincter (E), and the coccyx (C) are identified. The anal scan was obtained at rest. 2b. The individual has been asked to 'squeeze' the anal sphincter, having maintained the endoprobe at the same level. However, during the voluntary contraction of the anal sphincter, the external sphincter (E) has become 'brighter' and encircled the endoprobe in a powerful manner, displacing the internal anal sphincter, which is not seen in this scan. 2c. The internal anal sphincter (I) regained its position and thickness as soon as the individual was asked to relax, always without moving the endoprobe in the anal canal.
In this manner, continuous recording of muscle changes after commands such as ‘squeeze’ was obtained.

RESULTS

External anal sphincter

Gender. The EAS thickness in the male group was 0.87 cm (95% CI, 0.80, 0.91), whereas in the female group it was 0.75 cm (95% CI, 0.70, 0.80). Thus, the male group had a significantly ($p < 0.02$) thicker EAS than the female group.

Age change. The group was further divided into two categories, one that included 23 young subjects (12 men, 11 women) with an age range of 20–23 years, and a second one that consisted of 7 older subjects (6 women, 1 man) with an age range of 41–75 years. A significant difference in the thickness of the EAS was found between the young and the older subjects ($p < 0.005$), the EAS being thinner in the older (median, 0.68 cm) than in the younger (median, 0.86 cm) subjects. The EAS thickness in the overall group (men and women) correlated inversely with age ($p < 0.001$). This indicates a tendency to a ‘thinner’ EAS in the older population.

The EAS thickness versus its dynamic activity. When attempts were made to relate the EAS thickness to the squeeze pressures representing the activity of this muscle, no significant correlation was found ($p > 0.05$) in either male or female groups. The apparent EAS thickness was not therefore directly related to the dynamic properties of this muscle.

Internal anal sphincter

Gender. The IAS thickness was 0.20 cm (95% CI, 0.13, 0.25 cm) in the male population and 0.21 cm (95% CI, 0.19, 0.27 cm) in the women, which was not significantly different ($p > 0.05$).

Age change. The IAS thickness in the younger group was contrasted with that of the older subjects. There was a very significant ($p < 0.0002$) difference between the IAS thickness of the young (median, 0.20 cm) and that of the older subjects (median, 0.30 cm). A significant correlation ($p < 0.001$) was shown between the IAS thickness and the age of the subjects, confirming that older subjects had a thicker IAS than younger ones.

The IAS thickness versus its dynamic activity. The IAS thickness was compared with the MRP derived by the anorectal manometry as a record of the IAS activity; no significant correlation ($p > 0.05$) was obtained in either the male or the female group. The apparent IAS thickness was therefore not directly related to the dynamic property of this muscle.

Anorectal manometry

Gender. In the male group the MRP was 120 cm H$_2$O (95% CI, 85, 137), and the SQP was 170 cm H$_2$O (95% CI, 131, 180). In the female group the MRP was 120 cm H$_2$O (95% CI, 100, 130), and the SQP was 110 cm H$_2$O (95% CI, 100, 140). There was no significant difference in the measurement of the anal canal resting pressure between men and women ($p > 0.05$); however, the external sphincter contraction was greater in the male group than in the female one ($p < 0.005$).

Age change. In the young group the MRP was 110 cm H$_2$O (95% CI, 89, 130), and the SQP was 120 (95% CI, 99, 151). In the older group, the MRP was 135 cm H$_2$O (95% CI, 94, 160), and the SQP was 110 cm H$_2$O (95% CI, 67, 146). There was no difference either in the anal canal resting pressure or in the pressure increment during EAS contraction between the old and young groups ($p > 0.05$).

Relationship between the internal and external anal sphincters

Dynamic observations were also made during video recording of the ultrasound scans. The subject was asked to

![Fig. 3. The relationship between the internal and external anal sphincter thickness in 30 healthy volunteers. It shows a reciprocal relationship between the thicknesses of the sphincters, whereby a 'thicker' external sphincter associates with a 'thinner' internal one. (The Pearson correlation coefficient and its p value are shown.)](image-url)
squeeze to initiate EAS activity and increase the tone in the anal canal, with the endoprobe in it, imaging both the IAS and the EAS (see Fig. 2a). The IAS appeared to become thinner, as if being displaced by the EAS, during squeezing (Fig. 2b). At the same time the echogenicity of the EAS appeared to increase. As soon as the individual was asked to relax and without moving the endoprobe, the IAS regained its original position and thickness (Fig. 2c).

To investigate this interrelationship, the thicknesses of the two sphincters were compared. A significant \( p < 0.001 \) inverse correlation was observed in the anal sphincter thicknesses in the 30 subjects studied (Fig. 3). This implies a compensatory relationship between the two sphincters—that is, a thicker EAS relating to a thinner IAS and vice versa. The IAS and EAS thicknesses versus their dynamic activity.

Above (Fig. 3), a compensatory relationship concerning the thicknesses of the two muscles was suggested. Thus, it has been of interest to relate the thickness of these muscles as a whole to the intra-anal maximum resting pressure formed by the tonic activity of both muscles. A significant correlation \( (p < 0.001) \) was observed between the anal canal resting pressure and the sum of the thicknesses of the two sphincters (Fig. 4).

DISCUSSION

Anal endosonography is a simple, minimally invasive technique that has been shown to be well tolerated by the subjects examined. The studies were all made using a 1-cm-diameter endoprobe tip, since it has been shown (10) that various probe sizes lead to different measurements of sphincter thickness. Ultrasound evaluation of the anorectum has been used as a method for examining the configuration of the IAS and the EAS. In previous studies (2) much attention has been devoted to the appearance of the IAS and to detectable defects of the EAS. The present study consisted of an assessment of both the IAS and the EAS, comparing these results with manometry to assess structure and function of the sphincters in the same subject.

Laurberg & Swash have shown (11) that the internal anal sphincter, considered important in the control of continence, is subject to fibrofatty degeneration and cellular infiltration in the older normal population. This may explain the increase in IAS thickness in the older age group as compared with the young men and women. This may also explain the apparently increased IAS thickness seen by Burnett & Bartram (8) and ourselves. Gender, however, did not appear to influence the thickness of the IAS in the normal population. Changes in the architectural structure of the IAS might also imply hypertrophy of this muscle; this is known to occur in the circular muscle coat, in particular in the pelvic colon, as part of an age change (12) but also in association with diverticular disease (13).

In contrast to the IAS, the EAS thickness has a subjectivity in its measurement. This is because it is dependent on the anatomically variable level of the coccyx, with regard to which the measurements were made. The EAS nevertheless showed a significant reduction in size with age and, contrary to the case of the IAS, showed differences with regard to gender. This observation is compatible with the general reduction in the striated muscle bulk of the human body with age and is at variance with studies in the rat (6) which showed an increase in the EAS thickness with age. The increase of the thickness in the male population compared with the female group observed is in agreement with other studies (14) showing the male external sphincter to be different in shape and length and greater in barrier pressures than that of nulliparous females.

The present study shows that the thickness of the IAS and the EAS are inversely related to one another, as measured

![Graph](https://example.com/graph.png)

**Fig. 4.** The relationship between the sum of the internal and external sphincter thicknesses and maximum resting pressure in the anal canal in 29 healthy volunteers. The direct relation of the anal sphincters' thickness to their tonic activity presented above suggests an affinity and synergy in function. (The Pearson correlation coefficient and its \( p \) value are shown.)
at rest. We envisage that this comes about by a normally ‘thick’ EAS supporting the ‘thinner’ IAS. With the diminution of the EAS with age the increasing thickness of the IAS replaces it. The EAS in health may play a protective role, whereby it lends mechanical support to the IAS and thus gives it added effectiveness (15), more so given the trends occurring in both sphincters in the healthy individual.

Furthermore, the change in the appearance to a more prominent EAS and a lessened IAS during dynamic activity supports the concept of a compensatory mechanism between these two structures in health. This phenomenon is compatible with physiologic observations made by other investigators, who suggested a mutual relationship between the EAS and the IAS, such that the EAS protects the IAS, giving it a basis on which to function (14). It is this harmony in function, both contributing to the intraluminal barrier pressure, that ‘unites’ the two sphincters. Hence it is the sum of the two sphincter thicknesses that has been shown to have a direct relation to this pressure, and not each sphincter separately. The measurement of these two structures may thus be of diagnostic value and even more of interest to ascertain whether this is disturbed in the incontinent patient.

The reciprocal relationship between the thicknesses of the anal sphincters that we have observed in this study seems to be an important factor in the maintenance of continence. To confirm this, further studies are required to determine the thickness of these sphincters in incontinent patients. The increased thickness of the IAS in the older controls might be part of the general process of the smooth-muscle thickening in the ageing population, which has been implicated in the pathogenesis of diverticular disease. The distal thickening of the IAS could in turn provoke the increased smooth-muscle thickness in the pelvic colon described in diverticular disease. How significant these changes are in the pathogenesis of pelvic colon disease is still debatable. Anal endosonography is an effective method of investigating the structure and function of the sphincters, providing valuable information about their role in health and disease.

ACKNOWLEDGEMENTS

Dr. M. Papachrysostomou was supported by a Scottish Home and Health Dept. Clinical and Biomedical Research Grant (K/MRS/5001202). Current address: Gastrointestinal Unit, Dept. of Medicine, Western General Hospital, Edinburgh. Miss N. Clare is thanked for her technical assistance.

REFERENCES


Received 23 July 1992
Accepted 17 November 1992
A regional audit of the investigation and treatment of colorectal and pelvic floor disorders (1984–1991)*

J.S. Varma, N. R. Binnie, B. Kawimbe, M. Papachrysostomou, A. N. Smith

University Department of Surgery, Western General Hospital, Edinburgh EH4 2XU, UK

Abstract. The activities of a regional physiology unit established for the investigation of colorectal and pelvic floor physiology in health and disease in a clinically relevant setting has been audited and its evolution described over a period of eight years. Trends in surgical treatment of some of these disorders over the same period have also been documented in the Lothian Region. Although there has been little change in the number of patients investigated annually patterns of investigation appear to change. Sphincter manometry, proctometrography and somatosensory reflex measurements have remained the most frequently performed and useful investigations. Spinal stimulation studies increased transiently because of a collaborative investigation of bowel and bladder function in patients with spinal injuries. A considerable increase in surface EMG tests and dynamic proctography has occurred. These trends are thought to be related to interest in defining evacuation dysfunction of the rectum and related problems of the pelvic floor. Isotope proctography now rivals barium videoproctography; at the same time the use of manometric colonic motility studies has diminished. Anal ultrasonography has replaced sphincter manometry in the last year and is being applied to other aspects of anorectal pathology. The last 4 years have seen the introduction and increasing use of non-surgical therapeutic modalities for the treatment of faecal incontinence and constipation: reflex electronic sphincter stimulation, biofeedback and the use of a prokinetic agent to promote colonic motility. Concomitant changes in the surgery of constipation and reconstructive anorectal procedures have been observed. It is recommended that proctology units should have easy access to at least one such investigation laboratory within their catchment area together with appropriate auditing facilities.

Résumé. Les activités d’une unité régionale de physiologie destinées à l’investigation de la physiologie colo-rectale et du plancher pelvien chez les sujets sains et malades dans un contexte clinique adéquat a été l’objet d’un audit et son évolution décrite sur une période de 8 ans. Les tendances dans le traitement chirurgical de certains de ces désordres ont été aussi étudiées dans la même période. Bien qu’il y ait eu peu de changement dans le nombre des patients étudiés chaque année, l’aspect des explorations semble changer. La manométrie sphinctérienne, la proctométrie et la mesure des réflexes somato-sensitifs sont restés les examens les plus utiles et les plus fréquemment utilisés. Les études de la stimulation spinale ont augmenté provisoirement en raison d’une étude en collaboration des fonctions intestinale et vésicale chez les patients ayant un traumatisme médullaire. L’augmentation considérable de l’électromyographie de surface et de la proctographie dynamique est survenue. Ces tendances sont dues probablement à l’intérêt qu’il y a à définir les disfonctions d’évacuation rectale et les problèmes en relation avec le plancher pelvien. La proctographie isotopique est maintenant en rivalité avec la vidéo-proctographie au barium. Pendant ce temps l’utilisation des études de la motilité colique par manométrie ont diminué. L’échographie endo-rectale a remplacé la cartographie sphinctérienne dans la dernière année et a tendance à être utilisée pour les autres aspects de la pathologie ano-rec-tale. Les 4 dernières années ont vu l’introduction et l’utilisation croissante des thérapeutiques non chirurgicales pour le traitement de l’incontinence fécale et de la constipation: stimulation reflexe sphinctérienne électronique, biofeedback et utilisation d’agents prokinétiques pour augmenter la motricité colique. Des changements concomitants dans la chirurgie de la constipation et de la reconstruction ano-rec-tale ont été observés. Il est recommandé que les unités de proctologie puissent avoir un accès facile à au moins un tel laboratoire d’investigations dans leur aire de travail en même temps que des facilités appropriées de vérification.

Table 1. Diagnostic and therapeutic facilities

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manometry</td>
<td>Electronic sphincter stimulation</td>
</tr>
<tr>
<td>Sphincter manometry</td>
<td>Biofeedback</td>
</tr>
<tr>
<td>Proctogram</td>
<td>Drug trials</td>
</tr>
<tr>
<td>Colonic motility</td>
<td></td>
</tr>
<tr>
<td>Electrophysiological</td>
<td></td>
</tr>
<tr>
<td>Sphincter EMG</td>
<td></td>
</tr>
<tr>
<td>Surface: Integrated EMG</td>
<td></td>
</tr>
<tr>
<td>Stool: Single fibre</td>
<td></td>
</tr>
<tr>
<td>MUPD: Mapping</td>
<td></td>
</tr>
<tr>
<td>Anisum index</td>
<td></td>
</tr>
<tr>
<td>Anal reflexes</td>
<td></td>
</tr>
<tr>
<td>Coronal evoked potential</td>
<td></td>
</tr>
<tr>
<td>Conduction velocity</td>
<td></td>
</tr>
<tr>
<td>Cauda equina</td>
<td></td>
</tr>
<tr>
<td>Endoanal</td>
<td></td>
</tr>
<tr>
<td>Anorectal studies</td>
<td></td>
</tr>
<tr>
<td>Manometry</td>
<td></td>
</tr>
<tr>
<td>Proctogram</td>
<td></td>
</tr>
<tr>
<td>Proctogram</td>
<td></td>
</tr>
<tr>
<td>Sphincter ultrasonography</td>
<td></td>
</tr>
</tbody>
</table>

The motility laboratory at the Western General Hospital, Edinburgh, has its origins in the investigation of disorders of colonic motility, particularly those relating to artificial disease as it was in the 1970s [1]. A decade witnessed a decline in the surgical importance of diverticular disease of the colon and its complications in Scotland, possibly a consequence of management by increasing intake of dietary fibre. This has been followed in turn by diminution in the study of motility disturbances associated with this disorder and the effect on them of various therapeutic regimens. At about the same time the importance of anorectal physiology, particularly relating to the pelvic floor muscles in relation to disorders of continence underneat increased and became the principal interest of this and other laboratories [2]. In 1984 the first fellow dedicated to the investigation of the physiology of anorectal and pelvic floor disorders was funded, followed by several others. From 1988 onwards the laboratory has also performed therapeutic trials for incontinence. This paper describes the evolution of the laboratory over 7 years and discusses the changing trends in the surgery of these functional disor-

Fig. 1. Numbers and sex of persons investigated. Symbols: — female; — male

found elsewhere [3–16]. The laboratory has had a major interest in proctometrography [4], somatosensory reflex latency studies [5–7], the investigation of bowel function following spinal injury [8–11] and pelvic surgery [12], isotope proctography [13], sphincter ultrasonography [14], neurostimulation [15] and biofeedback [16].

Data were collected from hard copies of each patient's referral letter, investigative results and final diagnosis at the end of each year and held in computerised records. Further information, if necessary, was able to be obtained from case records as most of the referrals were local.

Operative data were obtained from computerised records of the Lothian Surgical Audit. Graphics were generated from data entered into a Macintosh Cricketgraph™ database.

Results of audit

Patients

A mean of 190 patients are investigated each year (range 177 to 219, Fig. 1). The vast majority of them are female (72–80%, mean 76%) for known reasons such as chronic constipation and childbirth injury to the pelvic floor and its innervation [7]. Indications for investigation and therapy have not changed significantly over the years, the small changes mainly reflecting the research interests of individual fellows (Fig. 2). Approximately 75% of referrals originated from within our own hospital, mainly from the gastrointestinal and general surgical units. The remainder comprised referrals from other Edinburgh and Scottish hospitals.

Diagnostic investigations

Both the use of manometric investigation of sphincter function and of proctometrography has steadily risen over the years (Fig. 3). Colonic motility studies have constituted a small proportion of all manometric investigations and appear to be declining.

There has been a steady rise in the use of both somatosensory reflex latency measurements and surface electromyographic studies (Fig. 4). Measurement of the latency of the pudendo-anal reflex [5, 7] has been by far the most common electrophysiological investigation.
Fig. 2. Indications for investigations. Symbols: □ incontinence; ■ constipation; □ irritable bowel; □ radiation injury; □ inflammatory bowel; □ post-op, prolapse; □ diverticular disease; □ other; □ controls

Fig. 3. Manometric investigations. Symbols: ■ sphincters; ○ proctometrography; □ colonic motility

Mean motor unit potential duration measurements of the internal anal sphincter have increased from 1984 to a peak in 1986 and thereafter declined as has the interest in spinal stimulation nerve conduction studies seen during the first 3 years.

Plain abdominal x-rays, isotope studies and barium enemas have been the main imaging modalities before 1987, when the use of transit markers increased (Fig. 5). Since 1989 barium and isotope proctography have been increasingly performed. Anal ultrasonography for the investigation of a variety of anatomical disorders is increasing.

Fig. 4. Electrophysical investigations. Symbols: ■ somatosensory reflexes; – – surface EMG; □ – motor unit potentials; ○ spinal stimulation

Fig. 5. Imaging studies. Symbols: ■ transit markers; – – video-proctography; □ – isotope proctography; – – anal ultrasonography

Therapeutic trials

Figure 6 illustrates the development of interest in the non-surgical therapy of constipation and faecal incontinence. Trials of Cisapride in the treatment of various forms of constipation have been completed over the period 1986–89. Likewise, trials of electronic reflex stimulation of the striated pelvic floor musculature for neurogenic faecal incontinence have been conducted mainly over the 2-year period 1988–90 [15]. There has been an increasing interest in the treatment of anismus by biofeedback from 1987 to 1990 [16].

Treatment of chronic constipation

Figure 6 also illustrates the trends in the treatment of intractable constipation in the Lothian Region during the evolution of the laboratory. The initial rise in the rates for subtotal colectomy with ileorectal or ileosigmoid anasto...
Since 1987 a significant reduction in the number of abdominoperineal excisions of the rectum has occurred, with a concomitant rise in the number of anterior resections of the rectum for neoplastic disease. This trend is in keeping with other major coloproctology centres in the country.

Discussion

The evolution of an era of investigative physiology of the anorectum and pelvic floor and concomitant changes in therapeutic techniques is illustrated by this audit. This has occurred within the clinical setting of changing disease patterns, clinical demands and therapeutic techniques. For many years the anorectum had been a forbidden area for both the physiologist and clinical scientist. Few ventured near and as a consequence the region has been slow to reveal its secrets. Within the decline in the surgical importance of diverticular disease interest shifted to the anorectal area particularly as the problems of faecal incontinence, prolapse and severe constipation came to light in an increasingly ageing population [7].

Over the last 10 years the situation has changed dramatically. The impact of new technology and the enthusiasm with which many investigators have tackled basic physiological questions has been rewarded with an explosion of information related to the anorectum and its pathophysiology [7]. This has been the primary purpose of a motility laboratory such as ours and the provision of a “clinical service” has been a resultant bonus.

The range of available investigations has expanded and changed with increasing understanding of function and with better technology. Older, more invasive, methods have been replaced with equally sensitive but less invasive ones. For instance, motor unit potential duration (and single fibre EMG) which were excellent research tools have largely been replaced by measurement of nerve conduction velocities and somatosensory reflexes. Sphincter “mapping” by needle EMG is rapidly being replaced by ultrasonographic imaging and the investigation of colorectal motility using isotope technology will probably, in this context, replace barium and transit marker studies. Another factor responsible for the change has been the increasing awareness and demand from other specialties such as obstetrics and gynaecology, geriatrics, urology, paediatrics, urology and spinal injury units to liaise with coloproctologists in the investigation of functional disorders of the pelvic floor.

This audit illustrates the changing demands on an anorectal physiology laboratory which are affected by the current state of knowledge, interests of the institution, referral pattern and surgical “fashion”. The ability to be flexible and innovative is clearly important. A glance at the evolutionary trends enables one to perceive those tests that have been consistently used and presumably have withstood the test of time in their usefulness. These include sphincter manometry and the proctometrogram. Amongst the electrophysiological investigations, somatosensory reflex latency measurements re-
main a quick and useful source of information. In other centres other forms of pudendal nerve conduction tests are in greater use [7]. It seems that colonic motility and needle EMG will resort to being research tools only. Ultrasoundographic appears now to be established in the armamentarium of useful “non-invasive” investigations.

From this 8-year Lothian surgical audit review it is clear that the treatment of many functional anorectal disorders continue to change. One of the factors important in this change is the continuing audit of postoperative function assessed by the techniques described above. It may seem difficult to relate changing surgical practice directly to the laboratory audit. However, as the majority of patients were referred from and treated within the Western General Hospital it seems likely that the laboratory data have helped to decide treatment to a considerable extend. It has been estimated that approximately 60% of the laboratory investigations may influence clinical management. Other laboratory factors influencing surgical treatment have been the introduction of prokinetic agents and biofeedback in the treatment of constipation and neurostimulation in the treatment of neurogenic faecal incontinence, often on a trial basis.

The usefulness of the tests performed is important to clinical decision-making apart from their proven research value. Some of the patients investigated are tertiary referrals from medical gastrointestinal units and hence require comprehensive workup prior to definitive therapy. An investigation which has been performed concomitantly with all the other sphincter function tests is the rectosigmoid inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy. The detection of a significantly raised EMG voltage in the pelvic floor on attempted defaecation suggests an ischiocentric inhibition test which if negative almost always indicates aganglionosis of the distal bowel. Low anal canal pressures are highly supportive of sphincter weakness. This may be accompanied by a prolonged pudendo-rectal reflex to confirm a pudendal neuropathy.

*Acknowledgements:* We are grateful to Miss Nicola Clare, Physiological Measurement Technician, who assisted in these investigations. Mr SJ Nixon kindly provided data from the Lothian Surgical Audit.

**References**

Significance of the Thickness of the Anal Sphincters with Age and Its Relevance in Faecal Incontinence

M. PAPACHRYSTOMOU, S. D. PYE, S. R. WILD & A. N. SMITH
Depts. of Gastroenterology, Medical Physics, Radiology and Surgery, University of Edinburgh, Western General Hospital, Edinburgh, UK


Background: Ultrasonographic studies in healthy volunteers showed that the external anal sphincter (EAS) and internal anal sphincter (IAS) thicknesses were inversely related at rest. The functional importance of the two sphincters in continence control was demonstrated in the relationship between the sum of the thicknesses of the two sphincters and the anal canal resting pressure. The aims of the present study were to assess the morphometric appearance of the anal sphincters by endosonography in faecally incontinent patients and to contrast this with that of older healthy subjects. Methods: Twenty-eight female patients with neurogenic faecal incontinence (FI) were studied. An older group of 7 healthy women, aged 41–75 years, and a young group of 11 multiparous healthy women, aged 20–23 years, served as control groups. Anal endosonography was performed with a radial rotating endoprobe, with the subject in the left lateral position. Conventional anal manometry was performed in all subjects. Results: The EAS in the FI group was thicker than the EAS in the young (p < 0.04) but did not differ from the EAS in the young. The IAS thickness in the FI group did not differ from that in the older group. In both these groups the IAS was thicker than in the young women (p < 0.01). The anal pressures in the FI group were reduced compared with the normal groups (p < 0.04). There was a direct relationship between the two sphincters in FI (p < 0.001). Conclusions: The increased thickness of the IAS in the FI group does not seem to compensate for function and results in a failure of the sphincter mechanism to maintain continence, whereas in healthy elderly subjects the increased IAS thickness appears to be compensatory and important for continence control.

Key words: Anal endosonography; faecal incontinence; internal and external anal sphincters

Prof. A. N. Smith, Dept. of Surgery, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, UK (fax: +44 31 343 2570)

Idiopathic faecal incontinence is known to be due to weakness of the striated muscles of the pelvic floor (1), and electrophysiological and histologic evidence suggests anal sphincter denervation (2). It has been proposed that this denervation results from repeated traction of the pelvic nerves (3), as the perineum descends during chronic straining at stool (4), and this may also occur during prolonged childbirth (5). In the aetiology of faecal incontinence, apart from spinal cord mechanisms and other direct trauma, structural changes in the internal sphincter have also been reported (6).

It has been suggested that so-called idiopathic or neurogenic faecal incontinence (7) is accompanied by fibro-fatty degeneration in the internal sphincter. The presence of zones of atypical appearance and the effects of damage to the nerves might not just be an innervation problem but could also accompany degenerative changes in the muscle (8).

Studies show that there are no significant changes in the anal canal pressures in healthy elderly subjects (9). In the maintenance of continence a major role is played by competent external (EAS) and internal anal sphincters (IAS). It is known from previous ultrasonographic studies that an inverse relationship exists between the two sphincters at rest, whereby the normally thick EAS supports the thinner IAS (9). This relationship was confirmed dynamically on voluntary contraction of the EAS during video-endosonography (9). Furthermore, the sum of the thicknesses of the two sphincters was directly related to the anal canal resting pressure. This demonstrates the functional importance of the two sphincters in the continence control.

It is also accepted that the skeletal muscle bulk diminishes with age. Thus, it may be of interest to ascertain whether the aging process of skeletal muscle includes the skeletal muscle of the external anal sphincter. If so, the mechanism by which continence is controlled in the elderly—and its failure in incontinence—ought to be explored. Our aims were therefore to assess the morphometric appearance of the anal sphincters by endosonography in older healthy subjects and to contrast this with faecally incontinent patients.

MATERIALS AND METHODS

Subjects
Twenty-eight female patients (age range, 47–68 years) with faecal incontinence (FI) were studied. These patients had had FI for from 4 months to 20 years and did not appear
Internal Sphincter Thickness (cm)

Fig. 1. The relationship between the internal and the external anal sphincter thicknesses in 28 patients with faecal incontinence. It shows a direct relationship between the thicknesses of the sphincters whereby a 'thicker' external sphincter is associated with a 'thicker' internal one.

Methods

Anal endosonography was performed using a Bruel & Kjaer 6.5-MHz radial rotating endoprobe with a 1-cm tip diameter (10). This was fitted with a hard sonolucent plastic cone filled with degassed water to provide effective acoustic coupling within the anal canal. Each lubricated endoprobe was inserted into the rectum with the subject in the left lateral position. Video recordings of the ultrasound scanning were obtained on slow withdrawal of the endoprobe from the rectum down the anal canal. Hard copies were subsequently acquired on single-sided emulsion films, and measurements of sphincter thickness were made to ±0.2 mm. The smooth muscle of the IAS was clearly identifiable as a homogeneous hypoechoic circular band extending caudally to a level just proximal to the anal verge. The striated muscle of the EAS had a different acoustic texture, with mixed echogenicity and linear pattern, giving a 'streaky' appearance (11).

Between the two sphincters there was a narrow echogenic band representing the intersphincteric plane. Immediately adjacent to the endoprobe tip was a hypoechoic layer of mucosa. Between the mucosa and the IAS was the more echogenic submucosa, which became progressively thicker and denser caudally. The EAS thickness measurements were acquired by measuring the thickness of the subcutaneous portion of the EAS at the very distal part of the anal canal and relating its outer border to the hypoechoic shadow of the coccyx. It has been pointed out that the subjectivity in measuring the thickness of the muscle in this manner depends on individual anatomic considerations. The thickest terminal portion of the IAS was measured in the mid-anal canal lying between the two more echogenic bands of the submucosa and intersphincteric plane (10).

Anal manometry was performed in all subjects recruited. A station pull-through technique was used with a water-filled microballoon, 4 mm in diameter, connected to an external pressure transducer. The maximum resting pressure (MRP) and anal pressure during voluntary contraction 'squeeze' (SQP) of the external sphincter were elicited.

This protocol was approved by the Ethical Committee of Lothian Health Board, and the subjects recruited to the study gave informed consent.

Statistical analysis of the results used the median and its 95% confidence intervals (CI), the non-parametric sign test for paired comparison, the Mann–Whitney test for unpaired comparison, and the Pearson correlation coefficient and its p value for relating two variables of the same subject.

RESULTS

Faecal incontinence

The IAS thickness in the FI group was 0.3 cm (95% CI, 0.2, 0.3), which was not significantly different from the IAS thickness in the older group but was significantly different from the IAS thickness in the young group (p < 0.001). The EAS thickness in the FI group was 0.8 cm (95% CI, 0.7, 0.9), not significantly different from the EAS thickness of either the old or the young groups. Although no inverse correlation of the two sphincter thicknesses was observed in this group, the IAS was directly related to the EAS thickness (Fig. 1) (p < 0.001). The sum of the thicknesses of the two sphincters IAS + EAS in the FI group was 1.0 cm (95% CI, 1.0, 1.2); this again was not significantly different from the old or young groups (Table I). Although the sum of the two sphincters IAS + EAS in the FI group did not differ from the ones of the healthy continent groups, there was no
correlation between the ‘IAS + EAS’ thicknesses and the MRP.

Anorectal manometry showed an MRP in the FI group of 80 cm H2O (95% CI, 60, 110), significantly lower than the MRP of the old and young groups ($p < 0.02$, $p < 0.04$, respectively). The SOP in the FI group was 50 cm H2O (95% CI, 40, 60), significantly lower than the SOP of both old and young healthy groups ($p < 0.02$, $p < 0.0001$, respectively).

**Age change**

The IAS thickness in the older group was 0.3 cm (95% CI, 0.3, 0.3), and in the young group 0.2 cm (95% CI, 0.2, 0.2). The IAS thickness was therefore significantly greater in the older group ($p < 0.004$). The EAS thickness in the older group was 0.7 cm (95% CI, 0.6, 0.8), and in the young group 0.8 cm (95% CI, 0.7, 0.9). The EAS thickness was significantly less in the older group ($p < 0.04$). The sum of the thicknesses of the two sphincters added together showed no difference between the two groups (IAS + EAS, 1.0 cm, with 95% CI of 0.9, 1.0, in both the older and young groups).

Anorectal manometry showed the MRP in the older group to be 135 cm H2O (95% CI, 90, 160) and in the young group to be 110 cm H2O (95% CI, 90, 130). The SOP in the older group was 110 cm H2O (95% CI, 70, 150), and in the young group 120 cm H2O (95% CI, 100, 150). These manometric variables did not show any significant difference between the two age groups (Table I).

The IAS thickness was directly related to age; thus older women present with a thicker IAS, which is in agreement with observations by Burnett & Bartram (12). The EAS, in contrast, was inversely related to age; thus older women present with a thinner EAS, in agreement with previous observations (9). The IAS and EAS thicknesses were inversely related ($p < 0.02$) to each other in the older continent group, in agreement with observations described previously in a younger population (9). The sum of the thicknesses of the two sphincters in the older group showed a direct relation to the MRP ($p < 0.05$, Fig. 2), in contrast to observations reported by Law et al. (13).

**DISCUSSION**

In neurogenic faecal incontinence there is denervation of the EAS and pelvic floor muscles (14) as well as damage to the IAS (15), which is likely to produce or be the result of autonomic denervation (16). It is possible that the IAS damage is due to a mechanical effect resulting from loss of support from the surrounding EAS (17). Anal endosonography has been used as a method of examining the configuration of the IAS and the EAS to assess the morphology in contrast to function in FI.

Women who suffer from incontinence are in the majority older people. It was thus necessary to recruit older healthy women with no anorectal symptoms for comparison with older incontinent patients. Since the vast majority of patients with faecal incontinence are women (18), we have studied exclusively female subjects so as to avoid any fallacies due to gender differences, either morphologic or functional (9). If the concept of faecal incontinence presenting in an older population because sphincter function deteriorates with age is true, then it is important to detect any such differences, if they exist, between the old and the young; a young group of healthy women was therefore recruited as a control.

In the groups studied it has been shown that older women had a ‘thinner’ EAS than younger ones ($p < 0.04$), which is compatible with the general reduction in the striated muscle bulk of the human body as a result of the aging process. In the incontinent group the EAS was not significantly different from the older female group, these two groups being age-matched. Older women had ‘thicker’ IAS than younger ones ($p < 0.005$). In a healthy older female population this may signify a compensatory increase in the bulk of this muscle to make up for the ‘thinning out’ of the striated component of the EAS. This was supported by the inverse relationship of the IAS to EAS thickness and the correlation between the sum of the thicknesses with MRP, representing the sphincter function (Fig. 2). This signifies the maintenance of a direct relationship of the sphincters' structure and function in the older group, which has been observed earlier in 29 young healthy volunteers (9). Furthermore, the inverse correlation

---

### Table I. Anal sphincter thicknesses (cm), internal (IAS) and external (EAS), recorded during anal endosonography in patients with faecal incontinence (FI) and in older and young normal subjects. Anal canal pressures (cmH2O) were also recorded at rest (MRP) and during maximum voluntary contraction on ‘squeezing’ (SOP) of the anal sphincter*

<table>
<thead>
<tr>
<th></th>
<th>FI, median (95% CI)</th>
<th>Old, median (95% CI)</th>
<th>Young, median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>60 (47, 68)</td>
<td>56 (42, 73)</td>
<td>21 (21, 23)</td>
</tr>
<tr>
<td>IAS</td>
<td>0.3 (0.2, 0.3)</td>
<td>0.3 (0.3, 0.3)</td>
<td>0.2 (0.2, 0.2)</td>
</tr>
<tr>
<td>EAS</td>
<td>0.8 (0.7, 0.9)</td>
<td>0.7 (0.6, 0.8)</td>
<td>0.8 (0.7, 0.9)</td>
</tr>
<tr>
<td>MRP</td>
<td>80 (60, 110)</td>
<td>135 (90, 160)</td>
<td>110 (90, 130)</td>
</tr>
<tr>
<td>SOP</td>
<td>50 (40, 60)</td>
<td>110 (70, 150)</td>
<td>120 (100, 150)</td>
</tr>
</tbody>
</table>

* The statistically significant results are given in the text.
The relationship between the anal canal maximum resting pressure (MRP) in the older group and the sum of the thicknesses of the two anal sphincters, internal (IAS) and external (EAS). The higher the anal canal resting pressure, the greater the sum of the thicknesses of the two sphincters.

Fig. 2.

between the thicknesses of the two sphincters was preserved in the older healthy female group in a similar manner, as demonstrated in healthy subjects formerly, in both static and dynamic studies (9); therefore we would assume that the sum of both sphincters is responsible for the basal pressure control in the anal canal in health. Although our studies did not show a relationship between the IAS thickness and the MRP as Law et al. have described (13) in referring to seven incontinent patients with no detectable defect in either sphincter, we do not seem to contradict that observation. As we have shown in this study, the two sphincters in incontinence have a direct relationship; hence a 'thicker' EAS corresponds to a 'thicker' IAS, and that may relate to a higher MRP. The difference may lie in studying an incontinent group of greater diversity and longer evolution than the small selective group already mentioned (13).

There was no difference detected in the IAS thickness between the older group and the incontinent one, whereas a significant difference was found in the incontinent group compared with the one of the young groups \((p < 0.001)\). The IAS is subject to fibro-fatty degeneration, cellular infiltration, and collagenosis, all of which occur with age (19) and in patients with faecal incontinence (8). This may explain the increase in the IAS thickness in the older group and in the FI as not being due to muscle bulk. Moreover, Lubowski et al. (8) showed that similar structural changes—less compacted arrangements of muscle fibres and increased amounts of collagen in the interstices with some stretching of elastic tissue strands—were apparent in both older healthy and incontinent patients (6). This may imply that the IAS increased thickness in FI is merely an event attributed to the aging process rather than epiphenomenon of incontinence.

Anorectal manometric studies in these groups showed that there was no difference in the anal canal pressure measurements either at rest or on maximal voluntary squeeze of the anal sphincter in the two healthy groups. These tests of the function of both internal and external sphincters show that the older group is free of incontinence simply because the anal sphincters maintain good tonic control, which is as effective as in young individuals. The faecal incontinence group, on the other hand, was found to have significantly lower anal canal pressures both at rest \((p < 0.02)\) and on voluntary anal canal contraction \((p < 0.002)\) than either old or young groups.

It seems that the principles outlining the function of the anal sphincter musculature and its structure are important but may differ within the healthy female population with regard to age. Although the anal sphincter function is preserved in the aging population, the morphometric and histopathologic features are known to change. The protective role of the EAS in health, whereby the muscle lends support to the IAS and gives it added effectiveness (20), is not maintained with age. Moreover, the IAS, with an increased apparent thickness in the older women, allows for compensation in the anal tone and thus supplements function. However, the fibro-fatty degeneration that was described in older subjects (6) may predispose to a failure of sphincter function, as older people are known to have neurogenic incontinence more often than younger ones. Thus, the apparent increased thickness in the FI patients may not be related to tonic activity but resulted as an age event. It may be that this increase in thickness happened before dysfunction and incontinence as a natural process in the aging of these muscles. This change ultimately may predispose the older subjects with somewhat weaker EAS to incontinence.

The older female group was carefully selected from women who did not have any anorectal disease, have not had a history of constipation, and did not admit to difficult traumatic prolonged labour. Once again, the interrelationship between the IAS and EAS prevails as the essential requirement for continence control. In FI the two sphincters were directly related, as if a mechanism exists by which the EAS...
is recruited to compensate for the lack of function in the presence of a 'thicker' degenerated IAS. In older patients who lack the muscle bulk in EAS this may not be successful, and the morphometric appearances fail to represent the function. In patients with a 'thinner' IAS this inducement of EAS does not occur, and no attempt is seen by the EAS to compensate for function. The agreeable co-existence of the two sphincters is therefore crucial in the control of continence, with IAS gaining a more important role in this function as shown in the older healthy population.

This study has not shown any morphometric differences in the two groups of healthy elderly and FI patients. It will therefore be of interest in the future to study the small group of young incontinent women to see what structural and morphometric changes occur in the young. Another appealing study for the future is to follow the response to treatment, either surgical or conservative via electric stimulation of the pelvic floor (22), in those FI patients with 'thicker' IAS and EAS in contrast to those with 'thinner' IAS and EAS. This may lead to further proof of the role of the internal anal sphincter in continence control and particularly on its dependence on external anal sphincter function.

ACKNOWLEDGEMENTS

Bruel and Kjaer have kindly provided the ultrasound apparatus used in this study. M. Papachrysostomou has been supported by a Scottish Home and Health Department Clinical and Biomedical Research Grant (K/MRS/5001202). N. Clare is thanked for her technical assistance. These findings were presented at the XIVth Biennial Congress of the International Society of University Colon and Rectal Surgeons, Crete, Greece, October 1992.

REFERENCES

22. Papachrysostomou M, Smith AN. Does electrical stimulation of the pelvic floor alter the proctographic parameters in faecal incontinence? Gut 1993;34:S2S.
Does electrical stimulation of the pelvic floor alter the proctographic parameters in faecal incontinence?

Maria C. Papachrysostomou, Adam N. Smith and Alan J.M. Stevenson

Objective: To evaluate the effects of electrical stimulation of the pelvic floor on proctographic parameters in patients with faecal incontinence.

Design: Patients with faecal incontinence, resistant to medical or surgical management, were randomly selected for anorectal studies.

Patients: The study included 24 patients suffering from idiopathic faecal incontinence with anal sphincter weakness and detectable pudendal neuropathy randomly selected for treatment with a pudendo-anal reflex electrical stimulator.

Interventions: Manometric studies, electrophysiological tests and X-ray videoprostography were performed before and after chronic intermittent application of a pudendo-anal reflex electrical stimulator over 8 weeks.

Main outcome measure: Improvement in the parameters relating to continence control.

Results: The intra-anal pressures showed an increase in the cough (P < 0.0001), voluntary contraction (P < 0.03) and maximum resting (P < 0.004) pressures. The functional length of the anal canal was also enhanced (P < 0.004). The anorectal angles remained unchanged; however, there was a significant increase in the pelvic floor ascent (P < 0.02), with no change in descent. The poststimulator group had fewer patent anal canals (P < 0.04).

Conclusions: Chronic neuro-stimulation of the pelvic floor can be used to restore continence.

European Journal of Gastroenterology & Hepatology 1994, 6:139-144

Keywords: Stimulation, pelvic floor, proctography, incontinence.
study in young women, a portable stimulator was used to provide repetitive stimulation of the pudendal nerve and thus elicit contraction of the EAS [10]. This approach has now been adopted in an attempt to restore continence in an older group of patients by provoking reflex contraction, assessing both the EAS and pelvic floor muscles, via the pudendo-anal reflex which is easily fatigued [8].

The aims of the study were to assess, using videoprostography, motor and sensory responses of the anorectum and pelvic floor in patients with faecal incontinence before and after the application of the pudendo-anal electrical stimulator.

Materials and methods

Patients
The study included 24 patients (three men and 21 women), median age 66 years (range 51–70 years), with neurogenic faecal incontinence selected at random for reflex electrical stimulation of the pelvic floor. Although the selection of patients was random, this group comprised patients resistant to other forms of treatment, including medical, surgical and physiotherapy, who had been referred to the anorectal physiology laboratory, a tertiary referral centre, for the investigation and management of anorectal disorders.

Methods
On completion of an 8-week course of treatment with the pelvic floor electrical stimulator, the patients were asked to subjectively assess the effects of the stimulator using the following scoring system: 0, no clinical improvement; 1, some but not consistent clinical improvement; 2, consistent clinical improvement/asymptomatic.

Electrical stimulator
A portable stimulator (Unived Technologies Ltd., Edinburgh, UK) was used to provide a train of square wave stimuli, via saline soaked felt electrodes, to the dorso-genital nerve with a fixed frequency of 1 Hz and a duration of 0.1 ms [11]. The submaximal tolerable stimulation voltage used was approximately three times the sensory threshold depending on the individual's tolerability. Domiciliary self-administered treatment was applied daily for 5–10 min on two to three occasions per day for a minimum of 8 weeks.

Anorectal manometry
A standard water-filled microballoon system with external transducer was used to record the anal canal pressures at rest, voluntary contraction on squeezing and cough reflex contraction. The functional length of the anal canal was reflected in the anal canal high pressure zone.

Rectal capacity and compliance were recorded by proctometrography [12], which measured the rectal sensory threshold, the maximum tolerable rectal volume and rectal compliance.

Electrophysiology
An anal plug electrode was used with an electromyographic (EMG) integrator [13] to measure the amplitude of the resting and 'squeezing' EMG of the EAS. Pudendo-anal reflex latency was recorded after applying over 100 consecutive synchronized impulses (duration 0.1 ms, frequency 1 Hz) to the dorso-genital nerve using the Medelec MS 92a apparatus [8].

Radiological videoproctography
No bowel preparation was required prior to videoproctography since the rectum is usually empty. The contrast medium, with a consistency similar to that of normal stools, comprised a 50 ml suspension of barium sulphate (Baritop 100) mixed with potato mash and hot water until a smooth thick paste was formed (30 ml of hot water, for every teaspoon of potato powder). The cooled paste was injected into the rectum through a short wide anal catheter (Polibar ACB). The amount of contrast used varied depending on the sensory awareness and tolerability of each patient. A concentrated suspension of barium was used to obtain improved coating and a sharper outline of the rectal mucosa and was injected into the rectum prior to the paste. A fine Foley catheter was used as an anal canal marker. The patient was then seated on a specially designed commode and lateral pelvic X-rays were taken in the seated position at rest, during maximum 'squeeze' effort and on straining, followed by a period of videorecording during which the patient was ultimately asked to evacuate. The parameters measured were: anorectal angle at rest; during squeeze; on straining: during evacuation; pelvic floor level at rest; pelvic floor ascent during squeeze and pelvic floor descent on attempted defecation [11].

Changes in the configuration of the rectal wall during evacuation were noted as was the presence/absence of a rectocoele, persistent impression of the puborectalis sling on defecation and presence/absence of the descending perineum syndrome [14]. A descending perineum was considered to be present when the absolute movement of the anorectal junction on straining was greater than 2 cm. Correction for magnification was made for this parameter only with a magnification factor of 1.5. The values for the pelvic floor level in relation to the pubococcygeal line, pelvic floor ascent and descent were not corrected for as these are absolute movements. The state of the anal canal at rest was recorded, i.e. whether it was patent or closed, and the efficiency of evacuation was es-
The protocol was approved by the Ethical committee of the Lothian Health Board and all patients gave informed consent.

Statistical analysis
All results are expressed as median values and 95% confidence intervals (CI); the sign test was used for paired comparison of the pre- and poststimulator studies. Significance was set at the 5% level.

Results
A total of 24 patients suffering from faecal incontinence for at least 2 years were treated over 8 weeks with a pudendo-anal reflex electrical stimulator. On direct questioning after the completion of treatment, 33.5% of the patients reported some clinical improvement, while 52.3% experienced great clinical improvement in continence control. In fact, 19% became completely asymptomatic in contrast to 14% whom experienced no clinical change. The overall clinical improvement was 86%.

Anorectal manometry and electrophysiology
The patients were retested on their first visit to the hospital after the completion of electrical stimulation of the pelvic floor and EAS muscles. The anorectal parameters tested are listed in Table 1.

Table 1. Anal canal pressures recorded at rest, maximum resting pressure (MRP), during maximum contraction on coughing (CP) and maximum conscious squeeze (SQP) of the anal sphincter before and after electrical stimulation. Rectal volumes elicited at the sensory threshold level and at maximum tolerable rectal capacity. Rectal compliance (COMPL) and pudendo-anal reflex latency (PARD) are also recorded.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRP (cmH2O)</td>
<td>60 (50-60)</td>
<td>70 (60-84)</td>
</tr>
<tr>
<td>CP (cmH2O)</td>
<td>50 (38-62)</td>
<td>60 (60-80)</td>
</tr>
<tr>
<td>SQP (cmH2O)</td>
<td>40 (30-60)</td>
<td>60 (40-80)</td>
</tr>
<tr>
<td>Sensation (ml)</td>
<td>113 (87-127)</td>
<td>100 (83-110)</td>
</tr>
<tr>
<td>Capacity (ml)</td>
<td>263 (230-311)</td>
<td>280 (245-326)</td>
</tr>
<tr>
<td>COMPL (ml/cmH2O)</td>
<td>4.0 (3-5)</td>
<td>4.0 (3-5)</td>
</tr>
<tr>
<td>PARD (ms)</td>
<td>52 (46-57)</td>
<td>48 (41-54)</td>
</tr>
</tbody>
</table>

Results expressed as median (95% confidence interval).

The functional anal canal length was significantly enhanced (P<0.004) following treatment. There was a significant increase in the anal canal pressures on coughing (P<0.0001; Fig. 1), on voluntary 'squeezing' (P<0.03; Fig. 2) and at rest (P<0.004; Fig. 3) following stimulator treatment. Rectal sensory threshold, maximum tolerable rectal capacity and compliance did not change significantly. The was no significant change or improvement in delayed conduction of the pudendo-anal reflex.

Fig. 1. Maximum pressure recorded in the anal canal during the reflex response to a cough before and after the course of pudendo-anal reflex stimulation (n=24; P<0.0001).

Fig. 2. Maximum pressure recorded in the anal canal during maximal voluntary squeeze contraction of the anal sphincter before and after the course of pudendo-anal reflex stimulation (n=22; P<0.03).
Radiological videoproctography
Before treatment, videoproctography highlighted the following abnormalities: 15 patients had rectocelees (63%), 11 had persistent puborectal impression on defecation (46%) and three had descending perineum syndrome (12.5%); 12 patients had incomplete evacuation (50%) and 18 had a patent anal canal at rest (75%). After 8 weeks of treatment with the stimulator, proctography was performed which showed that the number of rectocelees remained unchanged, six patients had a descending perineum (25%), seven had incomplete emptying (29%), but there were now only 11 patients (46%) with a patent anal canal at rest ($P<0.04$).

Table 2. Anorectal angles recorded by radiological videoproctography before and after electrical stimulation.

<table>
<thead>
<tr>
<th>Anorectal angle</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>88° (60-96°)</td>
<td>85° (75-101°)</td>
</tr>
<tr>
<td>Squeeze</td>
<td>65° (54-76°)</td>
<td>68° (60-75°)</td>
</tr>
<tr>
<td>Straining</td>
<td>93° (74-115°)</td>
<td>105° (85-107°)</td>
</tr>
<tr>
<td>Evacuation</td>
<td>95° (82-115°)</td>
<td>105° (95-130°)</td>
</tr>
</tbody>
</table>

Results expressed as median (95% confidence interval).

There were no significant changes in the anorectal angles before and after pelvic floor electrical stimulation (Table 2). Pelvic floor movement on squeezing and straining measured before electrical stimulation was significantly changed compared with levels at rest ($P<0.0002$ and $P<0.0001$, respectively), and in relation to the resting level following stimulation ($P<0.0001$ and $P<0.00001$, respectively). Pelvic floor ascent (Table 3), therefore, was significantly increased ($P<0.02$; Fig. 4).

Fig. 3. The maximum resting pressure recorded in the anal canal before and after the course of pudendo-anal reflex stimulation ($n=24$; $P<0.01$).

Fig. 4. Pelvic floor ascent recorded by radiological videoproctography during a maximal voluntary squeeze contraction of the anal sphincter before and after the course of dorso-genital nerve stimulation ($n=22$; $P<0.02$).

Discussion
The pelvic floor and EAS are in a state of continuous tonic contraction which is dependent on a spinal reflex completed through the conus medullaris by afferent and efferent pathways in the sacral S2, S3 and S4 segments of the spinal cord [15,16]. The integrity of the arc can be tested by the pudendo-anal reflex [8,17]. Delay in conduction has been used as a sensitive indicator of neurogenic damage [8]. The 24 patients described here comprised older patients in contrast to a preliminary study where the mean age of the patients was 20 years younger [10]. These older patients were resistant to other forms of treatment (medical, surgical and physiotherapy). The pudendo-anal reflex was present, however, and continuous artificial stimulation of this reflex was possible. In this series, the majority of patients (86%) admitted that their symptoms improved supporting objective findings include lengthening of the anal canal with an increase in anal canal pressures and, in particular, in the cough pressure which
does not depend on patient motivation. This is by far the best reported success rate in the treatment of faecal incontinence compared with results of surgical procedures [18]. In the group with consistent clinical improvement, the anorectal parameters of function and pressure on cough reflex contraction changed significantly, whereas the group with no improvement had no significant changes in these parameters. This supports the conclusion that the effects on the anorectal parameters were not mere epiphenomena of clinical improvement.

Following electrical stimulation, there were no significant changes in the number of rectoceles, puborectalis impression on defecation and completeness of evacuation. However, the patency of the anal canal was significantly reduced and this was associated with enhanced continence control. In addition, pelvic floor ascent was significantly increased, demonstrating greater dynamic movement of the pelvic floor on voluntary contraction.

In contrast to previous studies of dynamic proctography performed in patients with faecal incontinence [5], in which patients had more obtuse anorectal angles compared with normal controls, the patients in this series presented with less obtuse angles. This implies that the puborectalis muscle may have been preserved or, at least, was unaffected by the pudendal neuropathy which appeared to be the cause of damage to the EAS [19]. There may be two reasons for this: the first is that any puborectalis muscle damage could be minimal compared with that of the EAS and, therefore, was not evident on videoproctography. The second reason could be that the puborectalis muscle is not supplied by the pudendal nerve in contrast to the EAS [20].

Swash et al. [21] have studied the innervation of these muscles and showed that the puborectalis and EAS muscles are innervated by different motor nerves, although both originate in the same spinal cord segments. An electrophysiological study of the motor nerve supply to these muscles showed that the puborectalis was innervated by a branch of the splanchnic nerve (S3 and S4), which lies above the pelvic floor, while the pudendal nerve supplies the ipsilateral EAS muscles [20].

On the other hand, an experimental study of the EAS in the monkey [22] showed that there is a substantial overlap in the pudendal innervation of the two sides of the sphincter. This has been related to the interdigitation of muscle fascicles across the anterior midline in this muscle. This functionally important overlap in the innervation facilitates re-innervation from the opposite side when pudendal nerve damage occurs in the incontinent patient [23]. Thus, the EAS may be influenced more efficiently by electrical stimulation compared with other pelvic floor muscles.

Direct stimulation has been used in an attempt to achieve transformation of EAS type 2 fibres, which is increased in neurogenic FI, to type 1 [24]. No histological studies were performed in this study either before or after completion of the 8-week course of reflex electrical stimulation; therefore, it is not clear whether improvement in the physiological anorectal parameters was accompanied by a change in the structural appearance arrangement of the type 1 and 2 fibres of the anal sphincter. Further studies, including sphincter biopsy, are required.

In conclusion, if there is no interruption in the continuity of the pudendo-anal reflex arc, as in the patients in this study, electrical stimulation of the pudendal nerve, and thus the EAS and the pelvic floor musculature, is possible. In this way, improvement in the tonicity of the anal sphincter and pelvic floor muscles can be achieved resulting in enhanced pelvic floor ascent and closure of the anal canal, which may restore continence.

Acknowledgements

The authors are grateful to Mr I. Loudon, Department of Bioengineering, Princess Margaret Rose Hospital, Edinburgh, UK, for the construction of the pudendo-anal reflex stimulator, and to Miss N. Clare for technical assistance.

References

Abstract

Twenty two patients with obstructive defecation were recruited for relaxation training by domiciliary self regulatory biofeedback. Each patient served as his or her own control for anorectal and proctographic assessments. Biofeedback training improved the obstructive symptoms of the patients and showed significant change in various parameters related to the obstructive defecation syndrome. As examined by isotope dynamic proctography: the defecation rate (% of evacuation/defecation time) was significantly increased (p<0.05), the anorectal angles at rest and during attempted defecation were made more obtuse (p<0.05), and the pelvic floor movements were made more dynamic on voluntary contraction of the anal sphincter (p<0.03). The external anal sphincter electromyographic voltage recorded during defecation was significantly reduced (p<0.0005) as was the surface anal plug electromyographic electrode voltage (p<0.001), which was associated with a greatly reduced anismus index (p<0.0001). The rectal sensation was improved (p<0.05), cocomitantly. Biofeedback thus improves the defecation act in patients suffering from inappropriate contraction of the pelvic floor and sphincter musculature. Furthermore, this study has shown that biofeedback objectively influences the defecation reflex leading to an improved quality of higher control of bowel function.

The applicability of instrumental learning to the relief of gastrointestinal disorders is now almost unquestionable. Biofeedback has been successfully achieved by strengthening the contractions of the lower oesophageal sphincter in patients with reflux oesophagitis through instrumental learning, which was promoted by displaying lower oesophageal sphincter pressure. It has been used similarly in patients with faecal incontinence, aiming at strengthening the contraction of the anal sphincter.

The study of the psychological as well as physiological characteristics of patients with severe idiopathic constipation encouraged the application of the biofeedback self regulation technique to constipation. The relief of functional constipation, or dyschezia, has become an obvious goal. Bleijenberg and Kuijpers have described a method of treatment of the spastic pelvic floor syndrome with biofeedback, after the patients have been in hospital for two weeks. This treatment though successful has caused concern to physicians and patients because of the comparatively long stay in hospital. The opportunity arose to apply this method to the treatment of the spastic pelvic floor syndrome, through the use of a small portable device suitable for domiciliary treatment. Since then, biofeedback treatment in obstructive defecation has become acknowledged as the foremost treatment for this condition with effects lasting for at least six months after treatment.

Although the subjective effects were, however, well appreciated by clinicians and patients, there was no objective evidence as to how and what is the influence of the biofeedback on the anorectal function. Our study investigates the objective effects of biofeedback treatment on anorectal function in patients with obstructive defecation. It examines aspects of the defecation reflex in disturbed defecation with anorectal manometry, electrophysiology, and proctography. The study also aims at an exploration of the mechanisms of the biofeedback influences in the neural control of defecation.

Patients and methods

SUBJECTS

Twenty two patients were recruited, median age 42 years (age range: 32 to 50). Seventeen of them were females (77%) and five were males (23%). Seven of the females were nulliparous (41%) and six were multiparous (with three children or more). Ethical permission for this work was obtained from the ethical committee of the Lothian Health Board, Edinburgh. Informed consent was also obtained from all patients.

The patients suffered from constipation for three to 25 years and complained of prolonged straining at stool. They could not perform rectal balloon expulsion and had inappropriate contraction of the external anal sphincter on straining as evidenced by electromyographic studies. Transit studies performed showed that radio-opaque pellets retained were less than 10, in a period of three to eight days after ingestion, thus excluding slow transit constipation. Conversely no markers were passed within the first 72 hours and the pellets were retained in the rectosigmoid region. All had a barium enema excluding organic disease and a normal rectosigmoid inhibitory reflex. Although all patients had detectable inappropriate contraction of the pelvic floor muscles on straining their symptoms varied as follows: the frequency of defecation ranged from three daily to once a week, but with 16 patients complaining of incomplete emptying of the bowels (73%); 15 patients complained of perineal pain and discomfort of defecation (68%), 14 complained of abdominal pain and distension (64%), nine patients could not evacuate without the use of...
Effects of biofeedback on obstructive defecation - reconditioning of the defecation reflex?

Biofeedback training entailed the attendance of the patient at the hospital on an outpatient basis on at least three occasions. During these visits theoretical and practical instructions were given of how to operate the biofeedback Myotron device. This was combined with rectal balloon expulsion exercises that aimed at improving rectal sensory awareness and stimulating anal sensation of the inappropriate contraction of the pelvic floor muscles obstructing the expulsion of the filled balloon. When the patient and investigator were satisfied about the competence of the patient in performing the rectal balloon expulsion exercises and the ability to operate the Myotron device, the patient was given the device for a domiciliary course of minimum four weeks duration.

METHODS

Anorectal manometry and electrophysiology

Conventional anorectal manometry using a 4 mm microballoon connected to an external transducer permitted measurements of the functional anal canal length, the maximum resting pressure, and the anal canal pressure increment on voluntary and cough reflex anal sphincter contraction. The rectosphincteric inhibitory reflex was performed in all patients to exclude aganglionosis as the cause of constipation. Proctometrograms were performed eliciting the volumes of the rectal sensory threshold, the maximum tolerable rectal capacity, and the rectal compliance. Electrophysiological tests included the latency of the pudendoanal reflex and integrated electromyography of the external anal sphincter via a surface electromyographic anal plug electrode. The anismus index was derived as the relation of the electromyographic voltage of the external anal sphincter on straining to the electromyographic voltage of the external anal sphincter on squeezing in the formula:

\[ \text{Anismus index} = \frac{\text{Increment of electromyographic voltage on squeezing}}{\text{Increment of electromyographic voltage on straining}} \times 100 \]

Isotope proctography

Isotope dynamic proctography combined with simultaneous recording of external anal sphincter electromyography, with the use of wire electrodes, and intrarectal telemetry were performed in all patients as described in an earlier study. The parameters recorded were the percentage of the activity evacuated (%EVAC), the defecation time (seconds), and the defecation rate (%EVAC/second); anorectal angle at rest, on maximal anal sphincter contraction during voluntary 'squeezing', on straining and during evacuation; and the pelvic floor movements on voluntary contraction of the anal sphincter, on straining and during evacuation.

Rectal balloon expulsion test

Before isotope proctography rectal balloon expulsion tests were performed in all patients. The proctometrogram balloon was inserted in the rectum and filled with saline up to a level of sensory awareness (approximately 140 ml). The patient was then asked to evacuate this balloon. (An unaided expulsion of the rectal balloon would have excluded at this stage any obstructive phenomena.)

Biofeedback training

The patients, after a preliminary evaluation of their symptoms and results of the investigations, and after consultation with the referring consultant were recruited to the biofeedback study. This entailed the attendance of the patient to the hospital on an outpatient basis on at least three occasions. During these visits theoretical and practical instructions were given of how to operate the biofeedback Myotron device. This was combined with rectal balloon expulsion exercises that aimed at improving rectal sensory awareness and stimulating anal sensation of the inappropriate contraction of the pelvic floor muscles obstructing the expulsion of the filled balloon. When the patient and investigator were satisfied about the competence of the patient in performing the rectal balloon expulsion exercises and the ability to operate the Myotron device, the patient was given the device for a domiciliary course of minimum four weeks duration.

STATISTICAL ANALYSIS

The statistical analysis of the results used the median values and their 95% confidence intervals (CI) and the non-parametric sign test for comparison of paired findings.

Results

ASSESSMENT BEFORE BIOFEEDBACK

Anorectal manometry and proctometrogram studies and also shows the results of the electrophysiological tests, which showed that the pudendoanal reflex latency was delayed and gives the integrated electromyographic voltage of the external anal sphincter elicited via the surface anal plug electromyographic electrode at rest and on straining. Obstructive defecation was implemented via a high anismus index.

Isotope proctography

The Table shows the results of the isotope dynamic proctography depicting %EVAC, defecation time and rate, anorectal angles at rest, on 'squeezing', straining, and during evacuation, as well as pelvic floor descent on straining and evacuation; the isotope dynamic proctographs at rest, on straining and on evacuation are also given. The electromyography of the external anal sphincter performed simultaneously during isotope proctography with wire electrodes depicted the electromyographic voltage at rest, on squeezing, on straining and on evacuation.

Rectal balloon expulsion test

All the patients could not expel the rectal balloon unaided in the first instance, but achieved successful expulsions by the end of the hospital training programme before the domiciliary biofeedback. The rectal balloon expulsion exercises ranged from 2 to 5 sessions, for each patient; each session lasting 1.5–2.0 hours duration.

ASSESSMENT AFTER BIOFEEDBACK

The patients completed a domiciliary course of biofeedback with a median duration of 36 days.
The effect of biofeedback training

<table>
<thead>
<tr>
<th></th>
<th>Before biofeedback (mean (95% CIs))</th>
<th>After biofeedback (mean (95% CIs))</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorectal manometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRP (cmH2O)</td>
<td>120 (110 to 140)</td>
<td>120 (92 to 128)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SQP (cmH2O)</td>
<td>80 (50 to 130)</td>
<td>90 (72 to 108)</td>
<td></td>
</tr>
<tr>
<td>SEN (ml)</td>
<td>138 (110 to 180)</td>
<td>100 (90 to 170)</td>
<td></td>
</tr>
<tr>
<td>CAP (ml)</td>
<td>425 (310 to 496)</td>
<td>415 (355 to 481)</td>
<td></td>
</tr>
<tr>
<td>COM (ml/cmH2O)</td>
<td>6.4 (4.2 to 7.3)</td>
<td>6.0 (5.0 to 8.0)</td>
<td></td>
</tr>
<tr>
<td>Electrophysiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AI (%)</td>
<td>67.5 (50 to 80)</td>
<td>0 (2 to 60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PARL (ms)</td>
<td>48 (42 to 52)</td>
<td>40 (37 to 48)</td>
<td></td>
</tr>
<tr>
<td>EASEMG (rest μV)</td>
<td>20 (10 to 40)</td>
<td>25 (10 to 45)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>EASEMG (evacuation μV)</td>
<td>50 (25 to 100)</td>
<td>25 (10 to 45)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>EASEMG (evacuation (μV)</td>
<td>100 (53 to 100)</td>
<td>15 (7 to 43)</td>
<td></td>
</tr>
<tr>
<td>Isotope proctography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVAC (%)</td>
<td>56 (46 to 72)</td>
<td>61 (42 to 71)</td>
<td></td>
</tr>
<tr>
<td>DTIME (s)</td>
<td>112 (52 to 167)</td>
<td>64 (40 to 117)</td>
<td></td>
</tr>
<tr>
<td>BRIEF (%)</td>
<td>0.5 (0.2 to 0.6)</td>
<td>0.8 (0.5 to 1.5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ARA rest</td>
<td>103 (92 to 106)</td>
<td>110 (104 to 114)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ARA straining</td>
<td>112 (96 to 117)</td>
<td>119 (106 to 121)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ARA evacuation</td>
<td>127 (106 to 135)</td>
<td>137 (129 to 139)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PFD starting (man)</td>
<td>9 (7 to 14)</td>
<td>6 (4 to 13)</td>
<td></td>
</tr>
<tr>
<td>PFD evacuation (mm)</td>
<td>57 (47 to 52)</td>
<td>52 (45 to 52)</td>
<td></td>
</tr>
<tr>
<td>Radiotelemetry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRP rest (cmH2O)</td>
<td>5 (5 to 10)</td>
<td>10 (5 to 20)</td>
<td></td>
</tr>
<tr>
<td>IRP straining (cmH2O)</td>
<td>30 (20 to 40)</td>
<td>20 (10 to 40)</td>
<td></td>
</tr>
<tr>
<td>IRP evacuation (cmH2O)</td>
<td>15 (10 to 20)</td>
<td>15 (10 to 60)</td>
<td></td>
</tr>
</tbody>
</table>

Anal canal pressures at rest (MRP) and on maximal contraction of the anal sphincter during voluntary "squeeze" (SQP); rectal sensory threshold (SEN), rectal capacity (CAP), and compliance (COM); anisimus index (AI), pudendoanal reflex latency (PARL), and external anal sphincter (EAS) electromyographic wire electrode recorded in 20 patients, before and after biofeedback. (The results were compared with the use of the sign test for paired samples, p value is shown).

(range: 30–53 days). At the end of this period the patient had the anorectal and proctography tests repeated as above.

Subjective assessment after the biofeedback most patients admitted to clinical improvement (57%), whereas 29% were completely asymptomatic, and only 14% had no appreciable symptomatic change.

The Table gives anorectal manometry, electrophysiology results, and detailed analysis of the results obtained from the isotope proctography tests, performed after the treatment with biofeedback and these are contrasted with those from studies done before biofeedback.

**Anorectal manometry and electrophysiology**

The anorectal manometry showed no significant change in the intra-anal canal pressures, maximum resting pressure or the increment on voluntary anal sphincter contractions. The proctometrogram, however, showed that the volume of the rectal sensory threshold was reduced (p<0.05) after the biofeedback, with no noticeable change in the rectal capacity and compliance.

Furthermore, the integrated electromyography recorded via the anal canal revealed an increase in the electromyographic voltage of the external anal sphincter on straining (p<0.0001), with the electromyographic voltage at rest remaining virtually the same. Thus, the anisimus index was greatly reduced (p<0.0001; Fig 1) after the biofeedback treatment.

**Isotope proctography**

The defecation rate, as the relation of the %EVAC to the defecation time, was significantly increased after the biofeedback (p<0.05; Fig 2). The anorectal angles at rest, on straining, and during evacuation became more obtuse (p<0.05; Fig 3) after the biofeedback. There was a significant increase in the upward ascent movement of the pelvic floor on "squeezing" (p<0.03), but no difference was seen in the pelvic floor descent.

The %EVAC during isotope dynamic proctography did not show any significant response to the biofeedback, however, the external anal sphincter electromyographic wire electrode recorded a significant drop in the electromyographic voltage on straining (p<0.02) and on evacuation (p<0.001) whereas the electromyographic voltage at rest was virtually unchanged.

**Discussion**

Obstructive defecation is understood to be present in the context of abnormal defecation when there is inappropriate contraction of the puborectalis and external anal sphincter muscles during attempted expulsion, narrowing of the anorectal angle, and an increased pressure in the anal canal. The prevalence of pelvic floor dyssynergia is estimated to occur in almost half of adults with dyschezia and a similar percentage of children with faecal incontinence associated with constipation.11,12 The underlying aetiology is "spastic pelvic floor" or anisimus is uncertain and it has been suggested that laboratory findings may not always resemble the clinical setting. Nevertheless, if reversal of...
In this study the patients were investigated before biofeedback, both for elicitation of 'defects' in their defecation mechanisms and for objective changes after biofeedback. The external anal sphincter and the pelvic floor muscles have a continuous level of 'spiking' electrical activity at rest. The external anal sphincter reflex contraction in response to transient rises in intra-abdominal pressure may be seen during the rectosphincteric reflex and proctomogram. 

By steadily increasing the volumes in the rectal balloon the external anal sphincter and puborectalis are inhibited at a certain level. On defecation, the sphincters relax to permit the passage of the faecal bolus by either the cerebral inhibition of the sphincter contraction or mechanical stimulation, or both in the anal canal. Once defecation has started, it can continue with no conscious effort, suggesting colonic contraction in response to the faecal bolus passing through the anus. On completion of evacuation the pelvic floor and sphincter muscles regain their previous resting activity and the anal canal closes.

It may be assumed that patients with obstructive defecation have inhibited their defecation reflex at some stage, presumably because of 'strong' environmental stimuli registering as a life event. As a result the voluntary control of the reflex by higher cortical centres may be lost, which can result in inappropriate use of the pelvic floor and sphincter muscles on attempted defecation, as shown by increased electromyographic voltage of the external anal sphincter activity recorded during proctography. The patients studied had difficulties in starting defecation as well as completing evacuation. This implies a disordered anorectal sensation and stimulation of colonic contraction.

Biofeedback improved the defecation rate by changing the anorectal angles, improving rectal sensation, and diminishing the electromyographic voltage of the external anal sphincter. It has influenced the defecation act at different levels. Therefore, although the act of defecation is a complex phenomenon dependent upon many linked factors in the anorectum and higher centres, it can be influenced by a self regulatory mechanism that depends on the patients' will and effort.

This study presents effects of biofeedback on anorectal function measured objectively for the first time, and shows that biofeedback therefore influenced positively the defecation reflex, reinforcing its afferent limb by improved anorectal sensation, recruiting the higher centres in the conscious control of the act, and through the efferent limb, provided increased relaxation of the pelvic floor and sphincter musculature.


6 Wald A, Hills JP, Cartana BJ. Psychological and physiological characteristics of patients with severe idiopathic constipation. Gastroenterology 1989; 97: 932-7.


Obstructive defaecation and slow transit constipation: the proctographic parameters

A. N. Smith, M. V. Merrick

Original articles

Abstract. Twenty-two patients with functional obstructive defaecation were compared with seven patients with slow transit constipation using isotope proctography. The obstructive defaecation patients were unable to perform a complete rectal evacuation (% of the activity excreted: 54%). The defaecation time in this group was prolonged (120 s) with a lower defaecation rate (0.5%/s) compared with the slow transit constipation subjects (1.8%/s). The ano-rectal angle (ARA) on straining did not change in the obstructive defaecation patients but became more obtuse in the slow transit constipation subjects (P < 0.02). The pelvic floor (PF) descent on straining and evacuation was greater in obstructive defaecation patients compared with the slow transit constipation ones (P < 0.01). Obstructive defaecation is characterized by prolonged defaecation and reduced evacuation rate compared with slow transit constipation. Obstructive defaecation patients present with more ARAs on straining, and abnormal perineal descent contrast to the slow transit constipation ones.

Conclusion. Vingt-deux patients souffrant de dyschésie ont comparé avec 7 patients souffrant d’une constipation à un ralentissement du transit au moyen d’une proctographie isotope. Les patients souffrant de dyschésie sont incapables d’évacuer complètement leur ampoule rectale (%). Le temps d’exonération de ce collectif était prolongé (120 s) avec une vitesse d’exonération inférieure (0.5%/s) comparativement aux sujets avec un ralentissement du transit (32 s et 1.8%/s). L’angle ano-rectal, lors de l’effort d’exonération, ne change pas chez les patients souffrant de dyschésie mais devient plus obtus dans le collectif de patients souffrant d’une constipation à transit lent (P < 0.02). L’abaissement du périnée lors de l’exonération et de l’évacuation était plus important chez les patients souffrant de dyschésie que chez ceux souffrant de constipation avec ralentissement du transit (P < 0.01). La dyschésie est caractérisée par un allongement du temps d’exonération et une diminution de la vitesse de l’évacuation de l’ampoule rectale comparativement à la constipation avec ralentissement du transit. La dyschésie s’accompagne d’un angle ano-rectal plus aigu lors de l’exonération et d’une descente anormale du péronée comparativement à la constipation à transit lent.

Constipation is not a disease but a symptom of several disorders. When conventional investigations reveal no organic causes [1], constipation is considered to be nonorganic, or functional [2]. There is no consensus regarding the pathophysiology of functional constipation; studies have suggested that it may be related to abnormally high sphincter pressures [3], an internal anal sphincter that fails to relax on rectal distension [4], impaired rectal sensitivity [5], reduced colonic propulsion [6], a functional obstruction of the sigmoid colon [7], failure of relaxation or paradoxical contraction of the puborectalis and/or external anal sphincter [8], or a combination of these abnormalities.

Dietary fibre has been regarded by many as a panacea in the treatment of constipation; however, some patients find that they are not helped by it and it may even make their symptoms worse [9]. Others remain resistant to all forms of treatment except enemas and large doses of saline cathartics and ultimately some require a colectomy to relieve the situation [10].

Two types of nonorganic functional constipation can be distinguished: the slow-transit type or colonic inertia and outlet obstruction or obstructive defaecation [8, 11]. The latter is an abnormal function of the pelvic floor muscles. Straining during defaecation provokes a contraction instead of relaxation of these muscles, thus creating a functional outlet obstruction. Slow transit constipation or colonic inertia is a common and serious problem in young women [12, 13], and may be identified by delayed transit of radio-opaque markers in the proximal colon [14]. Colonic motility does not seem to differ in
patients with slow transit constipation compared with normal controls [15]. Delayed transit of markers in the proximal colon, nonetheless may occur in functional obstruction of the distal colon [16].

The aims of this study were to characterise further the phenomena of nonorganic constipation and analyse its proctographic parameters qualitatively and quantitatively in functional obstructive defaecation in contrast to slow transit constipation.

Materials and methods

Subjects

Twenty-nine patients with functional constipation were studied, 25 of whom were women and 4 were men. Nine of the 25 women were multiparous and females of child bearing age had the possibility of pregnancy excluded prior to the study. All had been assessed clinically by the referring consultant surgeon or gastroenterologist. Barium enema examination and sigmoidoscopy did not show any organic abnormalities. Objective evidence of severe constipation was obtained by estimating the delivery of radiopaque markers in the faeces after ingesting 50 plastic radiopaque markers. Two groups were recognised; one with normal transit of the radiopaque pellets through the large bowel and another with slow transit via the proximal colon. The former group of 22 patients, exhibited obstructive phenomena and were selected from the normal transit group study. The latter group of 7 patients, showed no functional obstructive phenomena but delayed transit along the length of the colon.

Patients with evidence of obstructive defaecation (OD). Eighteen of them were women (82%), and 4 were men (18%). The patients median age was 44 years (range: 36–46 years), duration of symptoms from 1 year to 33 years, and defaecation frequency from once in 2 days to no bowel movement without the help of laxatives/enemas. These patients had been having difficulty in evacuating the bowels, often irrespective of whether the stools were hard or loose. The patients complained of lack of responsiveness to laxatives or enemas (32%), incomplete evacuation (59%) and the feeling of obstruction at defaecation (27%). All patients described prolonged straining at stool despite an urge to defaecate, some having to resort to anal digitation to aid evacuation of stool (14%). Amongst primary complaints were abdominal pain (59%), abdominal distension (9%), nausea (5%) and perineal pain (64%).

Patients with slow transit constipation (STC). The second group of patients studied were constipated subjects who had been suffering from infrequent defaecation. This group consisted of 7 women with median age of 38 years (range: 30–56 years). These patients have suffered from constipation from 1 year to 20 years, with a defaecation frequency from one every 2 days to once a month. Four of them were on regular laxatives. All of them admitted straining at stool and 6 of them had abdominal and/or perineal discomfort.

Methods

Dynamic scintigraphic proctography was performed in each patient. During this test the radiopharmaceutical used, approximately 200 MBq 99m-Tc Methylene Diphosphonate (99mTc MDP), was prepared as described earlier [17]. After the insertion per rectum of the isotope 'potato paste' at a volume approximated to the maximum tolerable capacity, a Foley catheter (12 CH) filled with approximately 20 MBq 99mTc MDP, was used as the anal canal marker. With the patient seated upright on a commode recordings were made of the rectal images, EMG of the external anal sphincter and intrarectal pressures, at rest and following commands such as 'squeeze', cough, straining and evacuation.

Statistical analysis

The statistical analysis of the results used the median values and their 95% confidence interval (CI), the Spearman’s correlation coefficient and its p value, the non-parametric Mann-Whitney test for unpaired comparison and the sign test for paired comparison observations.

Ethical permission

Ethical permission for this work was obtained from the Ethical Committee of the Lothian Health Board, Edinburgh. Informed consent was also obtained from all patients.

Results

Patients with OD features

The adequacy of rectal evacuation (%EVAC), the defaecation rate (%EVAC/sec) and the defaecation time involved were calculated as described in an earlier paper [17] (Fig. 1). The %EVAC was 54% (95% CI: 44, 72%), the defaecation rate (DRate) was 0.5%/s (95% CI: 0.2, 1%/s) and the defaecation time (DTtime) was 120 s (95% CI: 52, 208 s).

Anorectal angles (ARA) in OD

The ARAs at rest, on squeezing, straining and evacuation referred to are the ‘lower anorectal angles’ (Figs. 2 and 3) i.e. the ones formed by the anal canal midline and a parallel line to the posterior rectal wall. The ARA at rest was 103° (95% CI: 92°, 106°), the ARA on straining was 112° (95% CI: 96°, 117°) and on evacuation the ARA was 126° (95% CI: 120°, 131°).

Fig. 1. Proctogram curves recording isotope activity in the anal canal, rectum and overall anorectum (y-axis) against defaecation time, in a single study. Evacuation begins at arrow.
Isotope anorectal image at rest, in a patient with functional obstructive defaecation. The pelvic floor level is set to zero at the rectal junction. The upper and lower anorectal angle are indicated:

\[
\text{Upper rectal angle} = 113.0 \\
\text{Lower rectal angle} = 142.0
\]

Isotope anorectal image during ' evacuation' pelvic floor difference = -27.6 mm

\[
\text{Upper rectal angle} = 96.0 \\
\text{Lower rectal angle} = 117.0
\]

1. Isotope anorectal image at rest
2. Isotope anorectal image during evacuation
3. Isotope anorectal image at evacuation

Table 1. The percentage of the activity evacuated, the defaecation time and rate; the anorectal angles (ARA) at rest, on straining and during evacuation; the pelvic floor descent on straining and evacuation; in the two groups (OG groups, constipated subjects with obstructive defaecation features and STC group, constipated subjects with slow transit constipation)

<table>
<thead>
<tr>
<th></th>
<th>OD groups</th>
<th>STC group</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVAC (%)</td>
<td>54 (44, 72)</td>
<td>57 (49, 69)</td>
</tr>
<tr>
<td>DTime (s)</td>
<td>120 (52, 208)</td>
<td>32 (32, 62)</td>
</tr>
<tr>
<td>DRate (%/s)</td>
<td>0.5 (0.2, 1)</td>
<td>1.8 (0.7, 2.2)</td>
</tr>
<tr>
<td>ARA at rest</td>
<td>103° (92°, 106°)</td>
<td>111° (91°, 116°)</td>
</tr>
<tr>
<td>ARA strain.</td>
<td>112° (96°, 106°)</td>
<td>120° (104°, 142°)</td>
</tr>
<tr>
<td>ARA evac</td>
<td>126° (120°, 131°)</td>
<td>132° (127°, 156°)</td>
</tr>
<tr>
<td>PFD str. (mm)</td>
<td>-9 (-9, -5)</td>
<td>-6 (-14, 4)</td>
</tr>
<tr>
<td>PFD evac (mm)</td>
<td>-33 (-46, -23)</td>
<td>-18 (-50, 13)</td>
</tr>
</tbody>
</table>

The above results are presented in Table 1.

Correlation of proctographic parameters in OD

A proportional increase in the ARA on straining was observed compared with the ARA at rest \( (P = 0.001) \), whereas the ARA increment during evacuation related to the initial measurement of the ARA at rest \( (P = 0.02) \). The ARA on straining correlated with the PF movement on straining \( (P = 0.001; \text{Fig. 4}) \) and the ARA achieved on evacuation correlated with the PF descent on evacuation \( (P = 0.01) \).

In this group, 3 patients (14%) presented during isotope proctography with 'immobile perineum' (PF descent on evacuation less than 1 cm). These patients had %EVAC in a range of 8 to 47%; the DRate was within 0.1 to 1.0%/s; the DTime was 48 to 160 s; the ARA at rest was 62° to 98°; the ARA on straining 56° to 115°; the ARA on evacuation was 96° to 116°. Nine patients (41%) had an abnormal perineal descent (PF descent on evacuation greater than 4 cm). Thirteen patients (59%) had PF movement on evacuation greater than 1 cm and lesser than 4 cm. There was a greater increment in the ARA angle on evacuation in the 'abnormal perineal descent' subgroup compared with the subgroup with a 'normal pelvic floor descent' \( (P = 0.01) \). This greater ARA increment on evacuation correlated with the ARA at rest \( (P = 0.01) \). On the other hand, in the subgroup with a 'normal PF descent' the ARA on evacuation correlated with the PF descent on evacuation \( (P = 0.03; \text{Fig. 5}) \). This PF descent correlated to the ARA at rest \( (P = 0.001) \).

Patients with STC

Isotope dynamic proctography results are shown in Table 1. The %EVAC was 57% (95% CI: 49, 69%), the DRate was 1.8%/s (95% CI: 0.7, 2.2%/s), and the DTime was 32 s (95% CI: 32, 62 s).
Anorectal angle on straining (degrees)

Fig. 4. The relationship between the pelvic floor movement and the anorectal angle on straining in the 22 patients with functional obstructive defaecation. Patients with an upward PF movement presented with acute anorectal angles on straining. Patients with greater PF descent achieved more obtuse anorectal angles on straining.

Anorectal angles in STC

The ARA at rest was 111° (95% CI: 91°, 116°), on straining 120° (95% CI: 104°, 142°) and on evacuation 142° (95% CI: 127°, 156°).

Pelvic floor level in STC

The PF descent on straining was —6 mm (95% CI: —4 mm) and on evacuation was —18 mm (95% CI: —13 mm).

Correlation of proctographic parameters in STC

The %EVAC in the STC group correlated with the ARA on straining (P = 0.03; Fig. 6). The ARA on straining correlated with the ARA at rest (P = 0.01).

Comparison of OD and STC groups

The %EVAC was not any different in the two constipated A groups studied (P = 0.05). The defaecation rate, however, was significantly lower (P = 0.01) and the defaecation time was more prolonged (P = 0.03) in the OD group. In the OG group, the increment of the ARA on straining—ARA at rest) was significantly smaller compared with the STC group (P = 0.04). The PF descent on straining and evacuation was greater in the flex OD group (P = 0.01) compared with the PF descent in the STC group (P = 0.05).

Discussion

Isotope dynamic proctography has been used successfully to assess qualitatively and quantitatively the defaecation process in constipated subjects [17]. It has been shown to correlate with the conventional method of radio-videoproctography, for the various proctographic parameters such as anorectal angles and pelvic floor movements [18]. In addition, this method provides an accurate description of the defaecation act in terms of completeness of evacuation and defaecation time and rate [17]. The latter parameters are of particular importance in the assessment of the various types of non-organic constipation, i.e., functional obstructive defaecation or slow transit constipation. Yet, the precise pattern of pelvic floor function during straining in normals is not fully known exactly.

On the other hand, it should be easy to understand how a patient who is asked to evacuate unwillingly in the presence of his or her investigators may feel uncomfortable, during such tests and may contract the pelvic floor, thus mimicking the obstructive defaecation syndrome. However, we believe that isotope proctography provides a greater privacy for patients as the recordings may be performed in the absence of clinical observers; there is no restriction concerning the duration of the test in patients with difficult and prolonged evacuation since during the isotope test there is significantly less radiation exposure compared to the radiological one [17].
The patients investigated did not have any evidence of underlying disease or deficit, and any other organic cause of constipation by definition brought exclusion from the study. The OD group was in other respect a homogeneous group. Some patients had normal perineal descent on evacuation, some had a 'normal descent' of the pelvic floor on defaecation and present with an 'immobile perineum'. At a later stage, prolonged chronic straining may have led to pudendal neuropathy with relative weakness of the pelvic floor muscles and ultimately to abnormal perineal descent. Correlations of the ARAs and PF descent both on straining and evacuation show the relation between the two, the lesser the PF descent the less obtuse the ARA. This explains why a greater ARA was achieved on evacuation in the abnormal perineal descent subgroup.

Physiological observations have suggested that a more obtuse ARA on straining would facilitate a more complete evacuation being achieved [19]. Abnormal perineal descent, as a possible epiphenomenon of OD, after prolonged excessive defaecation straining may thus be associated with a more obtuse ARA at rest, reflecting the severity of the problem rather than be the cause of it [19]. Thus the consideration of the OD problem is made more meaningful by some factors being exposed as resultant rather than causal ones.

A number of patients with slow transit constipation, group, with no clinical or other evidence of outlet obstruction were recruited to the study to allow comparison of the proctographic features with those from patients with OD features. In the STC group the %EVAC related to the ARA on straining. Thus a more obtuse defaecating ARA may allow a better evacuation in agreement with prior observations [19]. The defaecation time, being significantly shorter in this group compared with the graphic floor, though the %EVAC was not significantly different from two constipated groups, the OD group had a significantly longer defaecation time associated with a lower evacuation rate. The ARA changes were significant in more patients with OD than in the STC group, with a number of patients attaining abnormal perineal descent subgroup. There was a significant PF descent on evacuation and straining, in the STC group, with a number of patients having an abnormal perineal descent in the OD group, demonstrating the effects of prolonged inappropriate evacuation straining.

Four points to consider in the OD syndrome are the demonstration of the process predisposing to impairment of pelvic floor muscles and therefore of their function. A myopathic condition may induce pelvic floor muscle weakness and then a vicious circle may be created. Iso-attenuation proctography despite the complexity and chronicity of the condition may allow differentiation between the two main types of functional disorder namely transit constipation and obstructive defaecation.

The patients with OD were not able to perform adequate defaecation in a normal, relatively short, time resulting in an abnormally low defaecation rate. On the other hand patients with STC have performed better in terms of defaecation having a greater defaecation rate. They have achieved a greater increment of ARAs on evacuation, with more obtuse ARAs, following relaxation of the pelvic floor on attempted defaecation. This was important as it was found to correlate with the percent of evacuation in this group.

In conclusion, isotope dynamic proctography assesses accurately proctographic parameters, i.e. increment of anorectal angles on attempted defaecation, defaecation rate as well as pelvic floor descent which are valuable in the study of functional constipation allowing discrimination between its different types.

Acknowledgements. Dr. M. Papachrysostomou was supported by a Scottish Home and Health Department Clinical and Biomedical Research Grant (K/MRS/5001202). Miss N. Clare is thanked for her technical assistance.

References


A. N. Smith
Department of Surgery
Western General Hospital
Crewe Road South
Edinburgh EH4 2XU
UK
Objective: To study patients with obstructive defaecation to determine quantitatively its pathophysiology and homogeneity.

Design: Twenty-two patients with obstructive defaecation were studied by isotope proctography and by conventional methods for quantitative analysis of the pathophysiological factors involved.

Methods: Examination of the patients included ano-rectal manometry, the rectal balloon expulsion test, pelvic floor electromyography and isotope proctography. Eleven asymptomatic subjects were studied for comparison.

Results: Pelvic floor electromyography revealed increased 'straining electromyographic activity' in all patients (P<0.001). Patients with obstructive defaecation had impaired rectal sensation and were unable to perform a complete rectal evacuation (54% rectal evacuation) on isotope proctography. The defaecation time was prolonged and was associated with a reduced defaecation rate. Simultaneous recording of intrarectal pressures and external anal sphincter (EAS) electromyography during proctography revealed increased intrarectal pressure (P<0.0001) and EAS electromyographic voltage (P<0.01) during evacuation. The anorectal angles correlated with the pelvic floor movement and the anismus index. The anismus index in these patients correlated with the intrarectal pressure (P<0.02). No increase in the electromyographic voltage of the EAS was observed in any of the control subjects who successfully performed rectal balloon expulsion.

Conclusions: Obstructive defaecation is a multifactorial condition involving derangements of rectal sensation and abnormal activity of the pelvic floor and anal sphincter musculature; its homogeneity is affected by the duration of the process.

European Journal of Gastroenterology & Hepatology 1994, 6:000-000

Keywords: Obstructive defaecation, isotope proctography, anismus index, intrarectal pressures, defaecation rate

Introduction

Among patients with chronic constipation, a group can be identified with disturbed relaxation of the striated pelvic floor and anal sphincter musculature leading to functional obstruction of defaecation [1]. This condition has been termed anismus [2], or spastic pelvic floor syndrome [3], but its underlying pathophysiological cause is not known. The term anismus was derived from analogy with the involuntary contraction of the pelvic floor muscles that occurs in vaginismus [2].

Anismus is more common in women and occurs in childhood or early adult life. Associated urological symptoms sometimes occur [4], but seldom neurological or gastroenterological disease [5]. Electrophysiological assessment shows paradoxical puborectalis and external anal sphincter (EAS) contraction during attempted defaecation. There is evidence that chronic straining at stool for many years may lead to stretch-induced damage to the pudendal innervation of the EAS [6].

The symptoms of obstructive defaecation may present as the descending perineum syndrome [7], solitary rectal ulcer syndrome [8], irritable bowel syndrome [9,10], complete rectal prolapse, mucosal prolapse, rectal intussusception, or idiopathic faecal incontinence [11]. Common symptoms include a sensation of incomplete
emptying at stool, excessive straining during attempts to defaecate and, in some cases, a desire to evacuate the rectum with no result [12,13].

Biofeedback treatment of anismus [14] and solitary rectal ulcer syndrome [15] have provided opportunities for studying the abnormal phenomena observed in obstructive defaecation. Biofeedback improves rectal expulsion by altering the anorectal angles, rectal sensation and the abnormal electromyography of the anal sphincter [16]. Biofeedback thus influences the defaecation reflex at different levels, which appear to be disturbed in obstructive defaecation [17].

Materials and methods

Subjects

Twenty-two patients, 18 (82%) women and four (18%) men, with symptoms of obstructive defaecation were studied. Eight of the 18 women were nulliparous and women of reproductive age had the possibility of pregnancy excluded. The median age was 44 years (range, 36–46 years), duration of symptoms 1–33 years, and frequency of defaecation from once in 2 days to no bowel movement without the help of laxatives or enemas. All patients had difficulty in bowel evacuation, irrespective of whether the stools were hard or loose. All patients described prolonged straining at stool despite an urge to defaecate, some having to resort to anal digitation to aid stool evacuation. Associated complaints were abdominal pain (59%), abdominal distention (9%), nausea (5%) and perineal pain (64%). Barium enema and sigmoidoscopic examinations showed no organic abnormalities. Objective evidence of severe constipation was obtained by estimating the delivery of 50 ingested plastic radiopaque markers in the faeces.

Eleven asymptomatic volunteers were recruited as normal controls. These subjects were free of anorectal or colonic problems. Nine were women (all nulliparous) and two were men (median age, 21 years).

Ethical permission for this study was obtained from the Lothian Health Board Ethical Committee and from the Administration of Radioactive Substances Advisory Committee. All patients gave informed consent.

Anorectal manometry

All patients and controls underwent conventional anorectal manometry using a microballoon and station pull-through technique followed by proctometrography to establish rectal sensory threshold (in ml), the rectal capacity and compliance [18].

The intra-rectal pressure during voiding of the rectal contents was measured by a pressure sensitive radiotelemetry capsule (Remote Control Systems Ltd). The radiotelemetry capsule was stabilized in a water bath at 37°C for at least 4 h before calibration in a pressure chamber against a manometer. The capsule was introduced into the rectum and the signal emitted was received by an omnidirectional antenna strapped over the patient's sacrum (Remote Control Systems Ltd).

An inhibitory recto-sphincteric reflex was demonstrated in each case, excluding congenital or acquired aganglionosis.

Rectal balloon expulsion test

A lubricated rubber balloon attached to a plastic catheter was inserted to lie in the rectal ampulla, with the patient in the left lateral position. The balloon was filled with saline up to 140 ml, to the limit of adequate rectal sensation. The subject was then asked to strain to expel the balloon with maximal effort. If unsuccessful, tension was applied to the balloon catheter to achieve balloon expulsion.

Electrophysiology

The pudendo-anal reflex latency [19] was calculated. The degree of anismus was estimated by an anismus index [20], which measured the EAS electromyographic activity using a surface anal plug electromyographic electrode [21], and expressed the incremental electromyographic change during straining versus the one during 'squeezing'.

The electromyographic activity during voiding was further recorded from the EAS using teflon-coated fine wire stainless steel electrodes, with the tip ends (0.25 cm) bared and hooked over to prevent displacement of the electrodes in the muscle. The wire electrodes were inserted into the EAS through the skin 1 cm lateral to the anal margin. A ground electrode was attached to the upper thigh. The wires were connected to an isolated electromyographic integrator (Ormed 4880, MX216) and the recorder calibrated to a range of 0–500 µV.

Isotope proctography

Dynamic scintigraphic proctography was performed on each patient. During this test the radiopharmaceutical used, approximately 200 MBq 99m-technetium methylene diphosphonate, was prepared as described previously [22]. Assessment of anal sphincter activity and anorectal function during simulated defaecation, electromyographic and intrarectal pressure tests were performed simultaneously with the patient seated upright on a commode. Recordings were made of the rectal isotopic images, electromyography of the EAS and intrarectal pressures, at rest and following commands such as 'squeeze', cough, straining by valsala and evacuation. The normal controls did not participate in this test because of the radiation exposure involved.

Statistical analysis

Statistical analysis of the results used the median values and their 95% confidence intervals (CI), the Spearman's correlation coefficient and P value, and the sign test for paired comparison of observations.
Results

Transit studies showed that less than 10 radiopaque pellets were retained in the bowel 3–8 days after ingestion. These were mostly retained in the distal colon.

Anorectal manometry

All the patients were unable to expel the rectal balloon, in contrast to the controls, suggesting lack of relaxation of the pelvic floor or inappropriate contraction of the sphincter muscles on straining.

The maximum resting pressure was 120 cm H2O (95% CI, 110–140 cm H2O) and squeeze pressure was 80 cm H2O (95% CI, 50–120 cm H2O). The recto-sphincteric inhibitory reflex was present in all patients. Rectal sensation, recorded proctometrographically, was 140 ml (95% CI, 110–180 ml). This value was significantly impaired (P<0.01) compared with the normal controls. The maximum tolerable rectal capacity was 425 ml (95% CI, 335–490 ml) and the rectal compliance 6 ml/cm H2O (95% CI, 4–7 ml/cm H2O) (Table 1).

The intrarectal pressure at rest was 5 cm H2O (95% CI, 5–12 cm H2O), on straining 30 cm H2O (95% CI, 21–40 cm H2O) and on evacuation 38 cm H2O (95% CI, 21–44 cm H2O), significantly increased (P<0.0001) compared with the normal controls. The corresponding normal values given by O'Connell et al. are a %EVAC greater than 60%, a defaecation time less than 40 sec and a rate 1.5%/sec [23].

Isotope proctography

The adequacy of rectal evacuation (%EVAC), the defaecation rate (%EVAC/sec) and the defaecation time were calculated as described previously [22]. The %EVAC was 54% (95% CI, 44–72%), the defaecation rate was 0.5%/sec (95% CI, 0.2–1%/sec) and the defaecation time was 120 sec (95% CI, 52–208 sec). The corresponding normal values given by O'Connell et al. are a %EVAC greater than 60%, a defaecation time less than 40 sec and a rate 1.5%/sec [23].

The anorectal angles at rest, on squeezing, straining and evacuation were the 'lower anorectal angles', i.e., those formed by the anal canal midline and by a parallel line to the posterior rectal wall [24]. The anorectal angle from the anorectal image at rest was 103° (95% CI, 92–106°), the anorectal angle on straining was 112° (95% CI, 96–117°) and on evacuation was 126° (95% CI, 120–131°).

The pelvic floor level was recorded with a negative sign indicating downward movements relative to its level at rest. The pelvic floor level on straining was −9 mm (95% CI, −9–5 mm); four patients performed an inappropriate upward movement and two patients had no pelvic floor movement recorded on straining. On evacuation, the pelvic floor descent was −33 mm (95% CI, −46–23 mm) (Table 2).

Proctographic parameters

The defaecation rate was inversely proportional to the maximum resting anal canal pressure (P<0.03) (Fig. 1).
A proportional increase in the anorectal angle on straining was observed compared with the anorectal angle at rest \((P<0.001)\), whereas the anorectal angle increment during evacuation related to the initial measurement of the anorectal angle at rest \((P<0.02)\). The anorectal angle on straining correlated with the pelvic floor movement on straining \((P<0.001)\) and the anorectal angle achieved on evacuation correlated with the pelvic floor descent on evacuation \((P<0.01)\) (Fig. 2). The anismus index was inversely proportional to the intrarectal pressure during evacuation \((P<0.02)\) (Fig. 3).

**Fig. 1.** The relationship between the defaecation rate and the maximum anal canal resting pressure. Patients \((n=22)\) with high intra-anal pressures achieved a low defaecation rate. \((r=-0.5; P<0.05)\).

**Fig. 2.** The relationship between the pelvic floor movement and the anorectal angle on evacuation. Patients \((n=22)\) with more acute anorectal angles achieved minimal pelvic floor descent on evacuation. \((r=-0.575; P<0.01)\).

Three (14%) patients presented with ‘immobile perineum’ (pelvic floor descent on evacuation less than 1 cm) during isotope proctography. In these patients, the %EVAC was in the range of 8–47%, the defaecation rate was 0.1–1.0%/sec, the defaecation time was 48–160 sec, the anorectal angle at rest was 62–98°, the anorectal angle on straining 56–115° and the anorectal angle on evacuation was 96–116°. Nine (41%) patients had an abnormal perineal descent (pelvic floor descent on evacuation greater than 4 cm). Ten (45%) patients had pelvic floor movement on evacuation greater than 1 cm but less than 4 cm. These two subgroups differed significantly in their resting EAS electromyographic voltage \((P<0.04)\) and in the straining EAS electromyographic voltage \((P<0.02)\).

**Fig. 3.** The relationship between the intrarectal pressure increment during evacuation and the anismus index. Patients \((n=18)\) with a high anismus index achieved only a minimal increment in their intrarectal pressures. \((r=-0.546; P<0.02)\).

**Fig. 4.** The relationship between the percentage of the activity evacuated and the rectal capacity in patients \((n=7)\) who had a more satisfactory rectal emptying. Patients with reduced rectal capacity emptied more adequately. \((r=-0.801; P<0.02)\).

Seven (32%) patients had ‘satisfactory’ rectal emptying of 78% (95% CI, 73–89%) on simulated defaecation. In these patients, the %EVAC was inversely related to both rectal capacity \((P<0.02)\) (Fig. 4) and compliance \((P<0.04)\); the anismus index inversely correlated to the anorectal angle on evacuation \((P<0.02)\) (Fig. 5). The remaining fifteen (68%) patients had an incomplete evacuation of 47% (95% CI, 11–55%). Similarly, the defaecation rate was lower in the patients with incomplete evacuation.
The anismus index and the anorectal angle during evacuation in patients who had satisfactory rectal emptying. Patients (n = 7) with a high anismus index achieved a less obtuse anal rectal angle on evacuation. ($r = -0.839; P < 0.02$).

The relationship between the anismus index and the anorectal angle at rest. ($r = 0.691; P < 0.01$).

All patients experienced an urge to defaecate as the proctometrogram balloon was distended in the rectum, thus lack of rectal sensation did not appear to be a factor in the failure to defaecate. Patients with impaired sensation may find it difficult to defaecate. The sensation in these patients, measured by proctometry, was significantly impaired compared with the normal control group. The delayed pudendal nerve conduction in this group, which was associated with a lower squeeze pressure, may well be the result of prolonged inappropriate straining on defaecation.

Changes in the anorectal angle were significant in that the attempted straining failed to achieve an adequate obtuseness in the angle. There was a significant pelvic floor descent on straining and evacuation, with a number of patients having abnormal perineal descent. The defaecation time was prolonged with a lower defaecation rate, although a number of patients were able to evacuate more than 50% of the isotope stool. In the latter subgroup this was related to the rectal capacity, which was significantly reduced.

Intrarectal pressure is important in initiating the evacuation process. There was an increase in the intrarectal pressure on straining, which persisted on evacuation, possibly due to unsuccessful straining. However, a greater intrarectal pressure on evacuation may indicate the patient's response to the observed increased EAS electromyography. Therefore, a higher intrarectal pressure may be needed to overcome the 'anal barrier' and to proceed to defaecation. Moreover, the defaecation rate was inversely proportional to the anal canal resting pressure, indicating the relevance of defaecation to the anal barrier.

We studied a group of patients with intractable constipation. Their primary abnormality was an inability to empty the rectum, with accompanying obstructive symptoms such as chronic straining at stool, a feeling of obstruction on defaecation and a common need for self dilatation. All were unable to expel a rectal balloon and most of them had difficulty in expelling a soft formed stool. This simple observation may explain why this severe type of constipation presents as such an intractable problem. All patients had normal recto-sphincteric inhibitory reflexes, none had any evidence of neurological disease or deficit, and a normal barium enema and sigmoidoscopic examination virtually excluded any organic disease.

Pelvic floor electromyography and proctography showed persistent increased pelvic floor activity in all these patients, indicating a contraction that may cause functional colonic outlet obstruction. It is understandable that a patient who is asked to evacuate in the presence of his/her investigators may feel uncomfortable during such tests and may contract the pelvic floor, thus mimicking the obstructive defaecation syndrome. Furthermore, the precise pattern of pelvic floor function during straining in individuals with normal function is not known exactly.

Studies in the normal control group, however, did not show any increased activity of the pelvic floor muscles on straining and all the controls were able to expel the rectal balloon. This evidence suggests that the increased activity of the pelvic floor muscles on attempted defaecation is a non-physiological event. To lessen patient discomfort at evacuating in the presence of other people, privacy was enhanced by using a small separate room in the Department of Nuclear Medicine kept for proctography alone, and the investigations were kept to a minimum (additional tests during proctography included electromyography of the EAS to record its activity and telemetering capsule for the simultaneous recording of intrarectal pressures). The activity of the puborectalis muscle, which may play an important role in the mechanism of obstructive defaecation, was assessed from the changes in the anorectal angle.
The anismus index was inversely proportional to the intrarectal pressure during evacuation. This suggests that obstructive defaecation patients may not be able to increase the intrarectal pressure to levels sufficient to achieve evacuation. Thus, relatively low intrarectal pressure can be part of the problem. Similar observations have been reported by other investigators who described a number of obstructive defaecation patients unable to increase the intrarectal pressure on attempted defaecation [25].

The group studied was in other respects a heterogeneous group. Some patients had abnormal perineal descent on evacuation, some had a 'normal descent' and some were unable to move the pelvic floor on defaecation. This may be a result of the duration of the problem. Patients with obstructive defaecation in the early stages may be unable to move the pelvic floor on defaecation and present with an 'immobile perineum'. At a later stage, with prolonged chronic straining, pudendal neuropathy develops leading to the relative weakness of the pelvic floor muscles and ultimately to abnormal perineal descent. Correlations of the anorectal angle and pelvic floor descent both on straining and evacuation show the relation between the two: the lesser the pelvic floor descent the less obtuse the anorectal angle. This explains the greater anorectal angle on evacuation in the abnormal perineal descent group.

It is noteworthy that the %EVAC was inversely related to the maximum rectal capacity. Therefore, the ability to evacuate depended on rectal capacity and motility; the higher the %EVAC the lower the rectal capacity. The anismus index in this subgroup was inversely correlated to the anorectal angle on evacuation; thus, the electromyographic obstructive features were associated with the proctographic features, i.e., a more acute anorectal angle.

Fifteen patients had incomplete evacuation. The defaecation rate in this subgroup correlated with the anorectal angle increment on straining; the lesser the increment the poorer the evacuation achieved. The anismus index related to the anorectal angle at rest, but this may be a consequence of obstructive defaecation rather than a cause: a later stage of development in obstructive defaecation is characterized by abnormal perineal descent, associated with an obtuse anorectal angle at rest. Thus, the duration of the obstructive defaecation problem adds to the complexity of the condition, since some factors result from rather than cause the problem.

The parameters derived from isotope proctography provide quantitative characteristics of the obstructive defaecation problem and are essential in the study of the pathophysiology of anismus, showing correlations with the anorectal angle, the electromyographic voltage of the pelvic floor muscles on straining and rectal capacity. The anismus index can be a reliable means of evaluating obstructive defaecation and can show correlations between the intrarectal pressures, the pelvic floor descent and the anorectal angles. Ambulatory studies may provide a more effective way of recording the incidence of obstructive defaecation [26], whereas combination studies including anorectal manometry, electromyography and proctography allow detailed investigation of the condition, and quantitative analysis may elucidate stages in its progression.

Anismus appears to be a complicated and multifactorial phenomenon of obstructive defaecation, involving altered rectal sensation and uncoordinated function of the pelvic floor and abdominal musculature. Anismus may be affected by the duration of the problem, presenting at an early stage with increased pelvic floor electromyographic voltage, acute anorectal angles, immobile perineum and inability to achieve satisfactory rectal evacuation. This may later progress to a condition associated with a weak pelvic floor, more obtuse anorectal angles, abnormal perineal descent and the continuous inability to achieve evacuation.

Acknowledgements

The authors are grateful to Dr M.V. Merrick, Head of the Department of Nuclear Medicine, for allowing the proctographic tests to be performed in his department, and to Miss Nicola Clare for her technical assistance.

References

Obstructive defaecation Papachrysostomou and Smith


Chapter 9.13

Neurostimulation

Maria Papachrysostomou and Adam N. Smith

TABLE OF CONTENTS

I. Introduction ...............................................................................................................241
II. Neurogenic Fecal Incontinence ..............................................................................242
III. Chronic Stimulation and its Effects in Fecal Incontinence .............................244
IV. Discussion .......................................................................................................................247
Acknowledgment ..................................................................................................................249
References ......................................................................................................................................249

I. INTRODUCTION

The importance of motoneurone activity in the long-term control of the contractile properties of mammalian muscle was demonstrated more than 25 years ago. It was revealed that a long-term decrease in impulse activity following tenotomy shortened contraction and relaxation times of rabbit soleus muscle. At the same time increases in impulse activity following tenotomy caused a slowing of contraction in both fast- and slow-twitch muscles. Further evidence for the role of impulse activity in determining contractile properties of muscles came from experiments which showed that chronic indirect stimulation of rabbit and cat fast-twitch muscles at 10 Hz, a frequency resembling that normally delivered to a slow-twitch muscle, had a pronounced slowing effect on the time courses of both contraction and relaxation.

Transformation processes were also shown to occur in stimulated, denervated muscle, as well as in noninnervated myotubes in vitro. Low-frequency stimulation of denervated soleus muscle of the guinea pig was shown to counteract atrophy of the majority of the fibers. Similar results were observed in low-frequency stimu-
lated, denervated fast-twitch muscles of the rabbit, which do not develop the increased fatigability typical of denervated muscle.6

It is apparent that chronic stimulation is capable of determining expression, as well as maintenance of phenotype-specific properties in innervated and denervated fast- and slow-twitch muscles.7 The main functional elements of the muscle fiber respond in an orderly time sequence.8 Therefore, ultimate fast-to-slow transformation of chronically stimulated fast-twitch muscle results from orderly sequential transitions of the preexisting fiber population. Recent observations indicate that some degenerative/regenerative processes occur initially in chronically stimulated fast-twitch muscle.9 There is sufficient evidence that chronic stimulation has many beneficial effects, such as increased capillarization, enhanced protein synthesis, and maintenance of various functional and phenotype-specific properties.10

II. NEUROGENIC FECAL INCONTINENCE

Neurostimulation may play an important role in the treatment of fecal incontinence (FI), since an increasing number of patients with FI are recognized to have a neurogenic causation. Neurogenic FI is known to be due to injury to the pelvic and pudendal nerves and is frequently associated with difficult labor11 and longstanding constipation.12 Prolonged straining, either as an acute episode during labor or as a chronic event in intractable constipation, damages the pelvic floor and external anal sphincter (EAS) muscle by a traction nerve injury and, as a consequence of that, impairs the function and voluntary control of continence.

Electrical stimulators have been used in attempts to return function to the pelvic floor and sphincter apparatus using direct stimulation (Faradism) and surface anal plug electrodes.13 An invasive method of stimulation was by implanting stimulators activated by a radio-frequency link outside the body with electrodes in the striated muscle.14 Problems due to wire breakages in the implants, anal pain, or anal ulceration have led to the abandonment of such methods. Brindley et al.15 devised a method that applied stimulation via the sacral segments of the spinal cord through the parasympathetic outflow to the bladder16 for electromicturition and urinary continence in paraplegic patients. The controlled electrical stimulation of the sacral anterior roots S2–S4 by operatively implanted electrodes16 was found to be influencing the motility of the left colon.17,18 Identical and reproducible motility responses of the left colon, rectum, and anal sphincters were obtained by sequential electrical stimulation of anterior sacral nerve roots S2, S3, and S4 in spinally injured patients. S2 stimulation provoked isolated low-pressure colorectal contractions. S3 stimulation initiated frequency-dependent high-pressure colorectal motor activity, which appeared peristaltic and was enhanced with repetitive stimuli. S4 stimulation enhanced colonic and rectal tone. Quantitative responses were maximal at the splenic flexure and rectum. Pelvic floor activity was stimulated in increasing magnitude from S2 to S4.19 Anorectal incontinence in spinal injury is often superseded by intractable constipation as the major problem following spinal injury and the Brindley stimulator has been used mainly for this purpose. However, continuous weak
Sacral root stimulation has also been used to improve anal continence in the same way as has been demonstrated for the nocturnal control of urinary incontinence. A newer generation of externally active stimulators were envisaged at the time of this work for the control of the lower bowel in the fecal incontinence of spinal injury subjects but this has not yet been realized.

This began an era when electrical stimulators were established in their use to control distal bowel function. Direct pudendal nerve stimulation performed transrectally\(^{20}\) established the characteristics required for evoking an EAS muscle response. Using identical nerve stimulation parameters this type of stimulation was applied to determine perineal nerve terminal motor latency by recording the response of the periurethral striated sphincter muscle.\(^{21}\) Similarly, transcutaneous spinal stimulation has been used to evoke pelvic floor muscle contraction and has enabled assessment of the proximal motor conduction in the nerve supply of the pelvic floor musculature.

Having applied stimulation to the pudendal nerve directly, to its roots and centrally transcutaneously to the spinal cord, it became apparent that a more physiological approach would have been through stimulation of a reflex involving both afferent, central, and efferent pathways. An already established reflex in urological practice is the bulbocavernosus one, which is elicited by applying electrical stimulation to the dorsal nerve of the glans penis or clitoris, evoking a reflex contraction of the bulbocavernosus muscle.\(^{22}\) This concept of reflex contraction of the striated muscle found its application in anorectal physiology: Varma and Smith\(^{23}\) adopted this idea, eliciting a reflex by stimulation of the dorsal nerve of the glans penis and clitoris and recording contraction of the EAS (Figure 1). The pudendo-anal reflex was further categorized in normal controls and in patients with FI.\(^{24}\) It has now become as conventional a method in the investigation of neurogenic FI\(^{25}\) as in urological patients.

Provided that there is no interruption in either the afferent or efferent limbs of the reflex and conduction of the impulses through the S2, S3, and S4 segments of the spinal cord, it seemed feasible that the pudendo-anal reflex could be utilized in the stimulation form of treatment.\(^{19}\) This has been made possible since this reflex is not easily fatigued and does not show signs of habituation, but is dependent on the intensity of stimulation.\(^{26}\) The portable electrical stimulator constructed for dorsogenital nerve stimulation (Figure 2) provided a train of square wave stimuli with a fixed frequency of 1 Hz and a pulse duration of 0.1 ms. These were the characteristics used for the other form of stimulation described above. A submaximal tolerable stimulation voltage (approximately 100 V) was used, depending on the individual's tolerability, that approximated three times the sensory threshold. The immediate effect of activating EAS contraction in response to electrical stimulation caused an increase in the EAS electromyographic (EMG) activity from mean (SEM) 11.6 (1.7) to 44.9 (1.9) μV (\(p < 0.01\)) with a corresponding rise in the maximum anal canal resting pressure from mean (SEM) 49.1 (4.0) to 89.0 (10.4) cm H\(_2\)O (\(p < 0.01\)) in a series of eight patients.\(^{27}\)
Pudendo-anal Reflex

Dorsal Genital Nerve

S2, 3, 4

External anal sphincter

FIGURE 1. Diagrammatic representation of the pudendo-anal reflex and neural arc. This is a polysynaptic reflex based on the S2, S3, and S4 segments of the spinal cord, the afferent limb being the dorsal genital nerve and the efferent being the pudendal nerve supply to the external anal sphincter. The inset shows a typical response of the external anal sphincter contraction recorded via a surface EMG electrode. The latency of the reflex is measured in milliseconds as the time interval between the stimulus artifact (1st peak) and the positive deflection of the sphincter (2nd peak). The reflex amplitude is indicated by the height of the peak deflection recorded in μV.

III. CHRONIC STIMULATION AND ITS EFFECTS IN FECAL INCONTINENCE

It seemed likely that a portable electrical stimulator providing repetitive stimulation of the pudendo-anal reflex and selectively provoking contraction of the EAS and the pelvic floor on a chronic basis might be efficacious in restoring continence as a long-term treatment effect.28 A prerequisite for this approach to treatment would be the presence of an uninterrupted pudendo-anal reflex, intact in both the afferent and efferent limbs, with conduction maintained through the S2, S3, and S4 segments of the spinal cord. A chronic application of stimulation has been feasible, as the pudendo-anal reflex has been shown to be a reflex which is not easily fatigued.29

The maximum anal canal resting pressure and the anal canal pressures on voluntary and cough reflex contraction of the EAS were recorded before and after an electrical stimulation course of therapy in a series of patients. These patients with fecal incontinence were incapacitated socially and had to wear incontinence pads. All had evidence of pudendal neuropathy elicited by a prolonged latency of the pudendo-anal reflex and motor unit potential duration. Electrophysiological studies allowed measurements of these parameters as well as any increase in the amplitude of the pudendo-anal response and EAS EMG voltage at rest, before, and after stimulation. The chronic stimulation consisted of a 5-min application of the portable electrical stimulator on three occasions per day for an 8-week course of treatment and was self-administered.
Table 1. Anorectal Manometric and Neurophysiological Tests Performed before and after the Use of a Pudendo-Anal Electrical Stimulator

<table>
<thead>
<tr>
<th></th>
<th>Prestimulation</th>
<th>Poststimulation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC cm</td>
<td>1.9 (0.2)</td>
<td>2.6 (0.3)</td>
<td>$p &gt; 0.05$</td>
</tr>
<tr>
<td>MRP cm H$_2$O</td>
<td>49.1 (4.0)</td>
<td>61.2 (4.5)</td>
<td>$p &lt; 0.01$</td>
</tr>
<tr>
<td>SQP cm H$_2$O</td>
<td>112.0 (12.1)</td>
<td>150.0 (17.3)</td>
<td>$p &lt; 0.01$</td>
</tr>
<tr>
<td>CP cm H$_2$O</td>
<td>80.6 (8.2)</td>
<td>106.1 (11.2)</td>
<td>$p &lt; 0.01$</td>
</tr>
<tr>
<td>PARL ms</td>
<td>55.9 (6.9)</td>
<td>65.9 (6.8)</td>
<td>$p &gt; 0.05$</td>
</tr>
<tr>
<td>PARamp µV</td>
<td>37.5 (10.5)</td>
<td>49.5 (9.2)</td>
<td>$p &lt; 0.01$</td>
</tr>
<tr>
<td>MUPD ms</td>
<td>12.7 (3.3)</td>
<td>12.8 (3.4)</td>
<td>$p &gt; 0.05$</td>
</tr>
<tr>
<td>EMG µV</td>
<td>11.6 (4.9)</td>
<td>26.9 (7.3)</td>
<td>$p &lt; 0.01$</td>
</tr>
</tbody>
</table>

AC, Anal canal functional length; MRP, maximum anal canal resting pressure; SQP, anal canal pressure increment on voluntary “squeezing” contraction of the external anal sphincter; CP, anal canal pressure increment on reflex contraction during coughing; PARL, pudendo-anal reflex latency; PARamp, pudendo-anal response amplitude; MUPD, motor unit potential duration; EMG, basal integrated electromyogram of the external anal sphincter. Statistical analysis of the results used the student’s $t$ test using logarithmic conversion of the data of the paired comparisons before and after stimulation. The results are expressed as mean (SEM).

Increased from mean (SEM) 80.6 (8.2) to 106.1 (11.2) cm H$_2$O after the period of stimulation ($p < 0.01$). The maximum voluntary contraction of the EAS was also increased significantly from mean (SEM) 112.0 (12.1) to 150.0 (17.3) cm H$_2$O after the electrical stimulation ($p < 0.01$). Although the latency of the pudendo-anal reflex was not significantly altered, the amplitude to the pudendo-anal response was significantly increased from mean (SEM) 37.5 (3.7) to 49.5 (3.3) µV ($p < 0.01$) after the period of stimulation.

The motor unit potential duration of the external anal sphincter was prolonged or widened with a mean (SEM) of 12.7 (1.2) ms (normal range: 5.3 to 6.9 ms). There was also a high mean number of polyphasic motor unit potentials recorded from the EAS in the treated subjects with a mean (SEM) of 25.9 (9.4)% (normal: 12%), in keeping with reinnervation of the muscle following a previous neurogenic insult. However, the motor unit potential duration values were not affected by the course of electrical stimulation, with a mean (SEM) of 12.7 (1.2) ms before and 12.8 (1.2) ms after stimulation. The basal integrated EMG of the EAS was increased significantly from mean (SEM) of 11.6 (1.7) to 26.9 (2.6) µV after the course of stimulation. The immediate effect of the EAS EMG response to activation of the EAS via the application of the stimulator after treatment again showed a significant increase from mean (SEM) 44.9 (4.9) to 72.3 (5.4) µV ($p < 0.01$), with a concomitant significant increase in the pressure response from mean (SEM) of 89.0 (10.4) to 128.0 (13.3) cm H$_2$O ($p < 0.01$). The eight patients corresponding to the above improved clinically in the control of feces and flatus, other than one patient who was able to control feces imperfectly but not flatus. Significant closure of the anal canal and more dynamic movement of the pelvic floor has been recorded during videoproctography after a stimulation course in such patients.
The results showed (Table 1) that the anal canal resting pressures in these patients were below 60 cm H$_2$O, which represented their continence threshold. In the anal canal this pressure was significantly increased from mean (SEM) 49.1 (4.0) to 61.2 (4.5) cm H$_2$O ($p < 0.01$) after the course of electrical stimulation. The pressure elicited by the cough reflex contraction of the EAS was significantly
IV. DISCUSSION

Skeletal muscle shows a remarkable ability to adapt its biochemical, physiological, and ultrastructural properties in response to changes in demand. Investigations in animals have shown that it is possible to modify the properties of mammalian muscles by chronic electrical stimulation, and fast muscle fibers have been induced to undergo a series of systematic changes resulting in complete transformation to slow contracting fibers. There is overwhelming evidence that these changes are directly related to imposed activity and that functional and metabolic characteristics of muscle fibers depend upon the activity of the motoneuron.

It is well known that the severance of a nerve results in paralysis of the dependent tissue and the most obvious result of denervation is muscle atrophy and paralysis. Reid in 1841 observed that electrical stimulation in denervated muscle retarded atrophy when he forced the denervated muscle to contract by electrical stimulation in an attempt to replace the loss of activity. Since then there has been continuing interest in preventing muscle atrophy with electrotherapy. Peripheral nerve injuries during the world wars were, for example, extensively treated with electrical stimulation. Gutmann and Guttmann proved morphologically an atrophy-retarding effect of electrical stimulation in rabbit extensor digitorum longus. The effects of either long-term or short-term low-frequency electrical stimulation on contractile and morphological properties of the denervated muscle (rabbit extensor digitorum longus) were examined. This showed that denervated muscle can be influenced by long-term isotonic and short-term isometric stimulation. The effects result in either retardation of denervation-induced degradation of muscle tissue or rearrangement of enzyme composition of muscle. The activity produced by stimulating the slow-twitch soleus muscle in animals was shown to prevent loss of oxidative enzymes and the atrophy associated with denervation. The changes were more marked when stimulation for longer periods was used. Different activity patterns, used as trains of 100- or 10-Hz bursts with different time intervals resulting in a mean frequency of 1 or 9 Hz, showed that the amount of activity plays a major role in influencing both fatigue behavior and contraction time. Passive electrical properties, such as membrane resistance and capacitance of single fibers in denervated muscles, were reported to be restored to normal by intermittent activity bursts. Mechanical latency, which depends on membrane properties, was not any different in denervated and denervated stimulated muscle. Physical parameters, e.g., the position of the denervated muscle, are to be considered, as vigorous contractions and stimulation of the muscle in a stretched position were mandatory to retard atrophy. Long-term stimulation of denervated muscle showed no effect of nerve regeneration; however direct stimulation of regenerating nerve increased the rate of functional recovery. Nevertheless, treating denervated muscle while permitting the nerve to regenerate may complicate the study and assessment of the effects of stimulation of the muscle properties.

Studies concerning the effect of chronic electrical stimulation on normal and diseased human muscle revealed that the stimulated muscles fatigued less than the
nonstimulated controls in normal adults. However, although chronic stimulation significantly increased the fatigue resistance of the muscle, it did not have an appreciable effect on the contractile properties. During the same study it was revealed that chronic stimulation of dystrophic muscle resulted in significant increase of the strength of the stimulated muscles compared with the controls. These studies show that the properties of human muscles are changed in response to superimposed electrical activity and have established the feasibility of subjecting the muscle of human subjects to prolonged low-frequency electrical stimulation.

Electrophysiological measurement of the pudendo-anal reflex latency provided a simple and reliable method of evaluating pelvic floor neuropathy. The latency of this response appears to be dependent on the intensity of stimulation and it shows little or no signs of habituation. Causes of nerve damage of the sphincter musculature can result in increased latencies. Binnie and colleagues have applied chronic stimulation on the pelvic floor and external anal sphincter using the pudendo-anal reflex. All the women in the study were shown to have neurogenic fecal incontinence due to pudendal nerve neuropathy and had a prolonged but intact pudendo-anal reflex prior to stimulation. After a period of stimulation there was a significant improvement in the symptoms of the patients, but there was no change in the pudendal reflex latency. However, the control of continence was greatly improved as demonstrated via the recordings of the intra-anal canal pressures. This is thought to be due to enhanced contraction of the external anal sphincter after the period of stimulation, which is responsible for the cough and "squeeze" pressure increments on contraction and partly due to its tonic control for the anal canal resting pressure. These effects are comparable to the results from animal and other human striated muscle stimulation.

Stimulation was applied to the external anal sphincter which is known to have crossover innervation of the two sides of the external sphincter by the pudendal nerves. This functionally overlapping innervation allows reinnervation to be partially accomplished from the opposite side when there is pudendal nerve damage, a feature of the muscle in incontinent subjects. Whether the muscle reacts differently to chronic stimulation, or whether it is denervated or reinnervated is a question to be answered. Biopsies of the external sphincter in fecal incontinence show few scattered striated muscle fibers embedded in fibrous and adipose tissue, reorganization of the normal mosaic distribution of the types 1 and 2 fibers, and hypertrophy of the remaining fibers. Nevertheless, the change in histochemical properties of the muscle after chronic stimulation needs to be confirmed with biopsies prior to and after electrical stimulation in the same subject.

Chronic electrical stimulation is a promising technique in the management of fecal incontinence, as it provides symptomatic relief and enhances the contractile activity of the striated anal musculature in the neurogenic fecal incontinence. Its advantage is the promotion of continence through physiological pathways via a reflex. Additional evidence in similar studies with a more extensive number of patients showed comparable results. The duration and degree of continence, as well as the length of its effectiveness, are being evaluated.
ACKNOWLEDGMENT

The pudendo-anal reflex stimulator has been constructed by Mr. I. Lowdon, Department of Bioengineering, Princess Margaret Rose Hospital, University of Edinburgh.

REFERENCES

APPENDIX II

With greater success in the therapy of painful, yet uncomplicated, diverticular disease, attention was turned to more distal disease. It seemed important - with an interest in distal bowel disease - to investigate the causes of radiation reactions, in motility terms, of patients being increasingly treated in National trials of radiation for various forms of pelvic cancer. One of the earliest was the MRC trial of adjuvant radiotherapy in operable rectal cancer (i-iv) and to investigate patients with proven radiation damage (v). This interest in functional ano-rectal disease was extended subsequently to various common causes of constipation and faecal incontinence.


(iv) Duncan W (Chairman), Smith A N (Secretary) and members of the Working Party. Third report of an MRC Working Party. Clinico-pathological features of prognostic significance in operable rectal cancer in 17 centres in the UK. Br J Surg 1984; 50: 435-442


M.R.C. Trial of Pre-Operative Radiotherapy in Operable Rectal Cancer

A. N. SMITH

Department of Clinical Surgery, University of Edinburgh and Western General Hospital, Edinburgh, EH4 2XU, U.K.

Despite advances in the detection and diagnosis of colonic and rectal tumours, together with markedly improved surgical and anaesthetic techniques, the death rate from these diseases is largely the same now as it was 30 yr ago. The Registrar General’s review of deaths in England and Wales in the 25 yr between 1943 and 1967 shows that deaths from rectal carcinoma have remained basically unchanged during this period. In Slaney’s review [1] of over 12,000 patients from the Birmingham cancer registry, it can be seen that the overall survival from rectal cancer is under 30%. This is probably the most realistic picture of the outlook in this disease in the U.K.; furthermore, his figures confirm little change over the years.

It has been suggested that surgery alone is unlikely to make any greater contribution to the cure of this tumour.

In an attempt to improve this situation several methods of treatment have now been explored, but probably that with the soundest theoretical basis is the use of adjunctive radiotherapy. The main clinical impetus for adjunctive therapy came in 1959 in a report from the Memorial Hospital in New York [2] in which the results of a retrospective study of patients treated for rectal carcinoma by surgery and radiotherapy, between 1939 and 1951, were presented. The patients in this study were not randomized in any way; often the reasons for giving radiotherapy were not clear. However, patients with Dukes C lesions of the bowel had a better 5 yr survival if they had received a course of low dose pre-operative radiotherapy. Further study of these patients showed that this also was the case at 10 yr. But there was found to be no advantage from such treatment in those patients with Dukes A or B lesions. A later prospective study of rectal cancer patients carried out in the same centre using a similar treatment regime failed to confirm these results. This trial showed however that the outcome was worst in low rectal tumours with confirmed lymph node spread and high grade of malignancy.

Stimulated by this work, the Veterans Administration Surgical adjuvant group of 23 hospitals in the United States, began in 1964 [3] a prospective, controlled, randomized trial of the use of low dose pre-operative radiotherapy in clinically-operable patients with carcinoma of the rectum.

Only male patients were investigated and when the study was closed in 1969, 700 patients had been included, 347 in the X-ray group and 353 in the control group treated by surgery alone. The radiation dose given was 2000–2500 rad in 10 daily fractions followed as soon as possible by surgery. All patients in the combined treatment group had their radiotherapy performed within 10 days after randomization and were operated on within 16 days. The striking features in the results of this trial were the findings of a significantly lower incidence of positive lymph nodes in the group which had had pre-operative radiotherapy; the percentage of lymph nodes found, whether involved or not, was the same in both groups, thus proving that nodes were not more difficult to detect in patients receiving X-ray therapy. Further there was a significant reduction in the number of cases in whom the surgeon considered residual disease to have been left behind, when the patient had been given pre-operative radiation. These findings were substantiated by the survival both at 18 months and at 5 yr which showed an improvement in those patients receiving the pre-operative treatment. This was mainly due to an improved survival in those patients in whom a resection was performed; further, if the patients treated by abdomino-perineal re-

*On behalf of the Members of the Working Party (Chairman: Professor W. Duncan, Department of Radiotherapy, University of Edinburgh) and Regional Co-ordinators of the Trial.
section were considered, the figures were seen to be even better, in that 45% of patients receiving pre-operative radiotherapy were alive at 5 yr, compared with 30% in the control group.

The M.R.C. Trial of Radiotherapy in operable cancer of the rectum [4] now being conducted in 16 centres in the U.K. is similar to that carried out by the Veterans Administration group. An important difference is the addition of a third arm to the trial, in which a single "biological" dose of 500 rad is used.

The evidence influencing the choice of a combination regimen may be summarized as follows. Firstly, although a tumour may be operable, neither radical surgery nor radiotherapy should be regarded as curative alone. Secondly, the dissemination of cells at operation should be a significant problem either in the form of local recurrence or of distant metastases and thus in the long term management of the patient. Thirdly, the cells disseminated both at the operation site and to distant parts should be well oxygenated implying that they are radio-sensitive, likely to be the case for any peripheral cells shed free unless the surgeon cuts deeply into the tumour; from survival curves for mammalian cells, 90% depopulation of well-oxygenated cells can be achieved with 500 rad. Fourthly, in a situation which is completely unknown, one must assume the worst possibility and accept that the cells may divide daily—which is the justification for proceeding to surgery almost immediately or at least within 24 hr.

There are thus three treatment options: 2000 rad over 10 days, single dose therapy of 500 rad, and a control group. Megavoltage radiation is employed with two parallel opposed fields 18 cm high x 15 cm across. The field should cover the pelvis from the level of the anal margin. Surgery follows as quickly as possible, preferably within 24 hr of the radiation. The selection of patients into the three groups, the control and the two radiation groups, is by random selection organized on a regional basis throughout the country. Patients, male and female, with adenocarcinoma of the rectum, the lower margin of which is within 15 cm of the anal verge and deemed suitable for radical resection may be included in the trial. Patients should be under the age of 80 yr and have no evidence of distinct metastases. History and physical examination should confirm that the patient is fit for radical surgery. It is expected that the haemoglobin level of all patients will be greater than 10G%o. Patients are assessed both clinically and radiologically prior to the definitive treatment being performed (Table 1). Details of the operation and operative findings are recorded (Table 2). The pathology is analysed from the operation specimen (Table 3), the type of tumour is determined together with its site, size and extent particularly in terms of local invasion, involvement of lymph nodes and the presence of tumour in veins. All the lesions are placed in a particular Dukes category. It has been repeatedly asserted that the grade of rectal tumours is of vital importance in prognostic terms and therefore this will be evaluated within the wider context of the trial. It will be interesting to see whether low dose radiotherapy can influence the outcome in patients with high grade tumours. Subsequently, follow-up data are added (Table 4). All these findings are now being correlated in a final evaluation of the various treatment modalities. Within the context of this investigation, individual centres are free to carry out studies on these patients which they may feel will add to the total pool of information; for example, serial CEA examinations may indicate recurrence and data on this will shortly be available in Edinburgh. The aim in the M.R.C. trial, when deciding how extensive pre-operative investigations should be, was to

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>M.R.C. U.K. Preoperative radiotherapy trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumour assessment</td>
<td>Mobile</td>
</tr>
<tr>
<td>Digital examination of tumour</td>
<td>Partially fixed</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>Fixed</td>
</tr>
<tr>
<td>Quadrant involved</td>
<td>Biopsy</td>
</tr>
<tr>
<td>Height above anal verge</td>
<td>Barium enema</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2.</th>
<th>M.R.C. U.K. Preoperative radiotherapy trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical assessment</td>
<td>Nature of operation</td>
</tr>
<tr>
<td></td>
<td>Abdomino-perineal excision</td>
</tr>
<tr>
<td></td>
<td>Anterior restorative operation</td>
</tr>
<tr>
<td></td>
<td>Resection not performed</td>
</tr>
<tr>
<td>Palliative colostomy</td>
<td>Findings at operation</td>
</tr>
<tr>
<td></td>
<td>Residual pelvic disease</td>
</tr>
<tr>
<td></td>
<td>Metastatic abdominal disease</td>
</tr>
<tr>
<td></td>
<td>Other colonic tumours</td>
</tr>
<tr>
<td></td>
<td>Postoperative complications</td>
</tr>
</tbody>
</table>
try to strike a balance between obtaining the minimum information necessary for a proper evaluation of treatment in operable patients, yet obtaining the maximum co-operation possible from a large number of surgeons. Therefore, the pre-operative assessment of the primary tumour is based on standard clinical examination, routine sigmoidoscopy and barium enema. Similarly, for the assessment of possible metastatic spread to the liver, only commonly performed investigations such as liver function tests are asked and the isotope scan is optional. Investigations required to detect the presence of distant metastases (radiology, biopsy etc.) are also kept simple and selected from those which can be performed in any centre. The pyelogram is optional for lesions of the middle or upper third of the rectum. The information requested from the surgeons is also fairly standard. Particularly of interest, in view of the Veterans Administration study, will be the nature of the surgical procedure carried out in relation to the radiotherapy treatment and whether any benefit is found to be confined to one type of operation. The incidence of other intra-abdominal diseases, the presence of other colonic tumours and whether the surgeon considers residual tumour to have been left behind, are all recorded.

Clinical progress is being assessed at repeated follow-up visits, every 3 months in the first year and every 6 months thereafter. The incidence of post-operative complications, late discharging or unhealed wounds and residual sinuses will be noted (Table 4). The suspicion of local recurrence and what evidence substantiates this, such as biopsy, will be recorded. Advanced or non-resectable cases will be grouped separately; in these, the presence and distribution of metastatic disease together with any subsequent treatment, e.g. post-operative radiotherapy or chemotherapy, are being detailed. Any significant differences in the mortality rates between the relevant groups of cases will be carefully evaluated. Although autopsy is not mandatory, it will be desirable in as many cases as possible. All evidence of residual or recurrent cancer will be noted at this time. The total number of patients entered from all 16 collaborating centres was by April 1977, 503, comprising 315 men and 188 women, Birmingham and West Central Yorkshire contributing the greatest number of patients to date. In each of the 16 areas, regional co-ordinators have a store of numbered envelopes each one indicating a treatment option. When the patient is entered into the trial as an “operable” case, an envelope is opened, the allocation to a treatment made, and a registration form of the clinical and operative details completed. Four hundred and thirty-five of the 503 patients completed the course of radiotherapy and went to operation without discoverable metastases. A further 13 had a palliative operation only; in 26 the operative or pathological information was incomplete.

Subsequent pathology details were completed and follow-up forms submitted after each attendance for 396 patients, the final details being entered on the one which recorded the recurrence of the disease and demise of the patient. Of the residual 396 patients 33.6% were of the C category in Dukes classification, these being, incidentally, the ones most likely to benefit from radiotherapy. By far the greater number had an abdomino-perineal resection (272) rather than a restorative resection of the rectum (93) and thus an “operability” figure of 91% has been maintained, with a survival at 12 months appreciably higher for anterior resection (84%), as compared to abdomino perineal (73%). One hundred and fifty-one patients received no radiotherapy, 133 received the multiple treatments, and 151 the single exposure. Fewer patients had the multiple treatment option because of administrative difficulties in carrying out this option in some centres; the disparity in numbers will soon be removed without any bias being introduced.

The rate of recruitment of patients into the trial of 25–28 per month has been a steady one. The survival-rate has now been estimated for each method of treatment for 396

---

**Table 3.**

<table>
<thead>
<tr>
<th>M.R.C. U.K. Preoperative radiotherapy trial</th>
<th>Pathological assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type</td>
</tr>
<tr>
<td></td>
<td>Grade</td>
</tr>
<tr>
<td></td>
<td>Associated pathology</td>
</tr>
<tr>
<td></td>
<td>Spread</td>
</tr>
<tr>
<td></td>
<td>Dukes classification</td>
</tr>
</tbody>
</table>

---

**Table 4.**

<table>
<thead>
<tr>
<th>M.R.C. U.K. Preoperative radiotherapy trial</th>
<th>Follow-up assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abdominal wound</td>
</tr>
<tr>
<td></td>
<td>Perineal wound</td>
</tr>
<tr>
<td></td>
<td>Complications</td>
</tr>
<tr>
<td></td>
<td>Local recurrence</td>
</tr>
<tr>
<td></td>
<td>Metastatic disease</td>
</tr>
<tr>
<td></td>
<td>Further treatment</td>
</tr>
<tr>
<td></td>
<td>Death</td>
</tr>
</tbody>
</table>
patients followed up to April 1977. The numbers are small and it is obviously too early to make any particular claims in regard to the various methods of management. There appears to be no deleterious effect in the treated groups compared with the non-irradiated group.

The most significant outcome thus far is of a lower percentage of Dukes C patients present in the 2000 rad group with a corresponding increase in B cases, suggesting that in this treatment option the lymph nodes could be favourably affected by radiotherapy.

It is hoped to recruit 750 cases into this trial and it should be possible only then to give a conclusive report on the outcome as to survival in each group.

**Acknowledgements**—We would thank the many surgeons and radiotherapists contributing their cases to the Trial, which closes in September 1978. Future reports will list all the main participants.

**REFERENCES**

A trial of preoperative radiotherapy in the management of operable rectal cancer

In a multicentre study, 824 patients with operable rectal cancer were randomized to receive surgery alone, surgery plus a single fraction of 500 rad (5 Gy) and surgery plus 2000 rad (20 Gy) in 10 equal daily, i.e. multiple, fractions. The ratio of abdominoperineal excision to anterior restorative operations was 3:1. There was no evidence of an increased morbidity or mortality following irradiation. The multiple fraction 2000 rad group had tumours which were significantly smaller than those of the other groups. There was also a reduction in the Dukes' C cases in the multiple fraction group. Neither the tumour size nor the lymph node status was altered in the single fraction group.

Interest in preoperative radiotherapy in the management of rectal cancer was initially stimulated by an analysis of over 20 years' experience at the Memorial Hospital and Sloan-Kettering Institute, New York (1). Among 727 patients who had been given low dose radiotherapy in the order of 1000-2000 rad (10-20 Gy) in 10 daily fractions. In this retrospective study it appeared that the group of patients who had received preoperative irradiation had a better survival (55 per cent at 5 years) compared to a group of 449 managed by surgery alone in the same period (45 per cent at 5 years) compared to a group of 449 managed by surgery alone in the same period (45 per cent at 5 years). In a multicentre study, 824 patients with operable rectal cancer were randomized to receive surgery alone, surgery plus a single fraction of 500 rad (5 Gy) and surgery plus 2000 rad (20 Gy) in 10 equal daily, i.e. multiple, fractions. The ratio of abdominoperineal excision to anterior restorative operations was 3:1. There was no evidence of an increased morbidity or mortality following irradiation. The multiple fraction 2000 rad group had tumours which were significantly smaller than those of the other groups. There was also a reduction in the Dukes' C cases in the multiple fraction group. Neither the tumour size nor the lymph node status was altered in the single fraction group.

The MRC trial was designed to assess the effectiveness of low dose radiotherapy given before definitive excision of operable carcinoma of the rectum. Two groups of patients would receive either 500 rad (5 Gy) single exposure or 2000 rad (20 Gy) given in 10 fractions over 2 weeks. A third 'control' group would be managed by surgery alone, either abdominoperineal excision or anterior restorative resection. Comparison of the treatment groups was to be made primarily by the analysis of local recurrence, metastases and survival rates. Assessment was also to be made of the complications of treatment in the three groups.

This first report is an analysis of the data concerned with the pre-treatment assessment, surgical management and the post-surgical staging and morbidity. It is not possible at this time to provide definitive data on survival and recurrence rates.

The MRC trial protocol

Patients with resectable adenocarcinoma, the lower margin of which was within 15 cm of the anal verge, were eligible for the trial. Both male and female patients were included if under the age of 80 years and considered fit to undergo definitive surgery. The patient had to be without evidence of intra-abdominal metastases on clinical examination. A palpable liver, however, did not exclude a patient from the trial unless it was thought to be involved with tumour. A chest radiograph was obligatory to exclude the presence of pulmonary metastases.

The primary tumour by rectal digital examination and by sigmoidoscopy was performed on all patients. An assessment was made of the circumferential extent of the tumour, its distance from the anal verge and its degree of fixation within the pelvis. All patients were required to have a biopsy and histological confirmation of adenocarcinoma of the rectum. The tumours were described according to the WHO classification and histological nomenclature of intestinal tumours (7).

A radiograph of the pelvis was obligatory to exclude local bone destruction. It was intended to assay serum bilirubin and alkaline phosphatase in all patients, although abnormal levels...
did not exclude patients from the trial. However, the results of these assays were documented in few patients.

Patients were randomly allocated to one of three treatment groups: a non-irradiated control group, a group which received a single X-ray exposure (SF) and a multiple fraction (MF) group. Randomization was carried out by secretaries working in 17 regional centres who were provided with sequentially numbered sealed envelopes containing the treatment allocation. The random allocation of patients to the treatment groups was balanced within each centre. On randomization, the patient’s name and clinical details were entered on a registration sheet by the secretary, copies of which were sent regularly to the Central Trials Office. Clinical coordinators were appointed in each region to encourage and maintain the participation of local surgeons, radiotherapists and pathologists. They were responsible for liaison between the Central Trials Office, the individual participants and the MRC Working Party.

The radiotherapy technique employed two parallel opposed fields 18 x 15 cm, the fields covering the pelvis from the level of the anal margin. Megavoltage radiotherapy was used in all patients and the prescribed central dose was either 300 rad (5 Gy) in a single exposure (SF) or 2000 rad (20 Gy) in 10 equal daily fractions (MF).

It was required that surgery should be performed as soon as possible after, or at most within 1 week of completion of radiotherapy. The definitive operation could be either abdominoperineal excision or anterior restorative resection. In patients who underwent anterior restorative resection, surgeons were asked to specify if the anastomosis had been washed with a cytotoxic agent. In female patients who were asked to record the number of lymph nodes found in the specimen and the number of nodes found to be histologically involved by tumour. The size of the primary tumour was recorded, together with the distance of the lower margin from the dentate line when abdominoperineal excision had been performed.

Patients were followed up by the surgeons and were seen at 3-monthly intervals in the first year after operation and 6-monthly thereafter. Particular attention was directed to recording complications in the abdominal and perineal wounds and to the general postoperative morbidity. Special care was taken to note the site and timing of local recurrence and of metastatic disease. The date of death and the clinical assessment of tumour status at that time was recorded, together with autopsy confirmation when performed.

Preliminary analysis of the MRC trial data

The trial was begun in March 1975 and was closed in August 1978 when 850 patients had been entered into the study. Patients were recruited within the 17 Regional Centres in the United Kingdom from 65 teaching and district general hospitals. One hundred and twelve consultant surgeons and 37 consultant radiotherapists participated in the trial.

Twenty-six patients were excluded from the trial: 22 patients were found not to have adenocarcinoma of the rectum and 4 other patients were excluded because of errors in the randomization procedure. Ten of the excluded patients were in the control group, 10 in the single fraction (SF) group and 6 in the multiple fraction (MF) treatment group.

Therefore, 824 patients (Table I) are included in this and subsequent analysis. The distribution of patients by sex was similar in all treatment groups, 63 per cent of patients being male. Distribution by age is shown in Table II where it can be seen that there is a slight preponderance of younger patients in the control group.

Pre-treatment assessment

The clinical extent of tumour found on rectal digital examination is shown in Table III. It can be seen that there was a similar proportion of patients with mobile tumours in the MF group. It was also found that there was a slightly greater proportion of patients in the MF group with more than one quadrant of the rectal mucosa involved. The height of the tumour, as assessed at sigmoidoscopy, is also shown in Table III and there again was a slightly greater number of patients with low-lying cancer in the MF group. Table IV gives the deviations from the criteria of entry required in the protocol in the three treatment groups, which will be seen to be similarly distributed.

Radiotherapy

A number of deviations were also recorded in the radiotherapy given in the two irradiated groups (Table IV). Two patients (0-8 per cent) in the control group were wrongly given radiotherapy. A much greater deviation rate was recorded in the MF group amounting to 19-1 per cent. Approximately half of these were the result of a delay exceeding 1 week between completion of irradiation and the time of surgery, the other half being a major change in the treatment allocated. Deviations were less frequent in the SF group but still amounted to 11-6 per cent. Approximately two-thirds of these deviations were the result of delay between radiotherapy and the time of operation.

Table I: NUMBERS OF PATIENTS FROM each CENTRE

<table>
<thead>
<tr>
<th>Centre</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>West Midlands</td>
<td>202</td>
</tr>
<tr>
<td>West Yorkshire</td>
<td>133</td>
</tr>
<tr>
<td>Sheffield</td>
<td>106</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>97</td>
</tr>
<tr>
<td>Glasgow</td>
<td>67</td>
</tr>
<tr>
<td>Manchester</td>
<td>49</td>
</tr>
<tr>
<td>Cleveland</td>
<td>36</td>
</tr>
<tr>
<td>Merseyside</td>
<td>28</td>
</tr>
<tr>
<td>Newcastle</td>
<td>24</td>
</tr>
<tr>
<td>Reading</td>
<td>21</td>
</tr>
<tr>
<td>Royal Free Hospital</td>
<td>14</td>
</tr>
<tr>
<td>East Anglia</td>
<td>12</td>
</tr>
<tr>
<td>Mount Vernon Hospital</td>
<td>11</td>
</tr>
<tr>
<td>St Mary's Hospital</td>
<td>11</td>
</tr>
<tr>
<td>St Mark's Hospital</td>
<td>7</td>
</tr>
<tr>
<td>Cardiff</td>
<td>4</td>
</tr>
<tr>
<td>Middlesex Hospital</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>824</td>
</tr>
</tbody>
</table>

*Twenty-six patients were excluded from the trial.

Table II: AGE DISTRIBUTION OF PATIENTS

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Controls</th>
<th>Single fraction</th>
<th>Multiple fractions</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>30-49</td>
<td>21</td>
<td>7.6</td>
<td>15</td>
<td>5.4</td>
</tr>
<tr>
<td>50-59</td>
<td>76</td>
<td>27.6</td>
<td>58</td>
<td>29.9</td>
</tr>
<tr>
<td>60-69</td>
<td>96</td>
<td>34.9</td>
<td>101</td>
<td>36.5</td>
</tr>
<tr>
<td>70-80</td>
<td>78</td>
<td>28.4</td>
<td>97</td>
<td>35.6</td>
</tr>
<tr>
<td>81+</td>
<td>2</td>
<td>0.7</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Not known</td>
<td>2</td>
<td>0.7</td>
<td>4</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.4</td>
</tr>
</tbody>
</table>

Table IV: deviations from the criteria of entry required in the protocol in the three treatment groups.
Table III: EXTENSION AND HEIGHT OF TUMOUR

<table>
<thead>
<tr>
<th>Treatment allocated</th>
<th>Controls</th>
<th>Single fraction</th>
<th>Multiple fractions</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Extension of tumour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobile</td>
<td>148</td>
<td>53.8</td>
<td>142</td>
<td>51.3</td>
</tr>
<tr>
<td>Partially fixed</td>
<td>77</td>
<td>28.0</td>
<td>79</td>
<td>28.5</td>
</tr>
<tr>
<td>Fixed</td>
<td>31</td>
<td>11.3</td>
<td>38</td>
<td>13.7</td>
</tr>
<tr>
<td>Not known/ not assessable</td>
<td>19</td>
<td>6.9</td>
<td>18</td>
<td>6.5</td>
</tr>
<tr>
<td>Height of tumour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 5</td>
<td>81</td>
<td>29.5</td>
<td>85</td>
<td>30.7</td>
</tr>
<tr>
<td>6 - 10</td>
<td>12</td>
<td>4.7</td>
<td>136</td>
<td>49.1</td>
</tr>
<tr>
<td>11+</td>
<td>56</td>
<td>20.4</td>
<td>47</td>
<td>17.0</td>
</tr>
<tr>
<td>Not known/ not assessable</td>
<td>7</td>
<td>2.5</td>
<td>9</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Table IV: CONTRA VEN TIONS OF THE PROTOCOL

<table>
<thead>
<tr>
<th>Type of protocol deviation</th>
<th>Treatment allocated</th>
<th>Controls</th>
<th>Single fraction</th>
<th>Multiple fractions</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exceeded 80 yr</td>
<td>2</td>
<td>0.7</td>
<td>1</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Not known</td>
<td>2</td>
<td>0.7</td>
<td>4</td>
<td>1.4</td>
<td>2</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>5</td>
<td>1.8</td>
<td>7</td>
<td>2.5</td>
<td>6</td>
</tr>
<tr>
<td>Not done</td>
<td>7</td>
<td>2.5</td>
<td>6</td>
<td>2.2</td>
<td>5</td>
</tr>
<tr>
<td>Height of tumour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above 15 cm</td>
<td>1</td>
<td>0.4</td>
<td>1</td>
<td>0.4</td>
<td>2</td>
</tr>
<tr>
<td>Not known</td>
<td>7</td>
<td>2.5</td>
<td>9</td>
<td>3.2</td>
<td>8</td>
</tr>
<tr>
<td>Bopsy result not known</td>
<td>1</td>
<td>0.4</td>
<td>2</td>
<td>0.7</td>
<td>5</td>
</tr>
<tr>
<td>Treatment given</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not according to protocol</td>
<td>1</td>
<td>0.4</td>
<td>32</td>
<td>11.6</td>
<td>52</td>
</tr>
<tr>
<td>Details of XRT not fully known</td>
<td>1</td>
<td>0.4</td>
<td>7</td>
<td>2.5</td>
<td>17</td>
</tr>
</tbody>
</table>

Table V: CONTRA VEN TIONS OF THE TREATMENT PROTOCOL

<table>
<thead>
<tr>
<th>Delay between XRT and surgery (wk)</th>
<th>Treatment allocated</th>
<th>Controls</th>
<th>Single fraction</th>
<th>Multiple fractions</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>1-2</td>
<td>12</td>
<td>4.4</td>
<td>20</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>6</td>
<td>2.2</td>
<td>8</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>&gt; 4</td>
<td>4</td>
<td>1.4</td>
<td>2</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Deviations from XRT protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No XRT given</td>
<td>7</td>
<td>2.5</td>
<td>15</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Alternate regimen given</td>
<td>2</td>
<td>0.7</td>
<td>1</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>XRT given after surgery</td>
<td>1</td>
<td>0.4</td>
<td>1</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Reduced XRT given</td>
<td>0</td>
<td>0.0</td>
<td>5</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>11.6</td>
<td>52</td>
<td>19.1</td>
<td></td>
</tr>
</tbody>
</table>

Surgery

The resectability rate in the trial was 92 per cent and the distribution of operative procedures is given in Table VI. It can be seen that in this series of patients the ratio of abdominoperineal excision to anterior restorative operations was 3:1. The total number of patients having these definitive operations was similar in all three treatment groups. There is no evidence that preoperative radiotherapy influenced the number of patients eventually undergoing definitive resection. However, there is an apparent difference in the three groups (SF vs. controls: $\chi^2 = 2.83$ on 1 d.f.; $P = 0.09$; MF vs. controls: $\chi^2 = 2.82$ on 1 d.f., $P = 0.09$). This difference may have been determined, in part, by the greater number of low-lying cancers in the MF group. It has also to be acknowledged that the choice of operative procedure may at times have been influenced by the surgeon's awareness of the preoperative treatment given. The operative mortality rates for both abdominoperineal excision and anterior restorative resection are similar in the three groups (Table VII).

There is no general increase in morbidity after anteroposterior excision as the result of preoperative radiotherapy, and the distribution and nature of the complications recorded in the three treatment groups are given in Table VIII. Similarly, there is no evidence of increased morbidity following irradiation in patients who had anterior restorative resections (Table IX). There is, however, a large difference in the numbers of anastomotic "leaks" in the control and the irradiated groups. Thirty per cent of patients in the control group had anastomotic leaks, almost all of clinical significance, compared to 8 per cent in the SF group and 16 per cent in the MF group ($\chi^2 = 10.5$ on 2 d.f.). After adjusting the resulting probability level to take account of the 14 other complications assessed statistically (giving $P = 0.08$), the disparity in rates is large enough to suggest a real difference between the anastomotic "leak" rate in the three treatment regimens.

Pathological assessment of excised tumours

The excised specimen was sent to the pathology laboratory for mounting and examination in a standard manner. The tumour site was noted and its size measured. Further histological examination of the tumour was carried out with histological grading. A record was made of the number of lymph nodes found in the specimen and the extent of tumour spread assessed by the Dukes' classification.

The distribution of tumour sizes by treatment groups is given
Table VI: SURGERY PERFORMED

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Controls No.</th>
<th>%</th>
<th>Single fraction No.</th>
<th>%</th>
<th>Multiple fractions No.</th>
<th>%</th>
<th>Total No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominoperineal excision</td>
<td>177</td>
<td>64-4</td>
<td>197</td>
<td>71-1</td>
<td>190</td>
<td>69-9</td>
<td>564</td>
<td>68-4</td>
</tr>
<tr>
<td>Anterior restorative operation</td>
<td>70</td>
<td>25-5</td>
<td>53</td>
<td>19-1</td>
<td>52</td>
<td>19-1</td>
<td>175</td>
<td>21-2</td>
</tr>
<tr>
<td>Hartmann's operation</td>
<td>4</td>
<td>1-5</td>
<td>6</td>
<td>2-2</td>
<td>5</td>
<td>1-8</td>
<td>15</td>
<td>1-8</td>
</tr>
<tr>
<td>Local excision</td>
<td>2</td>
<td>0-7</td>
<td>2</td>
<td>0-7</td>
<td>0</td>
<td>0-0</td>
<td>4</td>
<td>0-5</td>
</tr>
<tr>
<td>No resection of tumour</td>
<td>22</td>
<td>8-0</td>
<td>19</td>
<td>6-9</td>
<td>25</td>
<td>9-2</td>
<td>66</td>
<td>8-0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>275</strong></td>
<td><strong>64-4</strong></td>
<td><strong>277</strong></td>
<td><strong>68-4</strong></td>
<td><strong>272</strong></td>
<td><strong>68-4</strong></td>
<td><strong>824</strong></td>
<td><strong>68-4</strong></td>
</tr>
</tbody>
</table>

Table VII: DEATHS WITHIN 30 DAYS AFTER SURGERY

<table>
<thead>
<tr>
<th>Treatment allocated</th>
<th>Controls No.</th>
<th>%</th>
<th>Single fraction No.</th>
<th>%</th>
<th>Multiple fractions No.</th>
<th>%</th>
<th>Total No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominoperineal excision</td>
<td>177</td>
<td>64-4</td>
<td>197</td>
<td>71-1</td>
<td>190</td>
<td>69-9</td>
<td>564</td>
<td>68-4</td>
</tr>
<tr>
<td>Anterior restorative operation</td>
<td>70</td>
<td>25-5</td>
<td>53</td>
<td>19-1</td>
<td>52</td>
<td>19-1</td>
<td>175</td>
<td>21-2</td>
</tr>
</tbody>
</table>

* Two patients with no follow-up information.

Table VIII: IMMEDIATE POSTOPERATIVE COMPLICATIONS IN ABDOMINOPERINEAL EXCISION

<table>
<thead>
<tr>
<th>Complication</th>
<th>Radiotherapy allocated</th>
<th>None (n = 177) No.</th>
<th>%</th>
<th>Single fraction (n = 197) No.</th>
<th>%</th>
<th>Multiple fractions (n = 190) No.</th>
<th>%</th>
<th>Total No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal wound sepsis</td>
<td>25</td>
<td>14</td>
<td>20</td>
<td>10</td>
<td>33</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perineal wound/ pelvic sepsis</td>
<td>56</td>
<td>32</td>
<td>45</td>
<td>23</td>
<td>60</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileus</td>
<td>8</td>
<td>4</td>
<td>13</td>
<td>7</td>
<td>11</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstruction</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory/cardiovascular/cerebrovascular</td>
<td>12</td>
<td>7</td>
<td>21</td>
<td>11</td>
<td>11</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td>12</td>
<td>7</td>
<td>9</td>
<td>5</td>
<td>12</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colostomy</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table IX: IMMEDIATE POSTOPERATIVE COMPLICATIONS IN ANTERIOR RESTORATIVE OPERATIONS

<table>
<thead>
<tr>
<th>Complication</th>
<th>Radiotherapy allocated</th>
<th>None (n = 70) No.</th>
<th>%</th>
<th>Single fraction (n = 53) No.</th>
<th>%</th>
<th>Multiple fractions (n = 52) No.</th>
<th>%</th>
<th>Total No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal wound sepsis</td>
<td>13</td>
<td>19</td>
<td>8</td>
<td>15</td>
<td>8</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic sepsis</td>
<td>6</td>
<td>9</td>
<td>4</td>
<td>8</td>
<td>10</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileus</td>
<td>5</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstruction</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastomatic 'leak'</td>
<td>21</td>
<td>30</td>
<td>4</td>
<td>8</td>
<td>8</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory/cardiovascular/cerebrovascular</td>
<td>8</td>
<td>11</td>
<td>7</td>
<td>13</td>
<td>2</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colostomy</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The only significant difference is in the distribution of anastomatic leaks.

In Table X. A greater proportion of the smallest tumours (1-4 cm) was found in the MF group. The reduction in tumour size in the MF group was highly significant statistically ($\chi^2$ for difference in tumour size distribution = 15-4 on 4 d.f.; $P = 0-004$). No reduction in tumour size was seen in the SF group, but one would not expect to observe any reduction in the size of a characteristically slowly growing tumour immediately after a single exposure of X-rays.

When histological grading of resected tumours in the three randomly allocated groups was compared there was a tendency for there to be a greater proportion of high grade tumours in the MF group (Table XII). This difference approaches conventional levels of statistical significance ($\chi^2$ for trend comparing MF and controls = 3-53 on 1 d.f.; $P = 0-06$).

The distribution by Dukes’ classification is given in Table XII. There was a difference between the proportion of Dukes’ C stage cancers between the MF group (35-9 per cent) compared to the control group (44-6 per cent). This difference just fails to reach the 5 per cent significance level ($\chi^2 = 3-53$ on 1 d.f.; $P = 0-06$). No difference is seen between the SF group and controls.

It is also of importance to note that the number of histologically positive lymph nodes found in the resected specimens is less by about 30 per cent in the MF group than in the control group ($\chi^2$ for trend = 3-08 on 1 d.f.; $P = 0-06$). However, the number of negative nodes is reduced by the same proportion in the MF group which is highly significant statistically ($\chi^2$ for trend = 51-1 on 1 d.f.; $P < 0-0001$) (Table XIII). No difference is seen between the SF group and the controls.
Preoperative radiotherapy in rectal cancer

<table>
<thead>
<tr>
<th>Table X: SIZE OF TUMOUR AS MEASURED BY PATHOLOGIST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum diameter</strong></td>
</tr>
<tr>
<td>(cm)</td>
</tr>
<tr>
<td>Total measured</td>
</tr>
<tr>
<td>1-4 *</td>
</tr>
<tr>
<td>5-7 *</td>
</tr>
<tr>
<td>8+ *</td>
</tr>
<tr>
<td>Total not measured</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages. *Percentages are of the total number measured.

<table>
<thead>
<tr>
<th>Table XI: GRADE OF TUMOUR IN THE RESECTED SPECIMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Total assessed</td>
</tr>
<tr>
<td>Low*</td>
</tr>
<tr>
<td>Average*</td>
</tr>
<tr>
<td>High*</td>
</tr>
<tr>
<td>Total not assessed</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages. *Percentages are of the total number assessed.

<table>
<thead>
<tr>
<th>Table XII: DUKES’ CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dukes’ classification</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Total assessed</td>
</tr>
<tr>
<td>A*</td>
</tr>
<tr>
<td>B*</td>
</tr>
<tr>
<td>C*</td>
</tr>
<tr>
<td>Total not assessed</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages. *Percentages are of the total number assessed.

<table>
<thead>
<tr>
<th>Table XIII: LYMPH NODE ANALYSIS*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment allocated</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Controls</td>
</tr>
<tr>
<td>Single fraction</td>
</tr>
<tr>
<td>Multiple fractions</td>
</tr>
<tr>
<td>Ratio of mean in MF group to mean in control group</td>
</tr>
</tbody>
</table>

*Significance tests quoted in the text were performed by grouping the number of lymph nodes into five categories in ascending order and performing a z test for a trend in the proportion of patients in each category falling into the multiple fractions group (8).

Discussion
This preliminary analysis has established that there are real biological effects which can be measured after preoperative radiotherapy given in a dose of 2000 rad (20 Gy) in 10 daily fractions. There is a statistically significant reduction in the size of the primary tumour in the group of patients receiving multiple fraction radiotherapy. A reduction in the proportion of patients with Dukes’ C stage tumours and in the number of positive lymph nodes was also observed in the multiple fraction group. However, the number of negative lymph nodes found in the resected specimens was reduced by the same proportion. The observation of a smaller proportion of patients with Dukes’ C stage tumours and in the number of positive lymph nodes in the MF group may be due to sampling difficulties experienced by pathologists in examining irradiated specimens. It may not necessarily reflect a real alteration in stage distribution.

It has been shown that there is no increase in the operative morbidity or mortality after either the single fraction or the multiple fraction radiotherapy. Indeed, there is a considerable reduction in the number of anastomotic leaks recorded in the group of patients who received preoperative radiotherapy. The reason for this difference is not known, but we feel that it provides reassurance to surgeons that preoperative radiotherapy is not only safe but may have advantages in addition to reducing the size and extent of the cancer to be excised. It may be that surgeons took particular care in their operative technique, or perhaps observed more strict criteria in the selection of patients for anterior restorative resection, in those whom they knew had received preoperative radiotherapy.

It should be pointed out that in spite of randomization an imbalance has occurred by chance which has resulted in a higher proportion of patients with unfavourable prognostic features being allocated to the MF group. It is important that compensation be made for this imbalance in the subsequent statistical analysis of rates of survival, local recurrence and metastases, which will be presented in a second report.

References
518

MRC Working Party


Paper accepted 2 February 1982.

Appendix

The MRC Working Party would like to acknowledge the many surgeons, radiotherapists and pathologists who contributed from many centres to the trial. They are as follows:

<table>
<thead>
<tr>
<th>Surgeons</th>
<th>Radiotherapists</th>
<th>Pathologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glasgow</td>
<td>Glasgow</td>
<td>Glasgow</td>
</tr>
<tr>
<td>Kay Sir A. W.</td>
<td>Flatman G. E.</td>
<td>Anderson J.</td>
</tr>
<tr>
<td>Maxwell-Anderson J.</td>
<td>Scott J. S.</td>
<td>Rao S.</td>
</tr>
<tr>
<td>Fraser K.</td>
<td>Cowell M. A. C.</td>
<td>Dick A.</td>
</tr>
<tr>
<td>Mackay C.</td>
<td>McHattie I.</td>
<td>Stewart P.</td>
</tr>
<tr>
<td>McLean N.</td>
<td>Watson E. R.</td>
<td></td>
</tr>
<tr>
<td>Hamilton D. N.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peebles-Brown D. A.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forrest H.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min D. C.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crossling F. T.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wright Sir R.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Russell T. B.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cameron E.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leeds</td>
<td>Leeds</td>
<td>Leeds</td>
</tr>
<tr>
<td>Graham-Stewart C. W.</td>
<td>Campbell-Robson L.</td>
<td>Abbot C. R.</td>
</tr>
<tr>
<td>Tate G. T.</td>
<td>Firth L. A.</td>
<td>Alliston R. M.</td>
</tr>
<tr>
<td>Matheson T. S.</td>
<td>Joslin C. A. F.</td>
<td>Barkow A. M.</td>
</tr>
<tr>
<td>McCartney E. T.</td>
<td>Ward A. J.</td>
<td>Bates J. D.</td>
</tr>
<tr>
<td>Shaw D. L.</td>
<td>Corbett P. J.</td>
<td>Coleman P. N.</td>
</tr>
<tr>
<td>McAdam W. A. F.</td>
<td></td>
<td>Dosset J. A.</td>
</tr>
<tr>
<td>Martin F. R.</td>
<td></td>
<td>Eastwood J.</td>
</tr>
<tr>
<td>Addison N. V.</td>
<td></td>
<td>Edwards A. T.</td>
</tr>
<tr>
<td>Whittaker M.</td>
<td></td>
<td>Gomatopolous J.</td>
</tr>
<tr>
<td>Brown G. J. A.</td>
<td></td>
<td>Hamal P. B.</td>
</tr>
<tr>
<td>Bird G. G.</td>
<td></td>
<td>Hamilton M.</td>
</tr>
<tr>
<td>Smiddy F. G.</td>
<td></td>
<td>Hardy G. J.</td>
</tr>
<tr>
<td>Barst H. H.</td>
<td></td>
<td>Horsfield G. I.</td>
</tr>
<tr>
<td>London D.</td>
<td></td>
<td>Jacobs S. I.</td>
</tr>
<tr>
<td>Wilson K. W.</td>
<td></td>
<td>MacKinnon D.</td>
</tr>
<tr>
<td>Goligher J. C.</td>
<td></td>
<td>Mason M. K.</td>
</tr>
<tr>
<td>Benson E. A.</td>
<td></td>
<td>Pyrah R. D.</td>
</tr>
<tr>
<td>Johnson D.</td>
<td></td>
<td>Rose W. L.</td>
</tr>
<tr>
<td>Bell L. C.</td>
<td></td>
<td>Sibbald R.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simmons E. L.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Storey G. W.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Swinburne M.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tinsley E. G. F.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Piercy D. M.</td>
</tr>
<tr>
<td>Birmingham</td>
<td>Birmingham</td>
<td>Birmingham</td>
</tr>
<tr>
<td>Alexander-Williams J.</td>
<td>Banks A. J.</td>
<td>Brewer D. B.</td>
</tr>
<tr>
<td>Oates G. D.</td>
<td>Newsholme G. A.</td>
<td>Thompson H.</td>
</tr>
<tr>
<td>Dorrington N. J.</td>
<td>Freeman W. E.</td>
<td>Curran R. C.</td>
</tr>
<tr>
<td>Baddeley R. M.</td>
<td>Bond W. H.</td>
<td>Jones E. L.</td>
</tr>
<tr>
<td>Keighley M. R. B.</td>
<td>Kitchen G.</td>
<td>Chaplin A. E.</td>
</tr>
<tr>
<td>Bevan P. G.</td>
<td></td>
<td>Caldwell W. G. D.</td>
</tr>
<tr>
<td>Morrissey M. D.</td>
<td></td>
<td>Shortland-Webb W. R.</td>
</tr>
<tr>
<td>Kaufman H. D.</td>
<td></td>
<td>Abrahams R. G.</td>
</tr>
<tr>
<td>Morrison J. M.</td>
<td></td>
<td>Hoult J. G.</td>
</tr>
<tr>
<td>Slaney G.</td>
<td></td>
<td>van der Merwe S. B.</td>
</tr>
<tr>
<td>Strachan C. J.</td>
<td></td>
<td>Ramsey P. A.</td>
</tr>
<tr>
<td>Glick S.</td>
<td></td>
<td>Gordon E. G.</td>
</tr>
<tr>
<td>de Castella H. C.</td>
<td></td>
<td>McKinnell J. S.</td>
</tr>
<tr>
<td>Marcus R. T.</td>
<td></td>
<td>Barrowcliff C. F.</td>
</tr>
<tr>
<td>Cardiff</td>
<td>Cardiff</td>
<td>Cardiff</td>
</tr>
<tr>
<td>Hughes L. E.</td>
<td>Priestman T. J.</td>
<td>—</td>
</tr>
</tbody>
</table>
| Davies W. T. | | |}

| Sheffield | Sheffield | Sheffield |
| Duthie H. L. | Neal F. E. | Goepel J. |
| Talbot C. H. | Emmanuell I. G. | |
Manchester  Schofield P. F.  Manchester  Sutton M. L.
  Turner L.  Pointon R. C. S.
  Kingston R. D.  Manchester  Hasleton P. S.
  Sykes P. A.  Hancock B. D.
  Irving M.  

Edinburgh  Buchan R.  Edinburgh  Arnott S. J.
  Abercromby B. C.  Duncan W.
  Small W. P.  
  Smith A. N.  
  Ruckley C. V.  
  Falconer C. W. A.  
  McNair T. J.  
  Thomson J. W. W.  
  Hamilton T.  
  Dean A. L. B.  
  Macleod D. A. D.  
  Macleod I. B.  
  Forrest A. P. M.  
  Wallace I. W. J.  

Liverpool  Simkin E. P.  Liverpool  Dawson W. B.
  Helsby C. R.  
  Shields R.  
  Sagar S.  
  Corbett J. H.  

Middlesbrough  Edmondson J. L.  Middlesbrough  Robson N. L. K.
  Tooley A. H.  Young W. H.
  Devon H. B.  
  Thompson R. W.  
  Peel A. L. G.  

Reading  Goodwin D. P.  Reading  Bunting J. S.
  Bohm C. L.  
  Ross H. B.  
  Latto C.  
  Rothnie N. G.  
  Faer R. G.  

Middlesex  Slack W. W.  Middlesex  Spittle M. F.

Mount Vernon  Rothwell Jackson R.  Mount Vernon  Birch W. J.
  Mee W. M.  Dische S.
  Davis P. W.  

Royal Free Hospital  Lewis A.  
  Royal Free Hospital  Sennayake L. F. N.
  St Mary's Hospital  Hulbert M.
  Glaser G.  
  Fielding L. P.  

Cambridge  Hall J. H.  Cambridge  Brown C. M.
  Thornton Holmes J.  
  St Mark's Hospital  Sandland M. R.
  Hawley P. R.  

Newcastle  Venables C. W.  Newcastle  Evans R. G. B.
  Wilson A. R.  Koriche O. M.
  Taylor R. M. R.  
  Johnston I. D. A.  
  McNaught G. H. D.  
  Kirby R.  
  Sarson D.  

and the pathologists
of the Royal Victoria Infirmary, Newcastle
The evaluation of low dose pre-operative X-ray therapy in the management of operable rectal cancer; results of a randomly controlled trial

824 patients with operable rectal carcinoma were randomly allocated to be treated by surgery alone, 2000 rad in 10 daily fractions and 500 rad as a single fraction. No difference has been demonstrated in the actuarial survival rates to 5 years. The local recurrence-free and metastasis-free rates are similar in all groups. There is also no evidence that the pre-operative radiotherapy benefited patients in subgroups by Dukes' stage. The complication rates were also similar in the three treatment groups.

Keywords: Adjuvant X-ray therapy, rectal cancer, pre-operative treatment, survival rates, complication rates

This paper reports for the first time the results of a multicentre trial of pre-operative radiotherapy in the management of patients with rectal cancer conducted by the Medical Research Council in the United Kingdom. The details of the patients recruited to the study and their pretreatment assessment, surgical management and method of random allocation into treatment groups have been described earlier. In summary, patients were eligible for admission to the trial if they were under the age of 80 years, and fit for definitive surgery, for a histologically confirmed adenocarcinoma of the rectum within 15 cm of the anal verge. Patients were randomized to receive no adjuvant treatment, or a course of megavoltage X-rays to the pelvis of 2000 rad (20Gy) in 10 daily fractions or a single exposure of 500 rad (5Gy). Operation was to be performed as soon as possible, and no later than one week, after completing the course of X-ray therapy.

These regimes of pre-operative radiotherapy are similar to those employed in the Veterans Administration (VA) trial and in the Toronto trial. The Veterans Administration investigators had claimed to find a statistically significant improvement in the survival of patients who had received X-ray therapy before a 'curative' abdominopерineal excision for recto-sigmoid cancer. However, in a subsequent publication it is rightly pointed out that although the differences in survival between the irradiated and control groups do reach conventional levels of statistical significance, it would not be prudent to assume that the difference is real because of the highly selected features of the subgroups. However, the VA study did demonstrate a statistically significant reduction in the risk of cancer related deaths in those who had received pre-operative radiotherapy. The Toronto trial also showed a significant improvement in survival of a group of patients with Dukes' stage C cancer that were given a single fraction of 500 rad (5Gy) immediately before operation. This difference has been confirmed in a recent review by Rider (personal communication).

The MRC trial

824 patients from 17 centres in the UK were entered in this trial from March 1975 to August 1978, a period of 3 years and 6 months. The age and sex distribution are similar in the three groups. It had been observed, however, in an earlier analysis that a greater proportion of patients with tethered cancers and with more than one segment of rectum involved were included in the multiple fraction (MF) group. In addition, a slightly greater number of patients with low lying cancers occurred also in the MF group. It has to be recognized that a disproportionate number of patients with relatively poor prognostic features were included, one must assume by chance, in the MF group. There is no evidence that the randomization process was at fault. In this report the analyses of survival rates, local recurrence and metastasis rates have been adjusted to take account of the relative distribution influence of the most important of these prognostic features, the mobility of the cancer in the three treatment groups. In addition, since significant bias might be introduced by conducting an analysis by the treatment given, the actuarial analyses of survival, recurrence and metastatic rates have been made by the treatment allocated. This decision is discussed in more detail later.

A preliminary analysis of the results of the trial has demonstrated a real biological effect of the MF radiotherapy regime. There was a statistically significant reduction in the size of the primary cancer and the proportion of Dukes' stage C tumours was smaller in the MF group. It is also important to confirm that there was no evidence of any increased operative morbidity or mortality associated with the pre-operative radiotherapy. Indeed there was a reduction in the number of anastomotic leaks in the group who had pre-

\[
\chi^2 = 0.717 \text{ on } 2 \text{ d.f.; } P = 0.692
\]
Survival rate (%)

**Pre-operative X-ray therapy in rectal cancer: MRC Working Party**

**Figure 2**
(a) Survival by treatment for mobile tumours. 
\[ \chi^2 = 2.01 \text{ on 2 d.f.} \; P = 0.4 \]
(b) Survival by treatment for partially fixed tumours. 
\[ \chi^2 = 0.30 \text{ on 2 d.f.} \; P = 0.9 \]
(c) Survival by treatment for fixed tumours. 
\[ \chi^2 = 1.94 \text{ on 2 d.f.} \; P = 0.1 \]

operative radiotherapy. This paper also presents the long term morbidity observed in patients up to 4 years after admission to the trial.

**Statistical methods**

It was explained that a number of protocol violations had been identified in which the treatment determined by the random allocation had not been appropriately given. Examination of Tables 1 and 2 show that several patients allocated to receive single fraction (SF) or multiple fraction (MF) radiotherapy actually were not given radiotherapy. For this reason the number of patients who received the 'control' treatment is larger (295) than the number allocated to receive no radiotherapy (275). In addition several other patients received either SF or MF radiotherapy that was not specified in the protocol. Details of these contraventions of the protocol have been described in the First Report.

It has been found that patients who did not receive the allocated treatments tended to have a poorer prognosis than others in the study. For example, 20 patients were allocated to be given adjuvant radiotherapy, but did not receive it. Of these patients 9 (45 per cent) died within one year of treatment compared to a mortality rate of 25 per cent for those allocated to the control group and treated accordingly. It must be recognized that certain factors related to prognosis may also have, consciously or otherwise, influenced the management of these particular patients. It would not be valid to compare the three groups in the trial by the treatment given, since a greater proportion of patients with poorer prognosis would thereby be included in the 'control' group. Bias would, therefore, be introduced in the evaluation. The statistical analysis of the trial is, therefore, conducted by the 'treatment allocated'.

**Figure 3**
(a) Survival by treatment for Dukes' A cases. 
\[ \chi^2 = 0.76 \text{ on 2 d.f.} \; P = 0.7 \]
(b) Survival by treatment for Dukes' B cases. 
\[ \chi^2 = 0.85 \text{ on 2 d.f.} \; P = 0.7 \]
(c) Survival by treatment for Dukes' C cases. 
\[ \chi^2 = 0.2 \text{ on 2 d.f.} \; P = 0.9 \]
groups which, it is considered, provides an unbiased evaluation of the three treatment policies.

The mean period of follow-up is 5 years. Of 824 patients included in the trial, 504 (61 per cent) are known to have died; 180 (22 per cent) have been followed-up for a period of less than 4 years. Overall survival rates and disease-free survival rates have been calculated by the actuarial method. Treatment comparisons based on these rates were made using the logrank test.

Adjustments for the imbalance in prognostic features (for example, mobility of the primary cancer) were also carried out by the method described by Peto et al. Comparisons of the complete resection rate were made using the chi-squared test as described by Armitage.

Results

The distribution of the 824 patients included in this trial by treatment allocated is given in Table 1. Surgeons were requested to assess at the end of the operation whether or not it was considered that the cancer had been completely excised. It has been shown that this value judgment has a significant correlation with prognosis (to be published). It is clear (Table 1) that the complete resection rate is similar in the three treatment groups ($\chi^2 = 1.98$ on 2 d.f.; $P = 0.4$). In this series the resectability rate was 92.0 and 70.1 per cent of patients were considered to have had complete resection of the tumour. The actuarial survival rates for the three treatment groups up to 5 years are given in Table 2. This table gives the survival experience when deaths from all causes are taken into account (Table 3a and illustrated in Figure 1). The survival rate when deaths from rectal cancer alone are analysed are $99 (22\%)$ are reported alive at 5 or more years, 89 (11\%) have been followed-up for a period of less than 4 years. Overall survival rates and disease-free survival rates have been calculated by the actuarial method. Treatment comparisons based on these rates were made using the logrank test.

Adjustments for the imbalance in prognostic features (for example, mobility of the primary cancer) were also carried out by the method described by Peto et al. Comparisons of the complete resection rate were made using the chi-squared test as described by Armitage.

Table 1: Distribution of patients by treatment allocated with the proportions of patients undergoing complete resection.

<table>
<thead>
<tr>
<th>Treatment allocated</th>
<th>Total no. patients</th>
<th>Complete resection</th>
<th>Incomplete resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>275</td>
<td>201 (73.1%)</td>
<td>74 (26.9%)</td>
</tr>
<tr>
<td>Single fraction</td>
<td>277</td>
<td>193 (69.6%)</td>
<td>84 (30.3%)</td>
</tr>
<tr>
<td>Multiple fractions</td>
<td>272</td>
<td>184 (67.7%)</td>
<td>88 (32.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>824</td>
<td>578</td>
<td>246</td>
</tr>
</tbody>
</table>

Number of patients: Percentages of treatment group in parentheses

Table 2: Distribution of patients by treatment given with the proportions of patients undergoing complete resection.

<table>
<thead>
<tr>
<th>Treatment given</th>
<th>Total no. patients</th>
<th>Complete resection</th>
<th>Incomplete resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>275</td>
<td>210 (71.2%)</td>
<td>85 (28.8%)</td>
</tr>
<tr>
<td>Single fraction</td>
<td>265</td>
<td>188 (71.0%)</td>
<td>77 (29.1%)</td>
</tr>
<tr>
<td>Multiple fractions</td>
<td>249</td>
<td>171 (68.6%)</td>
<td>78 (31.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>15</td>
<td>9 (60.0%)</td>
<td>6 (40.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>824</td>
<td>583</td>
<td>241</td>
</tr>
</tbody>
</table>

Number of patients: Percentages of treatment group in parentheses

out that the treatment groups were not equally balanced with respect to the mobility of the cancers. It was, therefore, necessary to make adjustments for this imbalance in the overall comparison of the survival rates in the three treatment groups. Figure 2 gives the survival rates for patients with mobile, partially fixed and fixed cancers. The adjusted logrank test again showed no significant difference between the three treatment groups ($\chi^2 = 0.69$ on 2 d.f.; $P = 0.7$). The surprisingly poor 5 year survival rate for patients with fixed rectal cancer treated by surgery alone and the apparent advantage to those receiving pre-operative multiple fraction radiotherapy may attract some interest. However this advantage, although of interest, cannot be regarded as conclusive in view of the small number of patients ($P = 0.10$) and the fact that this difference is observed in one of a number of subgroup analyses.

Earlier reports of controlled trials of pre-operative radiotherapy have suggested that only patients with Dukes' C cancers seemed to benefit from pre-operative radiotherapy using doses similar to those used in this trial. Analysis has been made of the actuarial survival of patients with Dukes' A, B and C cancers (Figure 3). There is no clear difference in survival between the treatment survival rates in the three treatment groups.

Table 3: Actuarial survival of patients in the three treatment groups taking account of deaths from all causes, cancer related deaths, and intercurrent deaths (percentages + 1 year).

<table>
<thead>
<tr>
<th>Treatment allocated</th>
<th>Total no. patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>275</td>
<td>74.9 ± 2.6</td>
<td>59.4 ± 3.0</td>
<td>47.6 ± 3.0</td>
<td>42.6 ± 3.0</td>
<td>38.0 ± 3.0</td>
</tr>
<tr>
<td>Single fraction</td>
<td>277</td>
<td>69.6 ± 2.8</td>
<td>53.2 ± 3.0</td>
<td>48.8 ± 3.0</td>
<td>42.6 ± 3.0</td>
<td>41.7 ± 3.0</td>
</tr>
<tr>
<td>Multiple fractions</td>
<td>272</td>
<td>75.6 ± 2.6</td>
<td>59.3 ± 3.0</td>
<td>48.3 ± 3.1</td>
<td>43.2 ± 3.0</td>
<td>40.0 ± 3.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment allocated</th>
<th>Total no. patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>275</td>
<td>79.2 ± 2.5</td>
<td>64.9 ± 3.0</td>
<td>54.5 ± 3.1</td>
<td>50.5 ± 3.2</td>
<td>46.6 ± 3.3</td>
</tr>
<tr>
<td>Single fraction</td>
<td>277</td>
<td>75.4 ± 2.7</td>
<td>60.2 ± 3.1</td>
<td>56.3 ± 3.1</td>
<td>50.9 ± 3.2</td>
<td>49.9 ± 3.2</td>
</tr>
<tr>
<td>Multiple fractions</td>
<td>272</td>
<td>80.6 ± 2.5</td>
<td>64.6 ± 3.0</td>
<td>53.0 ± 3.2</td>
<td>49.4 ± 3.2</td>
<td>46.2 ± 3.2</td>
</tr>
</tbody>
</table>

The possible benefit of pre-operative radiotherapy should also be seen in a reduction in local recurrence rates and also perhaps in the proportion of patients who subsequently develop metastatic disease. The local disease-free rates in the three treatment groups are given in Table 4a. The rates are similar, being approximately 55 per cent, in the three treatment groups at 5 years (χ² = 0.81 on 2 d.f.; P = 0.7). In addition it can be stated that no statistically significant difference was seen in the local disease-free rates in the randomly allocated groups when subgroups are analysed by tumour mobility or Duke's stage.

The metastaoses-free rates are given in Table 4b and at 5 years are approximately 50 per cent and are also found to be similar (χ² = 0.65 on 2 d.f.; P = 0.8) in the treatment groups. It seems that the pre-operative radiotherapy regimens used in this controlled trial have not significantly influenced the probability of dissemination of the disease.

The First Report of the trial has confirmed that there is no increase in post-operative morbidity or mortality associated with the pre-operative radiotherapy. Analysis has now been completed of the complications observed up to 5 years after definitive surgery. Table 5 gives the rates of abdominal and perineal wound complications in patients who had an abdomino-perineal excision or anterior restorative operation in 5 time-intervals up to 4 years following surgery. In general the morbidity rates are similar in the three treatment groups. The excess rate of abdominal wound complications following anterior restorative operation is confined entirely to one period from 7 to 12 months and is moreover based on small numbers. Other types of morbidity were recorded, such as gastrointestinal and urological complications, but were not observed in greater numbers in the adjuvant radiotherapy groups.

Discussion

This analysis was undertaken when more than 4 years had elapsed since the entry of the last patient to the study, and many patients had already completed 5 years of follow-up. It is, therefore, possible to provide actuarial data up to five years with reasonable confidence. It is disappointing to report that no benefit has been demonstrated in survival rates, local control rates or disease-free survival rates after the adjuvant radiotherapy advised in this trial. The suggestion that the multiple fraction pre-operative radiotherapy regimes used in the Veterans Administration trial may be beneficial has not been confirmed in this study. And no significant benefit of a single dose of 500 rad (5 Gy) has been found, in contrast to the improved 5 years survival rate for patients with Duke's stage C cancer reported by Rider et al. Indeed we have failed to demonstrate any significant effect of the pre-operative dose of 500 rad (5 Gy) of X-rays. An earlier analysis had revealed a significant reduction in the size of the primary cancer in the resected specimen in patients who had received 2000 rad (20 Gy) in 10 daily fractions but, as would be expected from the short interval between radiotherapy and surgery, not following the single exposure of 500 rad (5 Gy). There was also a reduced number of patients with involved lymph nodes in the resected specimens in patients given the multiple fraction regime, although this difference just failed to reach conventional levels of significance. A measurable biological effect was therefore observed after the multiple fraction pre-operative radiotherapy regime. These changes unfortunately have not been reflected by improved survival rates or local or distant disease-free rates.

It is reassuring to confirm that the regimens of adjuvant radiotherapy have not increased the technical difficulties of radical surgery, or contributed to additional postoperative morbidity or mortality. Indeed there is evidence that the number of anastomotic leaks may have been reduced by pre-operative radiotherapy. The excess of abdominal wound complications observed at one particular interval after anterior restorative operations in the adjuvant radiotherapy groups is considered, in view of the small numbers, to be a chance event. It is concluded, therefore, that there is no difference in the long-term complications in the three treatment groups.

It is, therefore, now our view that patients with mobile cancer of the rectum should, if fit for surgery, proceed with minimum delay after assessment to definitive resection. At least one quarter of patients with mobile cancers will be found to have Duke's stage A lesions (28 per cent in this trial overall) for which adjuvant therapy cannot at present be advised. A curative resection should be possible in at least 90 per cent of the patients with Duke's stage A cancer and the 5 year survival rate should be about 65 per cent (Figure 3a) in a large and unselected population.

However, the prognosis for patients with operable rectal cancer found on examination of the resected specimen to be Duke's stage B and C lesions may be measured by 5 year survival rates of only about 50 and 25 per cent respectively. The effectiveness of adjuvant management is presently being evaluated by robustly controlled trials of post-operative radiotherapy, cytotoxic chemotherapy or a combination of both, in the USA and in Europe.

Patients with fixed or partially fixed cancer of the rectum but suitable for resection may benefit from pre-operative radiotherapy (see Figure 2c) and it is now considered that a higher dose level should be used than given in this trial. Only 30 per cent of patients with fixed rectal cancer in this trial (44 per cent of patients with tethered lesions) were found at operation to have a tumour able to be completely resected. The probability of local recurrence has been shown to be high and survival rates to be extremely poor in these patients. The Medical Research Council has recently begun a second randomly controlled trial of pre-operative radiotherapy for...
### Table 5: Actuarial assessment of complications in the three treatment groups experienced between I and 48 months following definitive surgery

#### Abdominal wound complication rates in patients following abdomino-perineal excision

<table>
<thead>
<tr>
<th>Time from surgery (months)</th>
<th>Control</th>
<th>Single fraction</th>
<th>Multiple fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. assessable</td>
<td>No. with complication</td>
<td>Rate (%)</td>
</tr>
<tr>
<td>1-6</td>
<td>153</td>
<td>15</td>
<td>9.8</td>
</tr>
<tr>
<td>12-24</td>
<td>138</td>
<td>11</td>
<td>8.0</td>
</tr>
<tr>
<td>24-36</td>
<td>125</td>
<td>13</td>
<td>10.4</td>
</tr>
<tr>
<td>36-48</td>
<td>99</td>
<td>8</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>76</td>
<td>3</td>
<td>3.9</td>
</tr>
</tbody>
</table>

#### Perineal wound complication rates in patients following abdomino-perineal excision

<table>
<thead>
<tr>
<th>Time from surgery (months)</th>
<th>Control</th>
<th>Single fraction</th>
<th>Multiple fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. assessable</td>
<td>No. with complication</td>
<td>Rate (%)</td>
</tr>
<tr>
<td>1-6</td>
<td>153</td>
<td>54</td>
<td>35.3</td>
</tr>
<tr>
<td>12-24</td>
<td>138</td>
<td>27</td>
<td>19.6</td>
</tr>
<tr>
<td>24-36</td>
<td>125</td>
<td>20</td>
<td>16.0</td>
</tr>
<tr>
<td>36-48</td>
<td>99</td>
<td>6</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>76</td>
<td>3</td>
<td>3.9</td>
</tr>
</tbody>
</table>

#### Abdominal wound complication rates in patients following anterior restorative operation

<table>
<thead>
<tr>
<th>Time from surgery (months)</th>
<th>Control</th>
<th>Single fraction</th>
<th>Multiple fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. assessable</td>
<td>No. with complication</td>
<td>Rate (%)</td>
</tr>
<tr>
<td>1-6</td>
<td>61</td>
<td>8</td>
<td>13.1</td>
</tr>
<tr>
<td>12-24</td>
<td>55</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>24-36</td>
<td>48</td>
<td>4</td>
<td>8.3</td>
</tr>
<tr>
<td>36-48</td>
<td>38</td>
<td>3</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>1</td>
<td>3.2</td>
</tr>
</tbody>
</table>

### References


Paper accepted 10 May 1983

Pre-operative X-ray therapy in rectal cancer: MRC Working Party

...
Clinico-pathological features of prognostic significance in operable rectal cancer in 17 centres in the U.K.

(Third report of the M.R.C. Trial, on behalf of the Working Party)

Working Party:

Summary Clinico-pathological features of prognostic significance in rectal cancer are described in 824 patients who were treated at 17 centres in the Medical Research Council Trial of radiotherapy in operable cancer of the rectum. Among the pre-operative assessments the mobility of the tumour was the one most strongly related to prognosis. Other variables predictive of outcome were the number of involved quadrants of the rectum, the distance of the tumour from the anal verge and the age of the patient. Of assessments made at surgery or immediately after, the report of a curative operation and the Dukes' classification most closely related to prognosis. The information presented supports the idea that a pre-operative clinical staging system for rectal cancer would be feasible and useful.

Following the studies of the Veterans' Association in the United States (Roswit et al., 1975) and the Princess Margaret Hospital in Toronto, Canada (Rider et al., 1977), the Medical Research Council of the United Kingdom began in 1975 a trial of pre-operative radiotherapy in patients with operable rectal cancer. The design and the protocol of the trial are described in the first report (First MRC Report, 1982). The patients were treated in 17 different regions throughout the UK by surgeons and radiation oncologists who agreed to participate in the study. In a period of just over three years, between March 1975 and August 1978, 824 patients with rectal cancer were recruited to the study. They were then randomly allocated to immediate definitive surgery or to pre-operative adjuvant radiotherapy of either 500 cGy in a single exposure, or 2000 cGy in 10 fractions over two weeks. Since there was no difference between the control and irradiation treatment group as to surgical outcome (Second MRC Report, 1984), the whole group can be used to determine the validity of factors in the pre-operative assessment and histology in determining prognosis. This paper identifies a number of clinico-pathological features important in this respect.

Pre-treatment assessment
Patients were entered into the trial to around 80 years of age if they had an operable tumour which was histologically confirmed as an adenocarcinoma which had its lower margin $\leq 15$ cm from the anal verge. Since the mean tumour diameter was $\sim 5$ cm the selection of patients with tumours confined to 15 cm allowed tumours of the rectum proper (i.e. up to 17-18 cm from the anal verge) to be included but effectively excluded tumours at the recto-sigmoid junction and above. The mean follow-up period for these patients is now 5 years, and only 6% (51 patients) have been followed for $< 4$ years.

Age and sex
There were 824 patients, of whom 516 (63%) were male. The age distribution of patients is given in Figure I. The youngest patient was 32 years old and the eldest 86, with an average age of 64.5 years.

Height
Sigmoidoscopy was carried out in 800 (97%) of the patients and the height of the tumour above the anal verge was measured. In 501 (61%) patients the lower margin of the tumour was within 8 cm of the anal verge, the remainder having lesions from 9-15 cm.

Mobility
Pre-treatment assessment by digital examination and sigmoidoscopy revealed that 401 (49%) tumours were mobile and that 364 (44%) were "tethered" in the pelvis. Examination under anaesthesia assisted in determining fixity in a few instances but was not a requirement of the trial.
Forty-three percent of the tethered tumours were later considered to be completely fixed. For 59 (7%) patients no assessment was recorded.

**Quadrants involved**

The number of quadrants of the rectum involved was recorded at sigmoidoscopy in 793 (96%) patients. The distribution of involved quadrants is given in Figure 2. In almost half the patients only one quadrant of the rectum was involved with tumour. Of patients with mobile tumours, the proportion with only one quadrant of the rectum involved was 59%, which was significantly greater than the proportion in the group with tethered tumours (41%) ($\chi^2 = 25.5$ on 1 df, $P < 0.001$).

It was noted that mobile tumours occurred more frequently in the higher rectum. One hundred and forty-seven (37%) of mobile cancers had their lower limit $>8$ cm from the anal verge compared with 106 (30%) of tethered tumours ($\chi^2 = 4.86$ on 1 df, $P < 0.03$).

**Operative procedures**

It was found that 739 (90%) patients considered eligible for the trial were suitable for radical surgery at the time of laparotomy. Abdomino-perineal excision was the most common definitive operation and was performed in 564 (68%) patients. Anterior restorative resection was performed in only 175 (21%). It will be noted that 85 (10%) patients were found at the time of operation to be unsuitable for definitive resection. Thus the surgeon's initial assessment of operability turned out to be correct in 90% of the patients.

Abdomino-perineal excision of the rectum was performed in 364 males and 200 females. Excision of the posterior vaginal wall was carried out in 76 (38%) of these female patients. It was noted that excision of the posterior vaginal wall was carried out more frequently (49%) when the cancer involved the anterior quadrant of the rectum, as it did in 108 female patients, than when the anterior quadrant was not involved (24%) ($\chi^2 = 11.7$ on 1 df, $P < 0.001$). Excision of the posterior vaginal wall was performed in 26% when the lower limit of the cancer was $>8$ cm from the anal verge compared to 41% when lower lying lesions were resected. This difference is not statistically significant ($\chi^2 = 2.71$ on 1 df, $P = 0.10$) but there is a consistent trend when the height of the tumour is subdivided into smaller intervals.

Anterior restorative operations were performed in 175 (21%) patients who were suitable for definitive surgery and more commonly in patients with tumours lying 11 cm or more from the anal verge than in the middle or lower rectum. In this series 96/143 patients (67%) with cancers 11–15 cm above the anal verge were managed by anterior restorative resection. This percentage may be compared with 77/657 patients (12%) with lower lying tumours which were removed by anterior restorative resection. It was also found that anterior restorative operations were performed significantly more frequently in females (27%) than in males (18%) ($\chi^2 = 8.53$ on 1 df, $P = 0.004$).

Radical surgery was carried out in 739 patients (90%) admitted to the trial. The feature which
related most strongly to operability was mobility of the tumour. Ninety-five percent of patients with mobile tumours were resectable compared to only 68% of those with fixed cancers.

A curative resection was defined as having been performed when a surgeon considered that the local excision of the cancer had been complete and that there was no evidence of intra-abdominal spread of the disease. Only 69% of the resectable group were considered to have had a curative resection. The proportion of patients considered to have a curative operation was similar after both abdomino-perineal excision (68%) and anterior restorative resection (73%) ($\chi^2 = 0.85$ on 1 df, $P = 0.36$).

Mobility of the tumour was again the feature which related most strongly to the surgeon's assessment of the resectability. Of the 739 patients who had radical surgery the proportion considered to have had a curative resection was 83% for those with a mobile tumour, 54% for those to be partially fixed and 42% for those with fixed cancers in the rectum.

Pathological examination of the resected specimen

The resected rectum was examined and reported in a standard manner in 741 (90%) patients in the series. Most of the other 10% represented the patients who did not have a radical resection, that is neither an abdomino-perineal excision nor an anterior restorative operation was performed.

The distribution of Dukes' staging is shown in Figure 3. The percentage of A cases is higher than that classically recorded by Dukes (1940) and later stated to be unchanged by Nicholls (1982). It has therefore to be considered whether this could be an effect of radiotherapy, but in the first report of the trial, however, the percentage of A cases was identical in the control and irradiated groups (First MRC report, 1982). The resected tumours were also graded histologically. Sixty seven percent were classified as average grade, 16% as low grade and the remaining 15% were considered to be high grade or anaplastic tumours with 2% not graded. The correlation between Dukes' stage and pathological grade is shown in Table I. The tumours of low grade have the highest proportion of Dukes' A stage, whereas the tumours of high grade have the highest proportion of Dukes' C stage ($\chi^2 = 32.3$ on 4 df, $P < 0.001$).

The Dukes' stage was also seen to be related to the maximum diameter of the cancer in the rectum ($\chi^2 = 12.55$ on 2 df, $P = 0.006$) (Table II). The proportion of patients with cancers greater than 5cms in diameter was 44% for tumours of Dukes' stage A, 59% in Dukes' B and 53% in Dukes' C.

This suggests that large size may influence the local invasion of the tumour more than it does the lymph node metastases. The Dukes' staging was also correlated to the fixity of the tumour in the pelvis. The proportion of Dukes' stages A, B and C for mobile, partially fixed and fixed cancers is given in Table III. It can be seen that there is a smaller proportion of Dukes' Stage A cancers and a larger proportion of Dukes' B for tethered tumours whereas the proportion of Dukes' Stage C lesions differs little between mobile and tethered tumours ($\chi^2 = 19.8$ on 4 df, $P < 0.001$).

Factors in prognosis

It is possible to relate a number of features, which were determined at pre-treatment assessment, operation or pathological examination of the tumour, with local disease-free rates and disease-free survival. In this section tables are presented for factors of possible prognostic importance. Each table gives information on the curative resection rate, the local disease-free rate, the survival rate and the disease-free survival rate. Curative resection has been defined above. The local disease-free rate is calculated as the actuarial proportion of patients clinically free of disease in the pelvis. The survival rate and the disease-free survival rates have also been calculated by the actuarial method. The total number of deaths which have occurred during the study is 504, of which 100 are not clearly ascribable to cancer of the rectum. Thirty-five of these occurred within 3 months of entry to the trial and were probably related to the operation. Most of the
### Table I  Dukes' stage related to histological grade

<table>
<thead>
<tr>
<th>Histological grade</th>
<th>Dukes' stage</th>
<th>Not known</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Low</td>
<td>43 (25)</td>
<td>34 (13)</td>
<td>44 (14)</td>
</tr>
<tr>
<td>Average</td>
<td>113 (67)</td>
<td>187 (72)</td>
<td>194 (62)</td>
</tr>
<tr>
<td>High</td>
<td>10 (6)</td>
<td>33 (13)</td>
<td>67 (22)</td>
</tr>
<tr>
<td>Not known</td>
<td>3 (2)</td>
<td>5 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Total</td>
<td>169 (100)</td>
<td>259 (100)</td>
<td>310 (100)</td>
</tr>
</tbody>
</table>

### Table II  Dukes' stage related to size of tumour

<table>
<thead>
<tr>
<th>Maximum diameter of tumour</th>
<th>Dukes' stage</th>
<th>Not known</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 cm</td>
<td>89 (53)</td>
<td>88 (34)</td>
<td>130 (42)</td>
</tr>
<tr>
<td>≥5 cm</td>
<td>75 (44)</td>
<td>153 (59)</td>
<td>163 (53)</td>
</tr>
<tr>
<td>Not known</td>
<td>5 (3)</td>
<td>18 (7)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Total</td>
<td>169 (100)</td>
<td>259 (100)</td>
<td>310 (100)</td>
</tr>
</tbody>
</table>

### Table III  Dukes' stage related to fixity of tumour

<table>
<thead>
<tr>
<th>Dukes' stage</th>
<th>Mobile</th>
<th>Partially fixed</th>
<th>Completely fixed</th>
<th>Not known</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>108 (28)</td>
<td>37 (16)</td>
<td>12 (15)</td>
<td>12</td>
<td>169 (23)</td>
</tr>
<tr>
<td>B</td>
<td>110 (29)</td>
<td>90 (39)</td>
<td>56 (43)</td>
<td>23</td>
<td>259 (35)</td>
</tr>
<tr>
<td>C</td>
<td>160 (42)</td>
<td>103 (45)</td>
<td>32 (40)</td>
<td>15</td>
<td>310 (42)</td>
</tr>
<tr>
<td>Not known</td>
<td>3 (1)</td>
<td>0 (--)</td>
<td>0 (--)</td>
<td>0</td>
<td>8 (--)</td>
</tr>
<tr>
<td>Total</td>
<td>381 (100)</td>
<td>230 (100)</td>
<td>80 (100)</td>
<td>50</td>
<td>741 (100)</td>
</tr>
</tbody>
</table>

The remainder were recorded as being due to diseases of old age. However, all deaths regardless of cause have been included in the calculation of the survival rates, this being considered to provide the most objective assessment. The tables give rates at 5 years. The statistical tests are based on the difference between the rates divided by the standard error of the difference as calculated by Greenwood's (1926) method.

**Age and sex**

Disease-free and survival rates of patients by age are given in Table IV. It will be seen that patients over the age of 70 have a significantly poorer survival than the younger age groups but Table IV shows that the disease itself is not responsible for the greater attrition as the disease-free interval is the same in all age groups. Males and females have similar overall disease-free survival rates.

**Height**

Patients with tumours ≤8 cm from the anal verge have a significantly poorer prognosis than those with higher tumours (Table V). Of 501 patients with tumours lying <8 cm from the anal verge, 35% were alive at 5-years, compared to 48% of the 299 patients with a cancer lying between 8 and 15 cm. There was, however, no significant difference in the proportion of patients having curative resections, being 62% for patients with low-lying lesions (<8 cm from the anal verge) compared to 65% in patients with cancer in the upper rectum or recto-sigmoid. The 5-year local disease-free rate is different for lesions above and below 8 cm, being 62% and 52% respectively. Similarly, the disease-free survival rate at 5-years is considerably better (40%) for patients with higher level cancers than the 29% rate in those with lesions within 8 cm of the anal verge (Table V).
Table IV Age related to prognosis

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>&lt;60 (n=252)</th>
<th>60-69 (n=300)</th>
<th>&gt;70 (n=270)</th>
<th>$\chi^2$</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curative resection rate ($%\pm\text{s.e.}$) 5yr</td>
<td>66 (3)</td>
<td>62 (3)</td>
<td>61 (3)</td>
<td>1.33</td>
<td>0.52</td>
</tr>
<tr>
<td>Local disease-free rate ($%\pm\text{s.e.}$) 5yr</td>
<td>56 (3)</td>
<td>58 (3)</td>
<td>51 (3)</td>
<td>2.44</td>
<td>0.30</td>
</tr>
<tr>
<td>Survival rate ($%\pm\text{s.e.}$) 5yr</td>
<td>45 (3)</td>
<td>44 (3)</td>
<td>31 (3)</td>
<td>14.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease-free survival rate ($%\pm\text{s.e.}$) 5yr</td>
<td>37 (3)</td>
<td>35 (3)</td>
<td>27 (3)</td>
<td>7.85</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*actuarial figures: not age corrected

Table V Height of tumour related to prognosis

<table>
<thead>
<tr>
<th>Height of tumour</th>
<th>(\leq 8 \text{ cm}) (n=501)</th>
<th>&gt;8 cm (n=299)</th>
<th>$\chi^2$</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curative resection rate ($%\pm\text{s.e.}$) 5yr</td>
<td>62 (2)</td>
<td>65 (3)</td>
<td>0.35</td>
<td>0.5</td>
</tr>
<tr>
<td>Local disease-free rate ($%\pm\text{s.e.}$) 5yr</td>
<td>52 (2)</td>
<td>62 (3)</td>
<td>6.87</td>
<td>0.008</td>
</tr>
<tr>
<td>Survival rate ($%\pm\text{s.e.}$) 5yr</td>
<td>35 (2)</td>
<td>48 (3)</td>
<td>12.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease-free survival rate ($%\pm\text{s.e.}$) 5yr</td>
<td>29 (2)</td>
<td>40 (3)</td>
<td>10.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Mobility**

The mobility of the cancer was seen to be of great prognostic importance. In 401 patients with mobile lesions 80% were considered to have had curative resections compared with only 44% of 364 patients who had tethered lesions. The 5-year local disease-free rate was greater in patients with mobile lesions (70%) compared to those with tethered cancers (37%). No great difference in prognosis was seen between patients with partially fixed and those with completely fixed tumours. For example, (Table VI) the 5-year survival rates were 30% and 25% respectively ($\chi^2 = 0.74 \text{ on } 1 \text{ df}, P = 0.39$). However, the 5-year survival rate for the 401 mobile tumours was 48% compared with 29% for the 364 tethered tumours (Table VI) ($\chi^2 = 29.1 \text{ on } 1 \text{ df}, P < 0.001$), and Figure 4.

**Quadrants involved**

Three hundred and ninety-four patients (48% of the total) were assessed as having only one quadrant involved. The prognosis is significantly better if one quadrant is involved. Curative resection was carried out significantly more often than when $\geq 2$ quadrants were involved; 72% of the 394 patients with one quadrant involved had a curative resection compared with 55% of 399 patients with $\geq 2$ quadrants involved. Quadrant involvement similarly influenced the disease-free rate, the survival rate and disease-free survival rate (Table VII). No information on the number of quadrants involved was available for 30 patients; their 5-year survival rate was 36%.

**Type of operation**

The type of operation performed appears to have comparatively little relationship to the prognosis in this series. The proportion of patients undergoing curative resection is similar (68% and 73%) after both types of operation, ($\chi^2 = 1.6 \text{ on } 1 \text{ df}, P = 0.21$). There is also no significant difference in the local disease-free rates at 5 years (59% and 66%) ($\chi^2 = 2.0 \text{ on } 1 \text{ df}, P = 0.16$). There is however an indication that the 5-year survival rate (41% and 55%) ($\chi^2 = 6.2 \text{ on } 1 \text{ df}, P = 0.01$) and the disease-free survival rate (34% and 44%) ($\chi^2 = 5.1 \text{ on } 1 \text{ df}, P = 0.02$) may be better in patients who were managed by anterior restorative resection.

**Curative resection**

Curative resection as earlier defined was found to be an extremely important factor in prognosis. In 519 patients who were considered to have undergone curative resection, the five year survival rate was 56% compared to only 13% of 304 patients who had residual disease at the time of operation ($\chi^2 = 209.7 \text{ on } 1 \text{ df}, P < 0.001$). It has already been noted above that the mobility of the tumours significantly affects the number of curative sections performed.
Figure 4 Mobility of tumour related to disease-free survival.

Table VI Mobility of tumour related to prognosis

<table>
<thead>
<tr>
<th>Fixity of tumour</th>
<th>Mobile</th>
<th>Tethered</th>
<th>$\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curative resection rate</td>
<td>80 (2)</td>
<td>44 (3)</td>
<td>117.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Local disease-free rate</td>
<td>5 yr</td>
<td>70 (2)</td>
<td>37 (3)</td>
<td>80.5</td>
</tr>
<tr>
<td>Survival rate</td>
<td>5 yr</td>
<td>48 (3)</td>
<td>29 (2)</td>
<td>29.1</td>
</tr>
<tr>
<td>Disease-free survival rate</td>
<td>5 yr</td>
<td>41 (3)</td>
<td>23 (2)</td>
<td>27.1</td>
</tr>
</tbody>
</table>

Table VII Number of quadrants involved related to prognosis

<table>
<thead>
<tr>
<th>Number of quadrants involved</th>
<th>1</th>
<th>2-4</th>
<th>$\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curative resection rate</td>
<td>72 (2)</td>
<td>55 (2)</td>
<td>27.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Local disease-free rate</td>
<td>5 yr</td>
<td>64 (3)</td>
<td>48 (3)</td>
<td>18.7</td>
</tr>
<tr>
<td>Survival rate</td>
<td>5 yr</td>
<td>47 (3)</td>
<td>33 (2)</td>
<td>16.7</td>
</tr>
<tr>
<td>Disease-free survival rate</td>
<td>5 yr</td>
<td>41 (3)</td>
<td>26 (2)</td>
<td>19.0</td>
</tr>
</tbody>
</table>
**Dukes' stage**

The probability of performing a "curative" resection was correlated with the Dukes' stage 91% of Dukes' A, 66% of Dukes' B and 58% of Dukes' C had a curative resection ($\chi^2=100.0$ on 2 df, $P<0.001$). The local disease-free rate is also related to Dukes' staging, being 82% at 5 years for patients with Dukes' Stage A, 63% for Stage B tumours and 42% for those with Stage C tumours ($\chi^2=77.9$ on 2 df, $P<0.001$). This parallels the highly significant differences in the survival (70%, 47% and 25%) ($\chi^2=108.8$ on 2 df, $P\leq0.001$) and the disease-free survival rates (65%, 31% and 20%) ($\chi^2=107.5$ on 2 df, $P<0.001$) of patients at 5 years in the Dukes' Stages A, B and C.

**Histological grade**

The histological grade of the cancer was recorded in 727 (98%) of 741 patients who had their operative specimen examined. There is an important difference in the 5-year local disease-free rate which is 69% for patients with low grade tumours, 62% for average grade and only 42% in the group of 111 patients with high grade lesions ($\chi^2=17.1$ on 2 df, $P<0.001$). The patients with low grade tumours had a 55% five year survival rate, whereas 45% of the patients with an average histological grading survived 5 years, as did 25% of the patients with high grade cancers ($\chi^2=25.2$ on 2 df, $P<0.001$). The disease-free survival is also strongly related to the histological grade of the tumour. A greater proportion of patients (51%) with low grade tumours than patients with average (36%) or high grade lesions (21%) were alive and free of disease at 5 years ($\chi^2=26.8$ on 2 df, $P<0.001$).

**Discussion**

The clinico-pathological features described in this paper have been extracted from the data of 824 patients recruited to the First MRC Trial of Pre-operative Radiotherapy in Operable Rectal Cancer (1982), who were treated in 17 centres in the United Kingdom.

In making the comparisons recorded in this paper it should be remembered not only that two-thirds of the patients had been given radiotherapy, but that the group of patients treated in this way had similar outcomes, curative resection rates, local disease-free rates and survival rates to the control group (Second MRC report, 1984). The protocol of this trial was designed specifically to recruit patients with operable cancers of the rectum and this may explain why the percentage of Dukes' A cases is higher than in other reported series. Yet only 49% of patients had completely mobile tumours on pre-treatment assessment. Another 30% of patients were reckoned to have partially fixed cancers also considered suitable for radical surgery and 15% of patients had fixed cancers at pre-treatment assessment, but were still considered operable. It is important to note that two-thirds of the patients with tethered tumours received radical surgery.

Patients eligible for admission to this trial had an operable adenocarcinoma of the rectum with lower margin within 15 cm from the anal verge. Since the mean diameter of the tumours was 4.7 cm this corresponds approximately to tumours whose centre is up to 17–18 cm from the anal verge. The majority of patients (68%) were managed by abdomino-perineal excision and only 21% of patients were considered suitable for anterior restorative resection. This reflects the fact that the trial began in 1975 and therefore antedated the stapling era in which lower resection and anastomosis have become more feasible for the general surgeon. It must also be considered whether surgeons refrained from anastomosing bowel in radiation-treated patients because of the risk of fistula. In the first report of the MRC trial of radiotherapy in operable cancer of the rectum the incidence of fistula was higher in the control group than in the irradiated patients. The survival rates for anterior restorative resection are usually reported to be better than those following abdomino-perineal excision of the rectum (Mayo et al., 1958; Deddish & Stearns 1961; Lockhart-Mummery et al., 1976) as was demonstrated, though not very significantly, in this trial. The relationship to prognosis of the operation performed may have been reduced because of the large numbers of surgeons involved in the trial. The entry criteria to the trial were however restricted to patients with rectal cancer only. If those patients thought to have a better prognosis and suitable for a sphincter-conserving operation in the upper rectum, i.e. tumours of the rectosigmoid and sigmoid, were added the advantage to the group receiving anterior restorative operation might have been further magnified. It should not, however be concluded that the operation is responsible for the improved prognosis, since tumours higher in the rectum may from their natural history be less lethal. Relating to this it was found that tumours were assessed to be mobile more frequently in the upper part of the rectum.

The operability rate in the series was 90% and of these 69% were considered to have had a curative resection, figures which are consistent with other published series (Lockhart-Mummery et al., 1976). The surgeons' assessment in this series that a curative resection had been performed agreed closely with the long-term prognosis.
The overall survival and disease-free survival rates were found to be strongly related to features determined at pre-treatment assessment; the single most important of which was the mobility of the primary cancer. Fixity of the tumour significantly reduced the probability of achieving a curative resection. This was subsequently reflected in a poorer disease-free survival in this group compared with patients who had mobile tumours. Evidence of local extension in relation to fixity, more than one quadrant involved and Dukes' Stage C generally indicated a poor prognosis as had been emphasised in other reports (Wood et al., 1981).

Yet a Dukes' C case could be either fixed or mobile, while the corollary was established that small tumours, less invasive through the wall, could readily have lymph node metaseses. It is therefore not surprising that many mobile tumours turned out to be Dukes' C stage. More surprising are the 12 instances of clinically fixed tumours which were reported as Dukes' A stage (Table III). One has to conclude that mobility may not always be accurately assessed by the surgeon for a number of reasons, among which may be included a wrong clinical appraisal but also surrounding inflammatory reaction. Nevertheless, despite the accepted margin of error in this assessment, it remains an important pre-operative prognostic factor (Figure 4).

Patients over the age of 70 years had a worse prognosis than younger patients. It was also found that patients with cancer arising >8 cm from the anal verge had a better disease-free survival rate than patients with lower lying cancers, although the curative resection rates were similar. Patients with only one quadrant of the rectum involved had a higher rate of curative resections and a higher disease-free survival rate than those with more extensive cancers. In view of the importance of these factors, all of which may be assessed pre-operatively, it would now seem possible to devise a method of clinical prognostic staging for patients with rectal cancer. Zorzitto et al. (1982) have suggested one such system. They do not include all the factors which we have found to relate to prognosis although their results agree with ours in that mobility of the tumour is found to be an assessment of primary importance. A clinical staging system would be useful in delineating those patients for whom adjuvant therapy might be considered, particularly if the adjuvant therapy were to be given pre-operatively. Dukes' staging, the histological grade of the cancer (Mayo et al., 1958) and the surgeons' assessment of a curative operation were all very strongly related to the prognosis, as is well documented in the literature but can only be used post-surgery. The analysis presented here has identified factors which individually relate to prognosis. Many of these factors are inter-related and the independent effects of each factor on prognosis need to be disentangled. Multivariate analysis of the data may help to achieve this and if so should form the basis of sound clinical and clinico-pathological staging systems for rectal cancer.

We wish to thank Mary Stone, previously of the MRC Statistical Research and Services Unit, Bethan Smith of the MRC Cancer Trials Office for co-ordinating the data collection and Petra Macaskill of the MRC Cancer Trials Office for computer programming. The surgeons radiation oncologists and pathologists are as listed in the First report of an MRC Working Party (1982).

References


Surgical Aspects of Intestinal Injury Due to Pelvic Radiotherapy

PAUL A. HATCHER, M.D.,* HUGH J. THOMSON, CH.M., SUSANNE N. LUDGATE, F.R.C.R., WILLIAM P. SMALL, CH.M., ADAM N. SMITH, M.D.

Seventy-one patients with intestinal injury secondary to pelvic irradiation had predominantly large bowel lesions. Seventeen cases were treated conservatively and 54 came to surgery, 28 patients having more than one operation. Following this essentially salvage surgery there were more ileal than colonic anastomotic leaks. Thirty-four patients died during the follow-up period (2-12 years), 19 from recurrent malignancy, and nine as a result of continuing radiation effects. Seventy per cent of the patients who had a radiation fistula died as a result of malignancy. Of 4200 cases of pelvic malignancy treated by irradiation over the decade 1972-1982, surgical referrals for complications constituted 1.7%, with an overall radiation-related mortality of 0.2%. It is our opinion that colostomy alone has little part to play in this condition, and a policy based on excisional surgery is suggested.

Radiotherapy plays an important part in the treatment of many abdominal and pelvic malignancies, including carcinoma of the cervix, bladder, and more recently, rectum. The radiation dose that can safely be administered is limited by the tolerance of the surrounding pelvic and abdominal tissues. Fifty per cent to 70% of patients suffer from acute side-effects, the majority of which respond to medical measures. Chronic radiation damage may affect sigmoid colon, rectum, cecum, ileum, and bladder, and two per cent to 17% of patients may require surgery for late complications at these sites. The incidence of radiation damage is rising with modern techniques, as increasing field sizes are employed in an attempt to improve cure rates. This study examines the pattern of radiation injury of the intestine, its management, and its outcome in patients treated in one surgical unit. Anseline et al. have suggested a conservative approach to fistulae, strictures, and proctitis by proximal colostomy. Our evidence is that a more radical approach is beneficial.

Patient Group

Between July 1972 and December 1982, 71 patients were referred to the Department of Surgery at the Western General Hospital, Edinburgh, with intestinal complications attributable to pelvic irradiation. These cases have been reviewed, and the diagnosis of radiation-induced injury accepted only if histological evidence was available on biopsy (Fig. 1) or surgically resected specimen (Fig. 2), or if typical radiological appearances were seen (Fig. 3).

The group comprised 16 male and 55 female patients aged 36 to 82 years. The primary sites of tumour for which the patients had received radiation therapy are shown in Table 1, almost half having been treated for cervical carcinoma. Most patients received 3000-5500 centigrays as external beam radiotherapy, and for patients with carcinoma of the cervix this was followed by intracavitary insertions of radium or cesium. Two patients with carcinoma in situ of the cervix had intracavitary therapy alone.

Results

The majority of patients presented to the surgical unit with abdominal pain and altered bowel habit (Table 2), with associated blood or mucus in the stools of those with damaged sigmoid colon or rectum. Late nausea and vomiting were mostly associated with small bowel injury. Chronic gastrointestinal symptoms were evident a median of 4.2 months postradiotherapy, and a median of 5.9 further months elapsed before surgery. Figure 4 shows that the rectum and sigmoid colon were most often the site of radiation damage, followed by the ileum and cecum. The nature of the pathology is shown in Tables 3 and 4. Stricture was the most common complication in the sigmoid colon, and fistulae were commonly located in the ileum or rectum.

Conservative Group

Fifteen patients were successfully managed conservatively with medical measures, including parenteral nutrition, steroids systemically or by enema, transfusion...
for blood loss, and intravenous fluids and nasogastric suction for episodes of obstruction. Bulking agents and dietary agents were occasionally of some benefit. A further patient had diathermy of a radiation ulcer in the rectum, and one other had the rectum packed for hemorrhage from a similar lesion.

**Surgical Group**

Fifty-four patients did not respond to conservative measures and required surgery: 18 patients had two operations, four had three operations, four had four operations, and two patients had five operations. Two additional patients had diagnostic laparotomy only and are not included in the analysis. Forty-three patients (80% of operated cases) had one or more bowel resections: 25 of these had a colostomy prior to, or at the time of resection, and this was subsequently closed in 15 patients. Colostomy without resection was performed in eight cases, and all of these patients were left with a permanent stoma. Twenty-four patients had one or more colocolic or colorectal anastomoses; these included eight cases who had the whole rectum excised with sphincter preservation by a sleeved coloanal anastomosis. Ten patients had ileocolic anastomoses and nine ileoileal anastomoses. Eleven patients developed 23 fistulae, 20 involving the gastrointestinal tract (Table 4).

**Anastomotic Problems**

Four cases of established anastomotic leakage occurred in 48 anastomoses—three out of ten ileocolic anasto-
moses leaked and all three patients died. One of the nine ileoileal anastomoses leaked and further resection was followed by a small bowel fistula that closed with conservative management. Although no colocolic, colorectal, or coloanal anastomotic leak was proven, three patients developed postoperative pericolic abscesses, and these may well represent cases of minor leakage. One patient whose ileal stricture was bypassed by ileotransverse anastomosis developed a fistula to the bladder and died of sepsis. No patient required revisional surgery for stoma problems.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma cervix</td>
<td>35</td>
</tr>
<tr>
<td>Carcinoma bladder</td>
<td>19</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>7</td>
</tr>
<tr>
<td>Carcinoma prostate</td>
<td>3</td>
</tr>
<tr>
<td>Carcinoma ovary</td>
<td>3</td>
</tr>
<tr>
<td>Carcinoma uterus</td>
<td>1</td>
</tr>
<tr>
<td>Carcinoma anus</td>
<td>1</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>1</td>
</tr>
<tr>
<td>Postmenopausal bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
</tr>
</tbody>
</table>

**Unsuccessful Surgery**

In a total of nine further patients, surgery was considered to have been unsuccessful, and these are detailed as follows. Three patients who had anterior resections developed recurrent stricture; one of these patients underwent further resection and one had a permanent loop sigmoid colostomy. Three further patients who had a resection developed recurrent proctitis requiring permanent defunctioning colostomies. One patient had a temporary colostomy closed which had to be reestablished due to recurrent rectal stenosis. A case of rectovesical fistula treated by Hartmann's procedure later required abdominoperineal excision of the rectum on account of a fistula from the rectal stump to the cecum, and subsequently died of pelvic sepsis and hemorrhage. A further patient with a rectovesical fistula who initially had a transverse colostomy died from massive hemorrhage per rectum.

**Deaths**

Thirty-four patients had died by the end of the study in December 1983. Of the remainder, 31 had been followed for more than 2 years following completion of...
radiotherapy, 17 for more than 5 years, and 12 for more than 10 years. Of those who succumbed, six died from incidental causes, 19 from recurrent malignancy, and nine from side-effects of irradiation.

Three of the nine whose death was attributable to the complications of radiotherapy died as the result of ureteric obstruction: two of these had septicemia (one of whom also had an ileovesical fistula), and one had renal failure. Three further patients died from massive hemorrhage associated with uncontrolled pelvic sepsis, and three had an anastomotic dehiscence with peritonitis.

Discussion

During the decade 1972–1982, approximately 4200 patients received pelvic irradiation in the Department of Radiation Oncology of the Western General Hospital in Edinburgh, and 71 of these patients (1.7%) were referred to the Department of Surgery. In recent years in the management of pelvic malignancy there has been a tendency to increase the treatment field size with the aim of improving cure rates. The incidence of intestinal complications has increased,6,7 in spite of more accurate estimation of dosage and the introduction of central pelvic shielding. Most patients (74% in our hospital) suffer acute side-effects such as diarrhea or vomiting during and immediately after treatment, but in the majority these settle with symptomatic measures. While some patients have continuing bowel symptoms, most have a respite for some months before serious radiation damage becomes apparent. In this study some patients were asymptomatic for as long as 4½ years. The mean time of referral for surgical opinion was 28 months (median 4.2 months) after irradiation. Jackson10 also found that the majority of patients had symptoms within 1 year of radiotherapy, whereas Kwitko et al.11 found a mean interval of 4.7 years.

The patients reported here represent a selected group with symptoms severe enough to warrant surgical referral, with 76% coming to major surgery. A quarter of patients considered for surgery had previous intraperitoneal surgery, and it has been suggested that adhesions may immobilise loops of bowel in the pelvis, making them especially susceptible to radiation damage.12 Moss et al.13 found type of lesion varied according to the area affected: stricture was seen more commonly in colorectal damage and fistula in the ileum. Almost half of the patients who required surgery had had previous intraperitoneal surgery, and it has been suggested that adhesions may immobilise loops of bowel in the pelvis, making them especially susceptible to radiation damage.12 Moss et al.13 found

<table>
<thead>
<tr>
<th>Nature of Radiation-Induced Pathology and Surgical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiation Damage to Sigmoid Colon and/or Rectum (56 Patients)</strong></td>
</tr>
<tr>
<td>Inflammation only (18)</td>
</tr>
<tr>
<td>- 8 Resections (4 permanent and 2 temporary colostomies)</td>
</tr>
<tr>
<td>- 2 Colostomy only (permanent)</td>
</tr>
<tr>
<td>- 8 Managed conservatively</td>
</tr>
<tr>
<td>Stricture (32)</td>
</tr>
<tr>
<td>- 18 Resections (4 permanent and 9 temporary colostomies)</td>
</tr>
<tr>
<td>- 4 Colostomy only</td>
</tr>
<tr>
<td>- 10 Managed conservatively</td>
</tr>
<tr>
<td>Radionecrosis and perforation (3)</td>
</tr>
<tr>
<td>- 2 Resections (1 permanent and 1 temporary colostomy)</td>
</tr>
<tr>
<td>- 1 Permanent loop colostomy</td>
</tr>
<tr>
<td>Fistulae (5)</td>
</tr>
<tr>
<td>(See Table 4)</td>
</tr>
<tr>
<td><strong>Radiation Damage to Ileum/Cecum (32 Patients)</strong></td>
</tr>
<tr>
<td>Inflammation only (9)</td>
</tr>
<tr>
<td>- 3 Resections</td>
</tr>
<tr>
<td>- 6 Managed conservatively</td>
</tr>
<tr>
<td>Obstruction Due to Adhesions or Stricture (10)</td>
</tr>
<tr>
<td>- 5 Resections (1 subsequent ileotransverse bypass)</td>
</tr>
<tr>
<td>- 2 Bypass (ileotransverse anastomosis)</td>
</tr>
<tr>
<td>- 3 Division adhesions</td>
</tr>
<tr>
<td>Radionecrosis and Perforation (6)</td>
</tr>
<tr>
<td>- All resected</td>
</tr>
<tr>
<td>Fistulae (10)</td>
</tr>
<tr>
<td>(See Table 4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fistulae Following Pelvic Radiation (11 Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileocolic (4)</td>
</tr>
<tr>
<td>- 3 Excised</td>
</tr>
<tr>
<td>- 1 Closed spontaneously</td>
</tr>
<tr>
<td>Recto-/Colo-vesical (4)</td>
</tr>
<tr>
<td>- All had colostomy carried out, which was not closed.</td>
</tr>
<tr>
<td>Ileocutaneous (3)</td>
</tr>
<tr>
<td>- 2 Resections</td>
</tr>
<tr>
<td>- 1 Managed conservatively (recurrent carcinoma)</td>
</tr>
<tr>
<td>Colocutaneous (2)</td>
</tr>
<tr>
<td>- 1 Resection</td>
</tr>
<tr>
<td>- 1 Managed conservatively (recurrent carcinoma)</td>
</tr>
<tr>
<td>Vesicovaginal (2)</td>
</tr>
<tr>
<td>- 1 Ileal conduit</td>
</tr>
<tr>
<td>- 1 Managed conservatively (recurrent carcinoma)</td>
</tr>
<tr>
<td>Ileovesical (2)</td>
</tr>
<tr>
<td>- Both managed conservatively</td>
</tr>
<tr>
<td>Cecocutaneous (3)</td>
</tr>
<tr>
<td>- Abdominoperineal excision of rectum</td>
</tr>
<tr>
<td>Colovaginal (2)</td>
</tr>
<tr>
<td>- Colostomy</td>
</tr>
<tr>
<td>Ileovaginal (1)</td>
</tr>
<tr>
<td>- Resection</td>
</tr>
<tr>
<td>Vesicocutaneous (3)</td>
</tr>
<tr>
<td>- Ileal conduit</td>
</tr>
</tbody>
</table>
that 25% of patients with gastrointestinal complications of radiotherapy for carcinoma of the cervix had had previous surgery. Kwitko et al. found that 24 out of 31 patients with ileal damage had previously had pelvic surgery, but in this study, at ten out of 21 patients, the proportion with previous surgery who developed small bowel damage was the same as the proportion who had rectosigmoid damage.

Eleven patients with rectosigmoid injury had a loop sigmoid colostomy alone as the initial treatment. In three cases this was done because disseminated malignancy was found at operation, and none survived more than 6 months. Of the remaining eight, two declined further surgery, but two died of pelvic sepsis and hemorrhage, and four required further surgery for persistent symptoms. It therefore appears that a proximal colostomy does not prevent progression of radiation changes in the defunctioned bowel, and indeed closure of such a colostomy is often followed by recrudescence of symptoms, as happened in three patients in this series. No patient in this study required surgery for complications of a colostomy itself, and this contrasts with the experience of Deveney et al., who reported that seven out of 32 patients with a colostomy developed necrosis and paracolostomy fistulation. It is clearly important to choose healthy bowel for formation of a colostomy.

Like defunctioning colostomy, bypass of a diseased segment of bowel may allow progression of radiation damage. It was the policy in this series to excise affected bowel whenever possible. Three patients, however, did have ileotransverse anastomoses to bypass ileocecal disease: two did well, but one patient developed a fistula from the bypassed ileum into the bladder and died from septicemia. Poor results from bypass have been reported by others, who recommend that it should be avoided, but Lillemoe et al. reported good results in nine out of 11 patients who had damaged ileum bypassed.

While left-sided colonic anastomoses are considered less secure than those in other sites in nonirradiated patients, all four cases of established anastomotic dehiscence in this series occurred among the 19 ileal anastomoses (ileoileal or ileocolic). In contrast there was only suspected leakage in three of 28 colonic anastomoses (colocolic, colorectal, or coloanal). When grossly diseased distal ileum is excised, the integrity of the anastomosis may be prejudiced by a minor degree of radiation damage more proximally, not apparent to the naked eye. The greater mobility of the small bowel increases the likelihood of fairly proximal small bowel coming down into the pelvis and hence being exposed to radiation effects. Colocolic and colorectal anastomoses were less subject to such problems because the colon brought down for an intrapelvic anastomosis is commonly the transverse colon and, as such, well away from the radiation area. Eight coloanal anastomoses were performed to eradicate distally placed disease, and all healed well without undue problems, although later one had to have an anastomotic dilatation.

It is clearly important to examine carefully the nine deaths resulting from the side-effects of radiation. The three patients with anastomotic leakage have already been discussed. Of those remaining, in three cases fibrosis and inflammation in the pelvis resulted in ureteric obstruction, and urinary sepsis or failure. In one of these patients, repeated attempts to fashion an ileal urinary conduit had been unsuccessful due to extensive small bowel damage. Uncontrolled sepsis always carries the risk of erosion of major vessels, and three patients died from hemorrhage in the presence of pelvic sepsis. Two of these had rectovesical fistulae which had been managed by defunctioning colostomy alone, and the third had a pelvic abscess following four operations for multiple fistulae. Only one of the nine patients who died directly from the effects of radiation had overt recurrent malignancy at the time of death.

The 11 patients with fistulae form a more complex group. Eight of these died of recurrent malignancy by the end of the study, indicating that they constitute a group with a poor prognosis regardless of the radiation problems, and suggesting that the presence of a fistula implies wider dissemination of the malignant process than may be recognized at first.

A reduction in the incidence of complications of pelvic irradiation might be achieved by decreasing the radiation dose. This, in the view of most radiation oncologists, would inevitably lead to a higher incidence of recurrent malignancy. To avoid this in turn, and maintain a thorough standard of tumor treatment, it seems that an incidence of complications from radiotherapy must be accepted.

Most of the effects of radiation in the gastrointestinal tract settle spontaneously, and it must be emphasized that serious complications affect only a small proportion of patients whose cancer has been effectively treated by radiotherapy. The majority of problems arising in patients referred to surgical units are, however, grievous enough to require remedial surgery. By delaying intervention in many instances, it becomes clear whether the principal problem is one of recurrent malignancy or radiation damage. This work suggests that, contrary to the findings of Anseline et al., direct surgical excision can eliminate diseased bowel with comparative safety. The number requiring such surgery is relatively small—over 98% of patients treated for pelvic cancer by irradiation never develop chronic problems. The results of excision of irradiated left colon in our series lead us to believe that the risks of anastomotic dehiscence are less than those for small bowel anastomosis following irra-
diation, which is a reversal of the accepted pattern. The most difficult area is surgery for fistulae. Although this may at first appear successful, over two-thirds of patients may be expected to succumb to recurrent malignancy. Yet the relief of symptoms by palliative surgery makes operation worthwhile in this group also.

Acknowledgments

The authors would like to thank Professor W. Duncan of the Department of Radiation Oncology, and Dr. A. Busuttil of the Department of Pathology, Western General Hospital, Edinburgh, for their assistance with this study.

References

Mucosal proctectomy and colo-anal anastomosis for distal ulcerative proctocolitis

J. S. Varma*, G. G. P. Browning†, A. N. Smith*, W. P. Small† and W. Sircus†

*University Departments of Surgery/Urology and Gastrointestinal Unit, Western General Hospital, Edinburgh EH4 2XU, UK
†Correspondence to: Professor A. N. Smith, University Department of Surgery/Urology, Western General Hospital, Edinburgh EH4 2XU, UK

The conventional surgical treatment of diffuse idiopathic ulcerative colitis is by proctocolectomy with either ileostomy or, in carefully selected patients, ileo-anal anastomosis with a pelvic reservoir. In approximately 20% of patients with ulcerative colitis the disease remains confined to the rectum and sigmoid colon. The treatment of segmental colitis by excision of only the affected part of the large bowel remains controversial. Clark and Ward reported the results of excision of the rectum and distal sigmoid colon with the establishment of a permanent colostomy in four patients. Although all four patients eventually developed proximal extension of the colitis, only one of them required coloectomy and ileostomy after 5 years. A report of four similar patients from St. Mark's Hospital made a case for limited excision. In Stahlgren and Ferguson's series of 18 patients treated in this way, 7 required total colec­tomy and ileostomy by 5 years. The same authors reported recurring distal ulcerative proctocolitis by excision of the affected bowel and restoration of intestinal continuity by caco-anal anastomosis. We report the late clinical results in four such patients treated by Parks' colo-anal sleeve anastomosis.

Patients and methods

Details of the four patients treated between 1979 and 1985 are shown in Table 1. The mean age was 42 years and the mean duration of symptoms was 10 years. The symptoms included bloody diarrhoea, frequency and urgency of defaecation and occasional incontinence. All four patients had undergone prolonged and intensive medical therapy but these incapacitating symptoms were uncontrolled by conservative measures. The diagnosis was established by clinical, histological and radiological features. All patients had undergone repeated colonoscopic assessment of the large bowel with multiple biopsies. These had shown a distal ulcerative proctocolitis clearly demarcated on histological criteria from healthy proximal colon. The proximal extent of the colitis in each patient is shown in Table 1. Only in one patient (patient 3) was there any evidence of proximal progression of the disease over the years from initial diagnosis to operation. In this patient the colitis had extended from the sigmoid colon to the descending colon. These patients were under surveillance by the inflammatory bowel disease medical review clinic of the Gastrointestinal Unit and were referred as possibly suitable for sphincter preservation by segmental colorectal excision. They were thought particularly suitable for a colo-anal anastomosis because of the limited extent of their left-sided colitis and because this had remained anatomically static for several years (Table 1). In addition three of the patients were relatively young and reluctant to accept a permanent stoma. Details of the technique are described elsewhere.

The proximal site of section was determined by the pre-operatively determined extent of the colitis. Protecting loop transverse colostomies were fashioned in the right upper quadrant in two patients and loop ileostomies in the other two. Stomas were closed when the anastomosis was clinically healed, and any stenosis had been dilated. The mean time to closure of the stoma was 15 weeks. Follow-up has ranged from 12 to 66 months (mean 32 months). Three patients have been followed-up for more than 5 years. At each clinic visit continence and bowel function were assessed objectively and the distal bowel examined by sigmoidoscopy.

Results

There was no operative mortality. The early complications (one fissure-in-ano, one thrombosed haemorrhoid, one subacute obstruction) were managed successfully by conservative measures. Frequency of defaecation in the early period after closure of the protecting stoma was a common feature. The late complications are of more interest. There was one anastomotic stricture which required repeated dilatation (patient 2). Symptomatic recurrence of the colitis occurred in all four patients (mean time 6 months after operation). Diarrhoea with frequency, urgency and occasional incontinence were the predominant symptoms.

In three patients this relapse did not respond to medical management and required total proctocolectomy with ileostomy. This was performed 24, 12 and 18 months after the colo-anal operation. The histopathology of the excised colon showed involvement of the entire colon in all three patients. The fourth patient has similar symptoms but is reasonably controlled by medical measures more than 5 years after operation. She is continent of solid stool but has occasional incontinence with loose bowel motions and wears an incontinence pad. The precise proximal extent of the colitis in this patient is not known.

There was no apparent relationship between the time to recurrence of the colitis and the pre-operative extent, severity or progression of the disease in this small group.

At the initial operation the macroscopic extent of disease in the resected specimen related accurately to the pre-operative assessment by colonoscopy and biopsies. A clear line of demarcation was easily seen between healthy and affected colon in the excised specimen (Figure 1).
Distal ulcerative proctocolitis: J. S. Varma et al.

Table 1 Clinical details of four patients with limited distal ulcerative colitis

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>Proximal pre-operative extent of colitis</th>
<th>Duration of symptoms (years)</th>
<th>Symptoms/complications</th>
<th>Protecting stoma and time to closure (weeks)</th>
<th>Time to extension of colitis postoperatively (months)</th>
<th>Time to proctocolectomy and ileostomy postoperatively (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>28</td>
<td>F</td>
<td>Sigmoid colon</td>
<td>9</td>
<td>Diarrhoea, haemorrhage, structure (13cm)</td>
<td>Loop transverse colostomy (15)</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>2.</td>
<td>39</td>
<td>F</td>
<td>Descending colon</td>
<td>18</td>
<td>Diarrhoea, haemorrhage, polyp</td>
<td>Loop ileostomy (20)</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>3.</td>
<td>59</td>
<td>F</td>
<td>Descending colon</td>
<td>10</td>
<td>Diarrhoea, haemorrhage, abdominal pain</td>
<td>Loop ileostomy (11)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>40</td>
<td>M</td>
<td>Rectum</td>
<td>3</td>
<td>Diarrhoea, haemorrhage, abdominal pain</td>
<td>Loop transverse colostomy (15)</td>
<td>6</td>
<td>18</td>
</tr>
</tbody>
</table>

Figure 1 Resected colon showing the clear demarcation between the inflamed and healthy mucosa

Discussion

The rectum is the commonest site of involvement in ulcerative colitis and the only site in approximately 20 per cent of cases. So-called 'idiopathic proctitis' differs from ulcerative colitis only in the extent of bowel involvement and appears to carry a better prognosis. Lennard-Jones et al. followed up 100 patients with 'idiopathic proctitis' of whom only four later came to operation. Proctocolectomy is the accepted treatment for uncontrolled colitis affecting the colon diffusely or segmentally. Clark and Ward, however, concluded that where incapacitating symptoms result primarily from rectal involvement, treatment by excision of the rectum is worthy of consideration. They treated four such patients by rectosigmoid excision and colostomy. All these patients developed symptomatic proximal extension of the colitis but only one needed to have a total colectomy with ileostomy at 5 years. Their maximum follow-up was 6 years.

A similar series from St. Mark's Hospital reported two recurrences out of four but they were able to be controlled medically. Stahlgren and Ferguson treated 18 patients with rectosigmoid excision and terminal colostomy. Seven patients required completion of the colectomy with ileostomy by 5 years and a total of 10 patients by 10 years. They, nevertheless, argued that this approach was justified on the assumption that colostomy, even if only for a few years, is preferable to ileostomy. Other workers, however, have recommended ileostomy as a far easier stoma to manage when rectal excision is required, and there is some evidence for this preference. The results of restorative caeco-anal pull-through operations are somewhat conflicting. Johnston et al. reported four out of five early failures although Roediger et al. appear to suggest promising long-term results.

We have treated four patients by excision of the left colon and colo-anal sleeve anastomosis, thus precluding the need for a permanent stoma. This technique, first described by Parks, has been used for a variety of rectal conditions including large rectal haemangiomas, extensive villous adenomas of the rectum, rectovaginal fistulae, low rectal carcinomas and severe radiation injury to the rectum. However, its validity in the treatment of segmental proctocolitis does not appear to have been recorded. The patients chosen for this study represented a very select group with segmental left-sided colitis and were unwilling to accept a stoma. Therefore, it was felt to be justifiable to perform a less extensive procedure than an ileo-anal pouch operation. Acceptable results have been previously reported with limited excision for right-sided colitis.

Furthermore, our long-term results for radiation proctocolitis treated by this procedure appeared encouraging. Several factors may be implicated in the aetiology of the poor functional results. The early postoperative symptoms probably represent reduced rectal capacity and might be expected to improve. Transposition of the transverse colon to the pelvis can itself result in a permanent hypermotile state in approximately 10-15 per cent of patients. However, extension of the colitis was largely responsible for the disappointing results, further aggravating symptoms by its effects on colorectal motility and stool consistency. Some internal anal sphincter dysfunction may also be present due to stretching of this muscle for the pararectal anastomosis. It must be noted, however, that one patient manages well without a stoma more than 5 years after operation. This is in keeping with the observations of other studies of limited excision, where some patients achieved months or years of symptom remission. Unfortunately, it is not possible to select these patients pre-operatively as the reasons for recurrence remain unknown. Late results of the treatment of severe distal radiation proctocolitis by this operation are considerably better compared with the ulcerative colitis group. This is simply due to the different aetiological background in these inflammatory bowel diseases.

Despite the small number of patients reported, this long-term study suggests that colo-anal sleeve anastomosis does not have a place in the surgical treatment of segmental proctocolitis. Alternatives such as proctocolectomy with ileostomy or, preferably, ileo-anal anastomosis with a pelvic ileal reservoir are recommended.
Acknowledgements

J.S.V. was supported by a Wellcome Trust Research Grant No. 121964 L and the British Digestive Foundation (Scottish Appeal).

References


Br. J. Surg., Vol. 74, No. 5, May 1987
Postanal repair and intersphincteric Ivalon sponge rectopexy for the treatment of rectal prolapse

Twenty-four consecutive patients (mean age: 74 years) with complete rectal prolapse, fifteen of whom were incontinent of solid stool, have been treated by postanal repair and intersphincteric Ivalon sponge rectopexy. There was no operative mortality, or serious morbidity. There was one recurrence of complete prolapse which occurred 14 days after operation. The other 23 patients have been followed for up to 4 years. All patients who were incontinent of solid stool pre-operatively have been rendered continent. This type of operation may be the treatment of choice in the elderly, where an abdominal procedure is considered unwise and in cases of rectal prolapse associated with faecal incontinence.

Keywords: Rectal prolapse, faecal incontinence

Complete rectal prolapse is associated with faecal incontinence and occurs predominantly in the elderly. Many procedures have been designed for the treatment of rectal prolapse and may be divided into abdominal and perineal procedures. It is widely held that an abdominal procedure is the best method to reduce and fix a complete rectal prolapse. The operations in common use are the Ivalon sponge rectopexy (Wells1) and the Marlex mesh rectopexy (Keighley2). The results of abdominal procedures are good with regard to control of the prolapse but the problem of associated faecal incontinence is far from solved with more than a third of patients remaining incontinent despite a successful rectopexy2,3,5. A proportion of these patients may require a secondary continence procedure2,6. The concept of a perineal procedure to reduce and fix a complete rectal prolapse is nearly 100 years old and there has been a recent revival of interest in this approach; in particular the perineal rectopexy described by Wyatt7 and the Delorme procedure8, whose advocates suggest that it is the preferred procedure in the elderly and frail. The popularity of Thiersch’s circumferential wiring and its modifications has waned over the years because of poor results achieved in control of the prolapse and concomitant difficulties with defaecation following the procedure8; often the encircling materials fracture, or ulcerate through the skin, requiring repeat procedures to be undertaken9,10,11.

All previously described procedures have been designed with the primary aim of treatment of the prolapse and not for their effect on associated faecal incontinence. We describe a new technique designed with the aim of restoring continence, in addition to the treatment of the prolapse. It combines a postanal repair with an Ivalon sponge rectopexy performed via the intersphincteric plane.

Patients and methods

Patients

Twenty-four patients (twenty-two women) aged 41–93 years (mean: 74 years, median: 76 years) had the operation between June 1982 and May 1986. Fifteen of the patients were incontinent of solid stool. Five had previous surgery for prolapse, two a Wells Ivalon sponge rectopexy and four the insertion of Thiersch wires. Seventeen of the twenty-four patients (70 per cent) were over 70 years at the time of the operation.

Surgical procedure

Patients were prepared for surgery with castor oil and rectal washouts. Antibacterial chemotherapy with co-trimoxazole 960 mg and metronidazole 500 mg IV was given preoperatively and for 24 h postoperatively. Under general or spinal anaesthesia the patient was placed in the lithotomy position and following standard skin preparation adrenaline 1:30000 in 0·9 per cent NaCl was infiltrated into the subcutaneous tissue between the coccyx and the anus. A curved incision was made bisecting the line between the anus and coccyx, convex posterior. The anterior flap of skin and subcutaneous tissue was raised to expose the sphincter complex. The intersphincteric plane was then developed using blunt and sharp dissection. Waldeyer’s fascia was divided above the puborectalis to enter the retrorectal space. This space was developed as high as possible by mobilizing the rectum from the sacral fascia, allowing the sacral curve to be seen. A 10 x 12 cm rectangle of Ivalon sponge was placed on to the sacrum. The rectum was allowed to fall back towards the sacral curve, resting on the bed of Ivalon sponge. A standard postanal repair12 was then performed, using braided nylon suture (Nurilon, Ethicon) to form a lattice between one side of the levator ani and the other, starting as high as possible at the iliococcygeus muscles. In separate layers further lattice sutures were inserted to draw together the subpubococcygeus, puborectalis and finally the external sphincter muscle posterior to the anal canal. It was important not to put excess tension in these lattice sutures in the upper layers of the levator musculature. The wound was closed with silk sutures after trimming of the redundant skin to gain a perfect closure.

Following surgery the patients were nursed in a lateral position for two days. From the third day two glycerine suppositories were inserted daily to ensure the patient had a comfortable bowel action and to reduce straining at stool.

Follow up was at 1 month, 3 months and 6 monthly thereafter. Assessment of continence was by direct questioning and whether patients required continence pads.

Results

Perioperative

The operation was well tolerated by this elderly group of patients. Three patients had the operation under spinal anaesthetic. In two patients the posterior wall of the rectum was breached during mobilization and the defects were closed by suture. These patients had not had previous surgery for prolapse. The operation time was between 45 min and 1 h. There was minimal intra-operative blood loss and no pulmonary or cardiovascular complications.

J. Rogers and P. J. Jeffery

Department of Surgery, Weymouth and District Hospital, Melcombe Avenue, Weymouth, Dorset, UK

Correspondence to: Mr P. J. Jeffery

© 1987 Butterworth & Co (Publishers) Ltd
APPENDIX III  (Contributions recorded by title only)


ACKNOWLEDGMENT

Miss Mary Wilson, formerly senior secretary in the Gastro-intestinal Unit and Department of Surgery, Western General Hospital, University of Edinburgh, assisted in the production of many of these papers and in the compilation of this thesis, while the author was successively Reader in Surgery and Honorary Research Fellow of the Department of Surgery and Wade Professor of Surgical Studies of the Royal College of Surgeons of Edinburgh.