THE AETIOLOGY OF DIVERTICULOSIS OF THE COLON WITH SPECIAL REFERENCE TO THE ACTION OF CERTAIN DRUGS ON THE BEHAVIOUR OF THE COLON

Hunterian Lecture delivered at the Royal College of Surgeons of England
on
28th November 1963
by

Neil Stamford Painter, M.S., F.R.C.S., D.Obst., R.C.O.G.
Senior Surgical Registrar, Northampton General Hospital*

INTRODUCTION

THE HUNTERIAN COLLECTION of this College contains a specimen that shows colonic diverticula, but unfortunately there is no mention of them in the writings of John Hunter. During the last century colonic diverticula were described (Cruvheilhier, 1849; Habershon, 1857; Lane, 1885), but they were regarded merely as a pathological curiosity until Graser (1899) pointed out that they were potentially dangerous. In the next few years, the complications of diverticulitis were recognized (Mayo *et al.*, 1907; Moynihan, 1907; Taylor and Lakin, 1910), and finally classified by Telling and Gruner (1917). It was only after the advent of radiological methods of examining the colon (de Quervain, 1914) that the prevalence of diverticulosis was realized. Spriggs and Marxer (1925) described the radiological appearances of the disease and advocated a medical regime that included a low residue diet in its treatment. Surgery was reserved for those complications of the disease that threatened life, and resection of the affected bowel was rarely undertaken until Smithwick (1942) showed that this could be accomplished with an acceptable mortality. His competent advocacy of more aggressive surgery was followed by advances in anaesthesia and the antibiotics, so that to-day elective resection of the colon for diverticulitis is a standard procedure.

Despite this progress in the treatment of established diverticulosis we are still unable to prevent its onset or halt its progress. It will therefore present a problem of increasing magnitude in our ageing society until some light is shed on the factors responsible for its causation.

FACTORS THAT MAY BE RESPONSIBLE FOR DIVERTICULOSIS

The anatomy of the colon has a direct bearing on the site of diverticula. The longitudinal muscle is grouped into taenia and normally it is between these taenia that diverticula emerge, usually in company with the blood vessels that pierce the circular muscle. These blood vessels further weaken the colonic musculature and predispose to diverticulosis to the same extent as the spermatic cord does to inguinal herniae (Drummond, 1917).

* From the Nuffield Department of Clinical Medicine, The Radcliffe Infirmary, Oxford, and the Nuffield Institute for Medical Research, Oxford.

However, this structural weakness is common to all colons, and other factors have been invoked to explain the defects in the colonic musculature in diverticulosis. The effects of age (David, 1933), fatty atrophy and debility (Edel, 1894) have been blamed and obesity was once thought to be important (Gross, 1845; Klebs, 1869), but, as the disease occurs in other than fat subjects, obesity has been discarded as an aetiological factor (Horner, 1958). Edwards (1934*a* and *b*) showed that in the " prediverticular state " the colonic musculature is uneven in thickness so that the mucosa is at times separated from the serosa by only a few muscle fibres, but this is no proof that diverticulosis is due to an initial abnormality of the colonic wall.

Whatever part the anatomy or the degeneration of the colonic wall play in the causation of diverticula, the mucosal herniation must be due to the force of intracolonic pressure. As this pressure is unknown (Thompson, 1959), the symptoms of distension have been interpreted as evidence of raised intracolonic pressure. Constipation, straining at stool and flatulence also have been thought to affect the sigmoid (Cruvheilhier, 1849; Bristowe, 1854; Miles, 1920; Telling, 1920), but these symptoms are not constant accompaniments of the disease (Todd, 1955) and would appear to be the result rather than the cause of diverticulosis. Disordered colonic muscular activity and " spasm " of the sigmoid also have been thought to be responsible for the disease (Judd and Pollock, 1924; Feldman and Morrison, 1949; Bevan, 1961), but Edwards (1954) failed to establish any causal relationship between spastic colon and diverticulosis.

The only experimental work that bears on the aetiology of diverticulosis is that of Carlson and Hoelzel (1949). These investigators carried out life span studies in 252 rats. Rats fed a low residue diet developed diverticula, while those whose similar diet was augmented with hemicellulose were almost unaffected by the disease. Rats who were first fed a bulky diet and later a low residue diet were most prone to the disease. No study of dietary habits has been made in man in relation to diverticulosis, but it is said to be rare in the West African Native, who eats a bulk-forming diet (Wells, 1949).

To sum up, all theories regarding the aetiology of diverticulosis rest ultimately on the deduction that diverticula result from an inherent weakness in the muscularis propria, high intracolonic pressure or a mixture of these two factors. As the colonic wall has been studied painstakingly without any initial defect in its structure being convincingly demonstrated, it seems probable that the intracolonic pressure may be at fault.

In an attempt to settle this question, it was decided to take the advice that John Hunter gave to Jenner, and to " try the experiment " by measuring these pressures. The full account of the methods used and the detailed results of these investigations are to be found in a thesis accepted for the degree of Master of Surgery in the University of London (Painter, 1962).

Method

The pressure in the human sigmoid colon was recorded by means of three open-ended water-filled polythene tubes connected to a Cambridge Three Channel Pressure Recorder with direct pen-writer. These tubes were inserted into the colon of volunteer subjects through a sigmoidoscope which was then withdrawn. Each tube was tipped with metal to allow the point of recording to be located radiologically. These tips were 7.5 cm. apart so that pressure could be recorded at three levels in the sigmoid simultaneously. The tube farthest up the bowel was called Lead 1, that nearest the anus Lead 3 and the other Lead 2.

The pressures were recorded on squared paper which moved at constant speed, so that 5 mm. represented four seconds recording time. A deflection of 5 mm. of the pen represented a pressure of 10 mm. Hg. When ciné-radiography was employed, one channel was converted to mark the tracing as each frame was exposed at the rate of one frame per second; this facilitated the joint analysis of pressure tracing and ciné-film. The squared paper moved twice as fast during ciné-radiography so that 5 mm. represented two seconds recording time.

TABLE I

NUMBER OF SUBJECTS STUDIED AND LEADS FROM WHICH PRESSURE TRACINGS WERE OBTAINED WHILE INVESTIGATING THE ACTION OF MORPHINE

	Resting pattern		*After morphine*	
	Number of subjects	*Number of leads analysed*	*Number of subjects*	*Number of leads analysed*
Normal	32	66	21	42
Diverticulosis	28	20 (related to diverticula) 31 (not related to diverticula)	25	19 (related to diverticula) 26 (not related to diverticula)

The intrasigmoid pressures were recorded for one hour with the subject at rest to yield the " Resting Pattern " and for another hour after a drug had been given to obtain the " Post-drug Pattern ".

Results

The number of subjects studied and the number of leads from which pressure tracings were obtained are given in Table I. The tracings were analysed in the manner of Chaudhary and Truelove (1961). The amplitude and duration of each wave were measured regardless of the shape of the wave, so that the average number of waves of any specific dimension registered by one lead in one hour could be calculated. In this way the activity of the healthy sigmoid could be compared with the sigmoid in diverticulosis both before and after drugs. The Colonic Motility Index of Chaudhary and Truelove was also determined for each lead. This index is an approximate measure of the " total pressure " recorded by one lead in one hour as it takes into account both the height of the pressure

waves and their duration, and it allows the average amount of pressure produced by two groups of colons under different conditions to be compared. The detailed results of these pressure studies will appear elsewhere (Painter and Truelove, awaiting publication) and only the more important findings will be mentioned here.

The resting pattern of pressures in the normal sigmoid colon (Fig. 1)

The basal pressure in the normal sigmoid colon remains within a few millimetres of mercury of atmosphere. Upon this basal pressure small waves of positive pressure are superimposed at irregular intervals, usually occurring singly but occasionally in series. The number of waves produced varied greatly from subject to subject and in the same subject on different days. The majority of waves lasted for between 10 and 30 seconds. Eighty per cent. reached a height that was less than 10 mm. Hg and few exceeded 20 mm. Hg in amplitude.

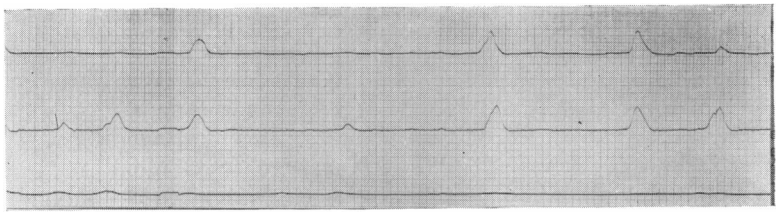

Fig. 1. The pattern of pressures in the normal sigmoid colon. The typical shape of the pressure waves can be seen in this tracing which represents six minutes of recording time. The basal pressure remains near atmosphere and waves of positive pressure are superimposed on it. The highest wave shown represents a pressure of 30 mm. Hg.

Pressures were frequently recorded by one lead while its neighbour registered no change of pressure. No temporal relationship between waves was observed that suggested that pressures progressed towards the anus so as to pass each lead in turn. It appeared that the pressure at one level in the sigmoid was independent of that at another level and that the sigmoid could localize pressure to the immediate vicinity of a recording tip.

The resting patterns of pressure in the sigmoid colon in diverticulosis

These pressure tracings were examined to see whether abnormal intraluminal pressures were present in diverticulosis, but there was no obvious difference between them and the tracings obtained from healthy colons. The variability of the simple wave forms and the irregular occurrence of waves that had been seen in the healthy colon were again observed. Moreover, the basal pressure was again within a few mm. Hg of atmosphere. No evidence was obtained to suggest that diverticulosis is accompanied by " intraluminal hypertension ".

It was then remembered that parts of the sigmoid that bear diverticula are frequently structurally different from their neighbours (Fig. 2). It therefore seemed possible that their different structure might lead to the production of different pressure patterns. So the tracings were subdivided according to the relationship of the recording tips from which they were derived to diverticula. Tracings obtained from leads whose tips were judged to be related to diverticula were analysed separately from those whose tips were situated in apparently normal segments of the sigmoid in diverticulosis. However, when the pressure patterns " related to diverticula " were compared with those that were " not related to diverticula " they were found to be essentially the same. This was confirmed by quantitative analysis of the tracings. No preponderance of high

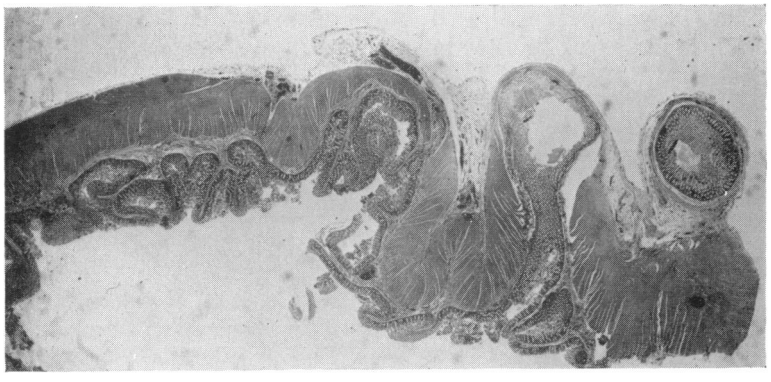

Fig. 2. Diverticulosis coli. Longitudinal section of sigmoid colon showing two diverticula. The bowel on the left of the illustration is apparently normal while that on the right is obviously diseased. The muscle coat is folded into two layers between the diverticula and between these folds the muscle is thinned or absent. The change in structure from normal to diseased bowel is abrupt.

pressures was recorded from the vicinity of diverticula and so no evidence was obtained to suggest that diverticulosis is caused by abnormal intracolonic pressures.

The effect of morphine on the pressures in the normal sigmoid colon

Morphine sulphate gr. $\frac{1}{6}$ was given either intravenously or intramuscularly to normal subjects after the resting pattern had been recorded for one hour. An intravenous injection of morphine changed the intrasigmoid pressure almost at once and was followed by the rhythmic generation of pressure waves for some minutes (Fig. 3). These would then cease and a period of a few minutes during which the pressure would remain at the basal level would follow. After this a similar cycle of rhythmic pressure production would follow, and this sequence of events usually would be repeated throughout the remainder of the hour's record-

ing. When given intramuscularly, morphine took effect in about 12 minutes and again caused the colon to generate pressure waves rhythmically for a few minutes and then to remain quiescent before repeating this sequence of rhythmic pressure production.

Morphine doubled the number of pressure waves in the sigmoid. These were usually less than 20 mm. Hg in height, but sometimes reached to 40 mm. Hg. These waves appeared to be produced independently at the three levels of the gut as the movements of the recording pens were not synchronous even when all three pens were active. The similarity of the waves forms (Fig. 3) suggested that they owed their origin to the same mechanism and that morphine activated this mechanism. (This mechanism was later found to involve segmentation of the sigmoid colon, see below.)

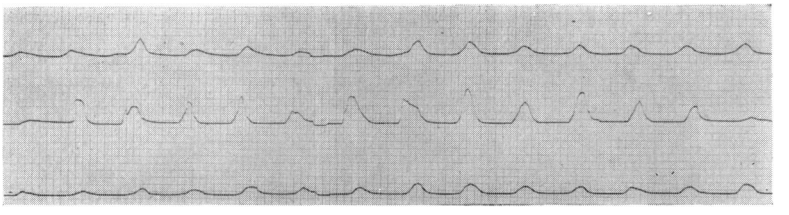

Fig. 3. The pressure pattern in the normal sigmoid after morphine. A succession of pressure waves is seen at all three levels of the sigmoid colon. The highest wave reached 45 mm. Hg. The similar form of these waves suggested that they were all caused by the same mechanism.

The effect of morphine on the intrasigmoid pressures in diverticulosis

The " post-morphine " tracings were subdivided according to whether they were derived from tips that were related to the diverticula or not. The pattern of pressures recorded from leads whose tips were not related to diverticula did not differ significantly from the pattern in the healthy sigmoid after morphine and so merits no further description.

However, the tracings recorded from the immediate vicinity of diverticula were markedly different. Morphine caused the segments of the sigmoid that bore diverticula to generate very high pressures (Fig. 4). While the rhythmic occurrence of waves of low pressure was again observed, these were interspersed with waves of very high pressure, whose ascending and descending limbs were very steep. Frequently pressures greater than 50 mm. Hg were recorded and sometimes the limits of the apparatus were exceeded, showing that these pressures may rise to heights of over 90 mm. Hg. These high pressures often followed one another in rapid succession, being only separated from each other by an interval of a few seconds.

Waves greater than 50 mm. Hg occurred only about once in five hours in the normal colon and diverticulosis under basal conditions. After morphine the frequency of occurrence of these waves hardly altered in the healthy colon and in segments of the sigmoid that did not bear diverticula in diverticulosis, but in the segments that bore diverticula these high pressures were generated every 24 minutes.

Clearly morphine evoked a different response from the diseased segments, showing that under certain conditions these segments are capable of functioning differently from their neighbours and from segments of the normal colon.

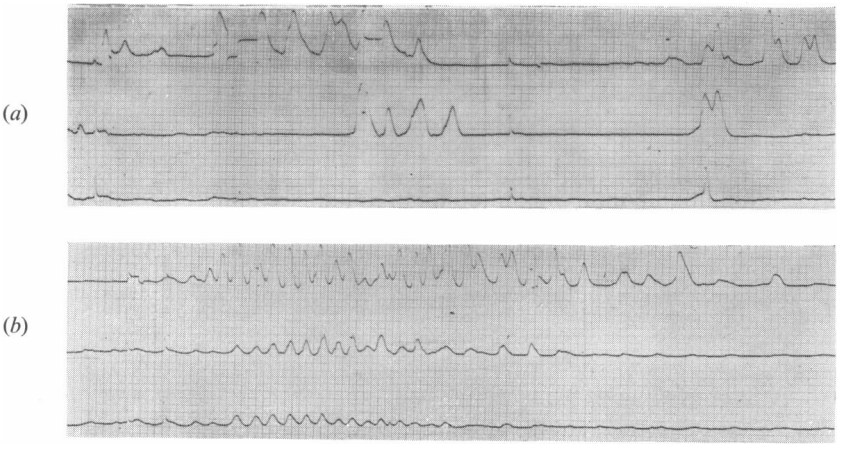

Fig. 4. The pressure pattern in the sigmoid colon in diverticulosis after morphine. (*a*) Upper tracing: The top two leads recorded very high pressures of up to 76 mm. Hg from the vicinity of diverticula. Note that high pressures recorded by the top lead did not always affect the middle lead, whose tip was only 7.5 cm. distant. The lowest lead was below the level of the diverticula and was unaffected by these pressures, showing that the sigmoid can localize pressure to the region of one recording tip. (*b*) Lower tracing: Top lead recording succession of waves of 60 mm. Hg from the neighbourhood of diverticula after morphine, in a subject recovering from acute diverticulitis.

The effect of prostigmine on the intrasigmoid pressures

Neostigmine methylsulphate (prostigmine) has a parasympathetico-mimetic action due to its ability to inhibit cholinesterase. It is thought to require an intact nerve supply to the gut if it is to exert its full effect, which is greatest on the colon (Goodman and Gillman, 1955). It may be considered as a physiological stimulus in that it enhances the effect of naturally occurring stimuli that reach the colon. The drug was given intramuscularly in a dosage of 1 mg. to 12 healthy subjects and to 12 with diverticulosis to see whether another drug, unrelated to morphine, would evoke a different response from the diseased segments.

In health, prostigmine caused pressure waves to occur more frequently. In particular it evoked more high waves of long duration than did morphine, but it also differed from morphine in that it did not cause pressures to be produced so rhythmically. Otherwise the effect of the drug in health was not remarkable.

In diverticulosis, prostigmine has a more marked effect. Waves of complex form consisting of several peaks were seen more commonly (Fig. 12). Waves of all amplitudes were recorded four times as often, but, unlike morphine, prostigmine did not cause the segments that bore diverticula to produce a preponderance of waves of high pressure. However, they did cause these segments to generate more high waves of long duration lasting for more than 40 seconds than the other types of segment. When both height and duration were taken into account, it became obvious that the diseased segments produced more " total pressure "

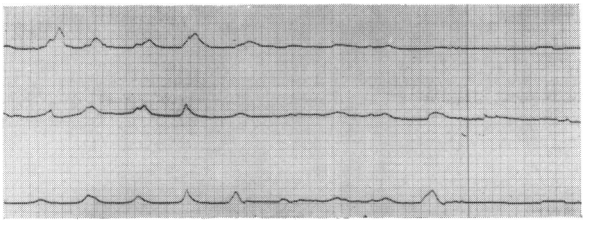

Fig. 5. The effect of probanthine on the pressures in the sigmoid colon that follow the use of morphine. The completion of an intravenous injection of probanthine is indicated by the vertical line on the tracing. The production of pressure waves that morphine had evoked ceased almost at once. Probanthine also abolished the high pressures that occurred in diverticulosis after morphine (see Fig. 4*b*).

than the unaffected segments after prostigmine. Thus, prostigmine evoked an exaggerated response from the diseased segments, but this response differed from that seen after morphine.

The effect of pethidine on the intrasigmoid pressures

The effect of 100 mg. of pethidine was studied given intramuscularly in six healthy subjects and in five with diverticulosis. Pethidine caused no dramatic change in the pressure patterns either in health or diverticulosis. It diminished both the frequency of occurrence and the dimensions of the waves whether the recording tips were situated in the vicinity of diverticula or not. After pethidine, pressures of over 20 mm. Hg were rare and no wave that exceeded 50 mm. Hg was recorded, either in health or diverticulosis.

The effect of probanthine on the intrasigmoid pressures

Probantheline bromide (probanthine) was given intravenously in a dosage of 30 mgm. to nine healthy subjects and to six with diverticulosis, all of whom had received morphine in the preceding hour. Within seconds

of its injection, the drug stopped all pressure production so that the intraluminal pressure remained at the basal level for the remainder of the experiment (Fig. 5). Probanthine was equally effective in abolishing the high pressures that followed morphine in a patient recovering from acute diverticulitis (Fig. 4*b*) and in stopping pressures evoked by prostigmine.

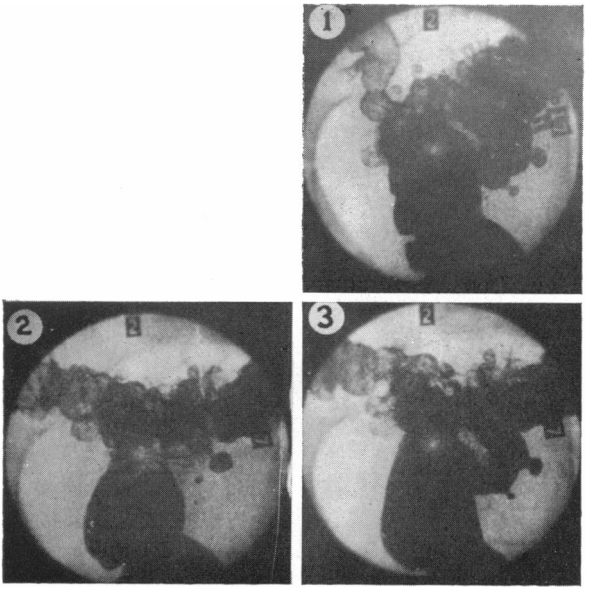

Fig. 6. The effect of drugs on diverticula. The two diverticula that are seen in the right lower quadrant of these frames of ciné-radiographic film altered in size in response to drugs. (1) Appearance before morphine. (2) After morphine. (3) After probanthine had reversed the changes wrought by morphine.

Ciné-radiographic findings

These pressure studies raised two questions:

1. Are diverticula affected by the high pressures that follow the use of morphine?

2. By what mechanism does the colon produce pressures and how does it localize pressure to the region of one recording tip, so that another tip only 7.5 cm. away remains unaffected by this pressure?

Ciné-radiography was used simultaneously with intraluminal pressure recording to link the behaviour of the sigmoid colon with the changes of pressure that occur within it.

The bowel was outlined with about 100 c.c. of a commercial barium suspension (micropaque) which was injected through one of the polythene tubes. This small amount of barium was used to avoid distension of the

colon. The frames of ciné-film reproduced in this paper represent a field that was five inches in diameter. A more detailed account of these studies will be given elsewhere (Painter *et al.*, awaiting publication).

The effect of drugs on the behaviour of the colon in diverticulosis

Like other herniae, diverticula are initially reducible, and ciné-radiography showed that they varied in size according to the pressure in the bowel from which they arose, enlarging as it contracted and becoming smaller as it relaxed. Under basal conditions these changes were usually

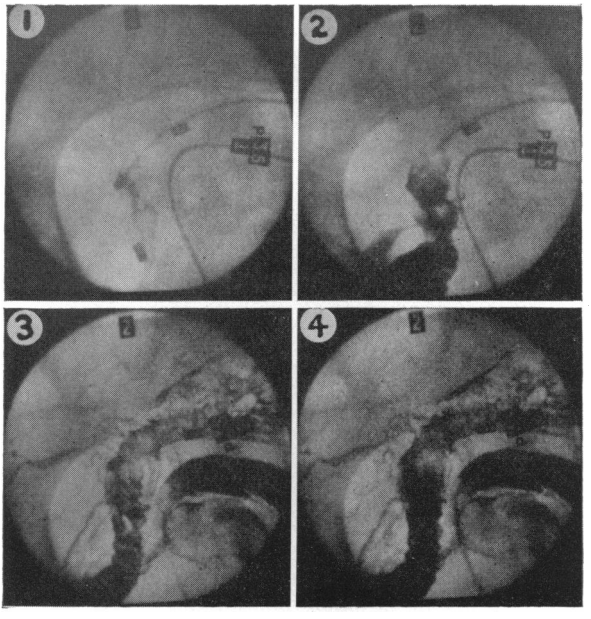

Fig. 7. The effect of pethidine on the sigmoid in diverticulosis. The upper two frames show recording tubes in the sigmoid colon which segmented in response to an injection of barium into its lumen. The lower two frames show it after pethidine, when it failed to respond to the same stimulus. (For description, see text.)

only moderate in amount, but after morphine or prostigmine the appearances of both colon and diverticula altered considerably.

Figure 6 shows frames of ciné-radiographic film of the colon of a woman of 70 years old. The two diverticula in the lower right-hand quadrant of the film varied in size spontaneously under basal conditions, enlarging as the loop of sigmoid bearing them contracted and becoming smaller as it relaxed. An intravenous injection of morphine was made while filming and this caused the bowel bearing the diverticula to narrow in about 20 seconds. Simultaneously the necks of the diverticula narrowed and the

diverticula enlarged markedly as barium was forced into them. The necks of the diverticula were at times completely occluded, but they reopened at intervals to allow barium to pass between the lumen and the diverticula. The movements of the colon were increased generally after morphine.

This was not a temporary effect that only occurred immediately after the injection of morphine, as a film taken 40 minutes later showed that the sigmoid was still active and the diverticula were still distended. Probanthine was given during this film and it stopped all movements of the colon during the next 130 seconds. Probanthine caused the colon to dilate so rapidly that it appeared to freeze into immobility. Concurrently the necks of the diverticula reopened and allowed barium to drain into the relaxed sigmoid so that the diverticula reverted to their former size.

These films show that morphine can cause distension of diverticula. The degree of protection from the intrasigmoid pressure that the narrowing

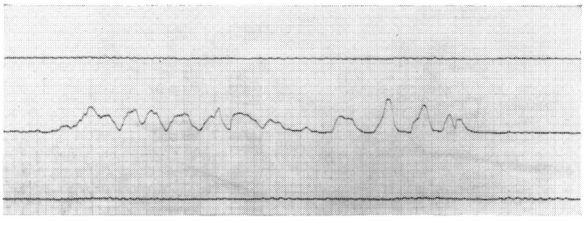

Fig. 8. The localization of pressure by the sigmoid colon. The tracing shows six minutes of recording time. After morphine a normal colon produced pressures of up to 40 mm. Hg, which were only recorded by the middle lead, while the other two leads, whose tips were situated only 7.5 cm. distant on each side, were unaffected by these pressures. Clearly, the sigmoid can localize pressure to a few of its segments.

of the necks of diverticula affords the herniated mucosa is unknown, but it is certain that this pressure caused the diverticula to be blown up like balloons.

The changes wrought by morphine vary with the state of the bowel and the degree of diverticulosis present. In the early stages of diverticulosis, morphine was seen to cause the colonic mucosa to herniate as the actual appearance of a diverticulum was filmed. This diverticulum disappeared later when the bowel relaxed, confirming that diverticula are reducible initially. When the disease is of long standing the colonic musculature may be damaged by recurrent inflammation so that it cannot narrow the necks of diverticula. They then remain exposed to the full force of the pressures that follow the use of morphine.

Pethidine reduces the number and height of the pressures in the sigmoid, and ciné-radiography showed that it achieved this effect by lessening the excitability of the colonic wall. Figure 7 shows three tubes in the sigmoid. Twenty cubic centimetres of barium were injected via the middle tube

while the other two tubes recorded pressure. This injection caused the colon to segment around the tips of the tubes and waves of 19 mm. Hg and 15 mm. Hg were recorded. Simultaneously two small diverticula were extruded from one of the segments thus demarcated.

After pethidine, another injection of barium failed to produce segmentation. The sigmoid stayed open like a drain as the barium flowed through it. The configuration of the bowel wall did not alter as it had before pethidine and hence offered no resistance to the passage of the barium. No change of pressure occurred. The diverticula remained undistended with open necks connecting them to the colonic lumen. Clearly pethidine

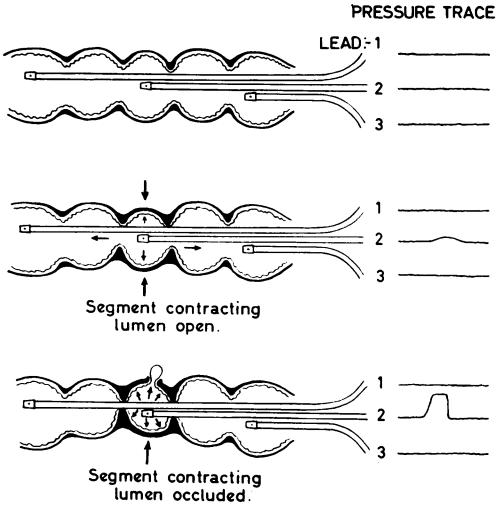

Fig. 9. Diagram to show the role of segmentation in the production of localized intracolonic pressures. (For description, see text.)

had reduced the excitability of the sigmoid so that it failed to respond to a stimulus that had previously excited it.

Segmentation and the pressures in the sigmoid colon

During these investigations, it became obvious that the colon could localize high pressures to the region of the tip of one recording tube. This was particularly apparent after morphine when high pressure might be registered by one lead while another, whose tip was only 7.5 cm. distant, was unaffected by this pressure (Fig. 8). Ciné-radiography combined with pressure recording revealed the mechanism responsible for this effect. It became clear that the colon localized pressure by altering the configuration of its wall as it was seen to be segmented in the vicinity of any tip that was recording changes of pressure. The colonic segments were defined by interhaustral contraction rings which narrowed and at times

completely occluded the colonic lumen, so that the colon functioned, not as a tube, but as a series of " bladders ".

The mechanism by which the colon produces localized pressures is shown in Figure 9. The top section shows a colon containing three recording tubes together with the relevant pressure tracing. Apart from the resistance due to their viscosity, the contents of this colon, being free to move through its open lumen, would offer almost no resistance to movements of the colonic wall and so the intraluminal pressure would hardly alter. In the middle section, one segment is partly separated from its neighbours by the contraction of the interhaustral rings which bound it. This segment's further contraction would be opposed by its contents, whose movements would be hampered by the narrowing of the lumen that has occurred. Pressure would develop and would be recorded by Lead 2, while Leads 1 and 3, being in open bowel, would record no change of pressure. In the bottom section, one segment is isolated from its fellows. Very high pressure would result if this segment contracted forcibly as its contents cannot escape. This pressure would only be recorded by Lead 2.

Two factors are involved in the production of localized pressure, first, segmentation and, second, contraction of the intervening segmental wall. When both factors operate, the colon is converted into a series of " bladders " whose outflow is obstructed and in which pressures may develop.

Forty-eight subjects were examined with ciné-radiography, and whenever pressures were recorded the relevant ciné-film showed the colon to be segmented about the recording tip, except on three occasions. On these three occasions, the recording tip was situated in a part of the sigmoid whose lumen was shut for a considerable distance. This radiological appearance is often loosely described as " spasm ", but equally it can be regarded as an extreme form of segmentation in which both the interhaustral rings and the intervening segmental wall have contracted to their maximum extent.

Whether localized pressures occurred spontaneously, as a result of emotion, or whether they followed the administration of drugs or the injection of barium they were always accompanied by segmentation. The degree of segmentation usually varied directly with the amplitude of the pressure waves. Both prostigmine and morphine increased the intrasigmoid pressures and the degree of segmentation. The most marked segmentation was seen after these drugs in diverticulosis, and it was then that the highest pressures were recorded.

On the other hand, pethidine, which lessened the tendency of the sigmoid to segment, also diminished the intrasigmoid pressures (Fig. 7).

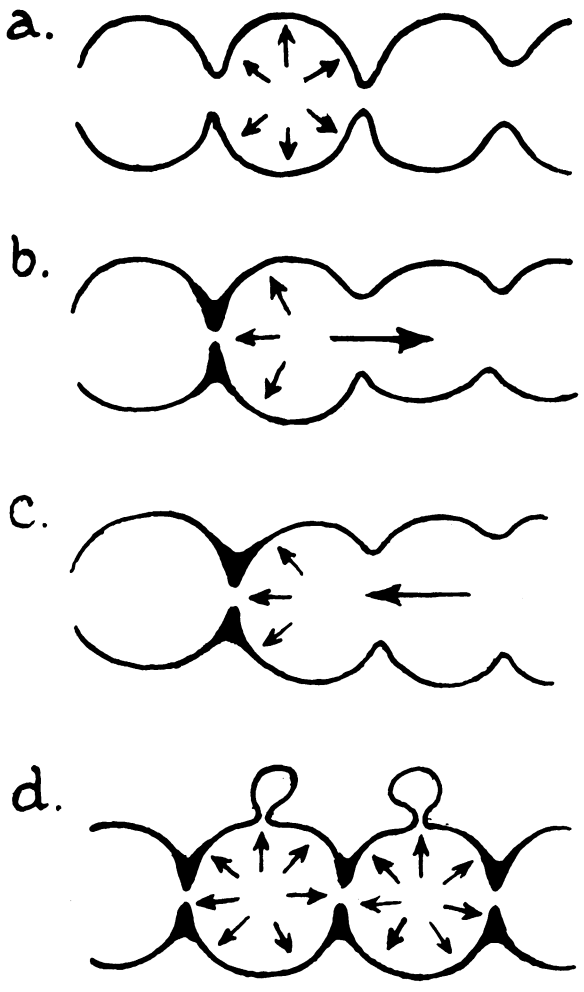

Fig. 10. The role of segmentation in colonic physiology (for description see text).

Probanthine paralysed the bowel musculature so that the colon was unable to segment. After probanthine the instrasigmoid pressure fell to and remained at the basal level, supporting the view that intracolonic pressures are the result of colonic muscular activity and not of passive distension of the bowel as has been suggested in the past.

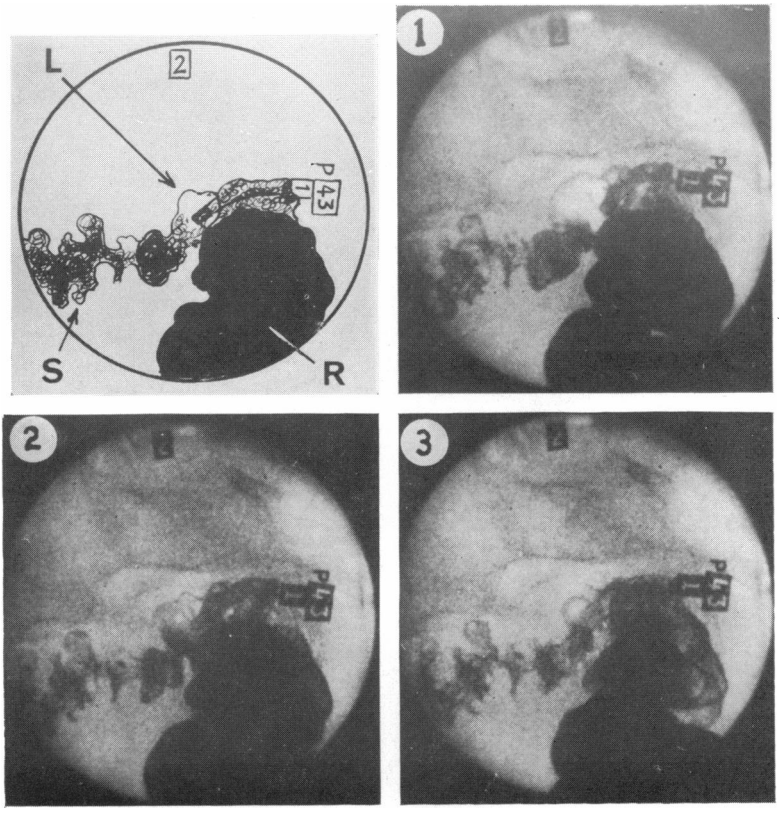

Fig. 11. The production of pressure by segmentation. The diagram shows the rectum (R) and sigmoid (S) of a patient with diverticulosis. The tip of a recording lead (L) is situated in a segment of the sigmoid. This segment was relaxed when it only harboured the basal pressure (Frame 1), but when it contracted, in an attempt to propel barium up the bowel, the pressure within it rose to 6 mm. Hg (Frame 2). As it contracted further, this pressure rose to 20 mm. Hg (Frame 3).

The role of segmentation in colonic physiology

Pressures produced by this " segmentation mechanism " play an important part in the transportation of the colon's contents. A segment may increase its contained pressure until it exceeds that harboured by its neighbours (Fig. 10*a*). If one of the contraction rings bounding this

segment then relaxes, the segment will pump its contents into the neighbouring bowel (Fig. 10*b*). Segmentation can slow or halt material that is moving through the sigmoid by narrowing or occluding the lumen, the interhaustral rings acting as baffles. The resistance offered to the moving

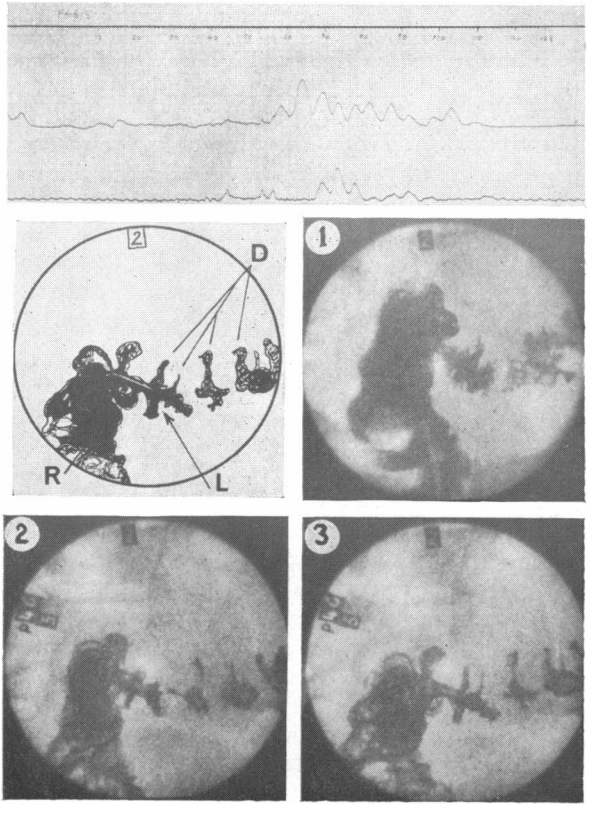

Fig. 12. The effect of prostigmine in diverticulosis. The pressure tracing shows a wave of 60 mm. Hg occurring after prostigmine. This was recorded by a lead (L in diagram) in the sigmoid, whose tip was in the immediate vicinity of diverticula (D). Before this pressure occurred, the diverticula were small (Frame 2), but they were distended as this pressure rose (Frame 3). Frame 1 shows this bowel before prostigmine had been given. Though it was less segmented, the diverticula were seen to fill better as their parent segments contracted.

contents causes a change in the intraluminal pressure (Fig. 10*c*). This may be considerable if material is propelled vigorously against a tightly closed contraction ring, as was often observed when barium was shunted to and fro in the sigmoid. No doubt the anatomical symmetry of the colonic segments enables them to function equally well in either direction.

Segmentation and the pathogenesis of colonic diverticula

When the healthy colon was studied by ciné-radiography, the contraction rings between the segments appeared to be constant in position in the bowel wall regardless of the degree of segmentation that was present and irrespective of the stimulus that had caused this segmentation to occur. This was also true in diverticulosis providing the disease was studied in its early stages. In the later stages of the condition it is well known that diverticula may fuse together (Fischer, 1900–01) or burrow intramurally (Cohen *et al.*, 1957) so that even their relationships with the segmental blood vessels is lost. Thus it was not surprising to find that the segmental arrangement of the colon was destroyed in some subjects who had suffered recurrent attacks of diverticulitis. Providing diverticulosis was studied in its uncomplicated state, the diverticula were always seen to arise from the wall of the colonic segments and never from the contraction rings between the segments. Moreover, this relationship of the contraction rings to the diverticula, which were fixed in their position, confirmed that the former were also constant in position.

This relationship of diverticula to their parent segments is represented diagrammatically in Figures 9 and 10*d* and can be seen in Figures 11 and 12.

Figure 12 shows the sigmoid of a man of 42 who had diverticulosis. When this film was projected the diverticula were seen to fill as the segments of the bowel from which they arose contracted. This was much more evident after the patient had been given prostigmine, which caused his sigmoid to become demarcated into segments by the intermittent occlusion of its lumen between the segments. These segments bore diverticula which enlarged as their parent segments contracted. A pressure of 60 mm. Hg was recorded by a tip in the lower sigmoid, and diverticula in the immediate vicinity of this tip were better filled as this pressure occurred. This sigmoid was functioning intermittently as a series of isolated " bladders " whose contractions produced the pulsion force that distended the diverticula arising from them.

DISCUSSION

1. The intrasigmoid pressures in diverticulosis

This systematic study of the intracolonic pressures in health and diverticulosis showed that when resting, the healthy sigmoid colon generates the same number of pressure waves of all dimensions as the colon that bears diverticula. Thus, no evidence was obtained to suggest that diverticulosis is caused by " intraluminal hypertension ".

However, this finding does not rule out the possibility that abnormal intraluminal pressures are to blame for diverticulosis as it may be that, under other than basal conditions, the diseased colon produces pressures

that are different from those in the normal colon. This suggestion is supported by the discovery that segments that bear diverticula react to two unrelated drugs, morphine and prostigmine, by producing pressure patterns that differ from those recorded from their neighbours and from segments of the healthy colon. Therefore it is possible that the diseased segments also react excessively to natural stimuli such as eating, drinking, defaecation and emotion, which are known to activate the colon.

Whether this ability of the affected segments to behave differently precedes the appearance of diverticulosis and is responsible for its causation or whether it is a result of the disease is as yet unknown. However, one subject was investigated in whom only a single diverticulum was detected and the segment that bore it responded to morphine by producing higher pressures than the neighbouring bowel. This suggests that this differential response is present in the early stages of the disease process and that it is at least responsible for the progressive nature of diverticulosis, even if it is not responsible for the initial appearance of the disease.

Although morphine and prostigmine cause the diseased segments to behave differently, their effects are not identical. Morphine leads to the production of an excess of high pressures, while prostigmine increases these waves in all types of segment. But prostigmine does evoke more high waves of long duration from the segments that bear diverticula, so that they produce and withstand more " total pressure " than their neighbours. It seems probable that the two drugs activate different groups of muscle fibres to differing extents, but at present our knowledge of colonic physiology is insufficient to explain these findings.

While these observations are of theoretical interest, the effect of morphine on the intrasigmoid pressures near diverticula is of practical importance. I have treated four patients with acute diverticulitis who did not develop generalized peritonitis until they had been treated expectantly for more than 24 hours. All were given morphine to relieve their pain, and in retrospect it seems possible that the drug may have been partly responsible for these failures of conservative treatment. Once it is realized that morphine can cause high intracolonic pressures that distend diverticula and that it may increase the movements of the colon, the wisdom of giving it as an analgesic in acute diverticulitis must be questioned. Furthermore, some authorities report that leakage of faeces occurs in nearly a quarter of anastomoses following anterior resection of the rectum; while the blood supply of these anastomoses is often impaired, it is possible that the postoperative administration of morphine also predisposes to their disruption.

These adverse side effects of morphine can be abolished by giving probanthine but this may cause a paralytic ileus. The value of probanthine in this respect awaits clinical trial, but in the meantime pethidine is readily available and it would appear to be the analgesic of choice in acute diverticulitis.

2. The role of segmentation in the aetiology of colonic diverticula

Segmentation is involved in the production of localized intracolonic pressure. The segmented colon does not function as an open tube but as a series of " little bladders " whose outlet is obstructed. These " bladders " by their contraction produce zones of high pressure. These pressures are initially confined to the segments that produce them so that they do not affect neighbouring segments. This segmentation mechanism of pressure production appears to be the final common mechanism that is responsible for the generation of localized intraluminal pressures, whether they occur spontaneously or as a result of emotion or whether they are evoked by drugs or by mechanical stimulation of the bowel. These pressures are caused by local muscular activity and are not the result of passive distension of the colon as has been suggested in the past.

The interhaustral or intersegmental contraction rings that are seen in life are the result of a differential contraction of the colonic wall, and this contraction appears to occur at the same point in the bowel wall regardless of the degree of segmentation present. These rings appear to be parts of the colonic wall that have a specialized function, namely to narrow and at times to occlude the colonic lumen, as they were never seen to relax while the intervening segmental wall contracted. This was true both in health and in diverticulosis, regardless of the stimulus that caused the colon to segment.

The recognition of the specialized function of these interhaustral rings enables the pathogenesis of diverticula to be better understood. Any theory that blames intracolonic pressure for the herniation of the colonic mucosa must explain the apparent paradox of concurrent strength and weakness of the colonic wall; for, if the muscularis propria is to be credited with the power to generate the pulsion force that drives the mucosa through the colonic wall, it must also be too weak to withstand this force.

These two apparently conflicting statements can be reconciled once it is realized that the muscle content of the intersegmental rings is augmented in amount (Poirier and Charpey, 1914) while the wall of the intervening segments is relatively weaker. This is very obvious in well established diverticulosis where the segmental wall may be very thin and the interhaustral rings consist of two layers of circular muscle (Fig. 2). Thus there is a structural basis, not only for the differential contraction of the intersegmental rings, but also for the relative weakness of the segmental wall between them, and it is through the weaker segmental wall that the mucosal herniation takes place.

The early investigators were immediately struck by the similar structure of colonic and vesical diverticula, and they were puzzled by the absence of any mechanical obstruction to the passage of the faecal matter (Bristowe, 1854). They were handicapped by being confined to the study of dead

tissues, as observation of the living colon shows that it can adopt a configuration that leads to its own temporary obstruction. The segmented colon functions as a series of bladders, which generate the pulsion force that drives the mucosa through the thinner segmental wall, usually where it is further weakened by the passage of the segmental blood vessels. The similar structure of colonic and vesical diverticula is thus explained.

Edwards (1934*a* and *b*) drew attention to the fact that even in the " pre-diverticular state " the circular muscle is uneven and thrown into ridges. Morson (1963) failed to find diverticula in specimens resected for clinical " diverticulitis ", but stressed that this muscle abnormality was already present. Their findings can be explained by postulating that the segments or bladders become trabeculated before the actual herniation of the mucosa takes place, and that diverticula are secondary to excessive segmentation of the colon.

In many of his specimens, Morson failed to find histological evidence of sufficient acute inflammation to account for the symptoms that had led to operation. It is possible that the pain of " diverticulitis " may sometimes be due to obstruction of the colon caused by excessive segmentation. The urinary bladder is painful when its outflow is obstructed even when it is not inflamed, and it may be that obstructed sigmoid " bladders " also are capable of causing pain in the absence of acute inflammation.

Although these remarks throw some light on the pathogenesis of diverticula, their aetiology remains unknown. The experimental work of Carlson and Hoelzel (1949) showed that the low residue diet caused rats' colons to become narrowed. They suggested that this led to obstruction of the colon at flexures so that pressure built up and caused diverticula to form. The recognition of the effect of segmentation on the intraluminal pressures allows another explanation to be put forward, namely, that the interhaustral rings, being smaller *ab initio* in the narrowed colon, are more readily brought into apposition by any further contraction that may occur. It is possible that a low residue diet leads to narrowing of the colon which renders segmentation more efficient so that pressures are produced more frequently. Similarly, the narrowing of the colon and the reduplicated interhaustral rings that are found in diverticulosis may increase the effectiveness of segmentation in producing pressure. This might account for the progressive nature of diverticulosis and for the different pressure response to drugs of the affected segments. By contrast, the distended colon of the West African native, referred to by Wells, is probably less able to segment and thus less likely to develop diverticula. Both Stout (1923) and Wilson (1950) agreed that contraction and not distension caused diverticula of the appendix, and ciné-radiography showed that the colon was less able to segment when it was distended with barium. It is possible, therefore, that a bulky diet lessens the probability of segmentation occurring and hence helps to prevent the onset of diverticulosis. If this is true,

the use of the low residue diet that is commonly recommended in the treatment of the disease may be actually harmful. Furthermore, we should study the effect of dietary habits to see what part they play in the causation of diverticulosis.

Segmentation is the hallmark of the colon that is capable of producing high localized pressures, and therefore the recognition of those factors that cause excessive segmentation to occur is likely to lead to the better understanding of the aetiology of diverticulosis coli.

ACKNOWLEDGEMENTS

This study was made with the collaboration of my colleague, Dr. S. C. Truelove. The ciné-radiographic investigations were performed with the cooperation of Dr. G. M. Ardran. Mr. M. Tuckey took the ciné-radiographic films. Dr. K. Lumsden helped me to interpret the radiographic appearances of the colon in diverticulosis. Dr. G. Dawes, Dr. F. Kemp and Professor L. J. Witts allowed me to use their departments. Professor P. R. Allison supported my application to the Nuffield Committee for financial support while engaged on this research. To these and many others I offer my sincere thanks.

REFERENCES

BEVAN, P. G. (1961) *Brit. med. J.* **1,** 400.
BRISTOWE, J. S. (1854) *Trans. Path. Soc. Lond.* **6,** 191.
CARLSON, A. J., and HOELZEL, F. (1949) *Gastroenterology*, **12,** 108.
CHAUDHARY, N. A., and TRUELOVE, S. C. (1961) *Gastroenterology*, **40,** 1.
COHEN, S. E., CUNNINGHAM, J. R., and SNEIERSON, H. (1957) *Arch. Surg., Chicago*, **75,** 800.
CRUVHEILHIER, J. (1849) *Traité d'Anatomie pathologique générale*, **1,** 593.
DAVID, V. C. (1933) *Surg. Gynec. Obstet.* **56,** 375.
de QUERVAIN, F. (1914) *Deutsch. Z. Chir.* **128,** 67.
DRUMMOND, H. (1917) *Brit. J. Surg.* **4,** 407.
EDEL, M. (1894) *Virchows Arch.* **138,** 347.
EDWARDS, H. C. (1934*a*) *Lancet*, **1,** 221.
———— (1934*b*) *Brit. J. Surg.* **22,** 88.
———— (1954) *Ann. Roy. Coll. Surg. Engl.* **14,** 371.
FELDMAN, F., and MORRISON, S. (1949) *Amer. J. digest. Dis.* **16,** 126.
FISCHER, M. H. (1900–01) *J. exp. Med.* **5,** 332.
GOODMAN, L. S., and GILLMAN, A. (1955) *The Pharmacological Basis of Therapeutics*, 2nd edit. New York, Macmillan Company.
GRASER, E. (1899) *Münch. med. Wschr.* **46,** 721.
GROSS, S. D. (1845) *Elements of pathological Anatomy*, p. 554. Philadelphia, Blanchard and Lea.
HABERSHON, S. O. (1857) *Observations on the Alimentary Canal.* London, Churchill.
HORNER, J. L. (1958) *Amer. J. digest. Dis*, **3,** 343.
JUDD, E. S., and POLLOCK, L. W. (1924) *Ann. Surg.* **80,** 425.
KLEBS, E. (1869) *Handbuch der pathologischen Anatomie*, p. 271. Berlin.
LANE, A. (1885) *Guy's Hosp. Rep.* **43,** 48.
MAYO, W. J., WILSON, L. B., and GIFFEN, H. Z. (1907) *Surg. Gynec. Obstet.* **5,** 8.
MILES, W. E. (1920) *Proc. Roy. Soc. Med.* **13,** Section of Surgery, p. 84.
MORSON, B. C. (1963) *Proc. Roy. Soc. Med.* **56,** 798.
MOYNIHAN, B. G. A. (1907) *Brit. med. J.* **2,** 1381.
PAINTER, N. S. (1962) M.S. Thesis, University of London.
———— and TRUELOVE, S. C. (Awaiting publication).
———— ARDRAN, G. M., and TUCKEY, M. (Awaiting publication).

POIRIER, P., and CHARPEY, A. (1914) *Traité d'Anatomie humaine*, **4**, 303.
SMITHWICK, R. M. (1942) *Ann. Surg.* **115**, 969.
SPRIGGS, E. I., and MARXER, O. A. (1925) *Quart. J. Med.* **19**, 1.
STOUT, A. P. (1923) *Arch. Surg., Chicago*, **6**, 793.
TAYLOR, G., and LAKIN, C. E. (1910) *Lancet*, **1**, 495.
TELLING, W. H. M. (1920) *Proc. Roy. Soc. Med.* **13**, 55.
——————— and GRUNER, O. C. (1917) *Brit. J. Surg.* **4**, 468.
THOMPSON, H. R. (1959) *Postgrad. med. J.* **35**, 86.
TODD, I. P. (1955) *Ann. Roy. Coll. Surg. Engl.* **16**, 118.
WELLS, C. (1949) *Brit. J. Radiol.* **22**, 449.
WILSON, R. R. (1950) *Brit. J. Surg.* **38**, 65.

HONOURS CONFERRED ON FELLOWS AND MEMBERS

IN THE RECENT New Year Honours List the following Fellows and Members were graciously honoured by Her Majesty The Queen.

SIR (EDWARD) CHARLES DODDS, P.R.C.P., M.R.C.S.	Baronet
SIR SOLLY ZUCKERMAN, C.B., M.R.C.S.	K.C.B.
EDWARD ROWAN BOLAND, C.B.E., M.R.C.S.	Knight Bachelor
VICTOR MARCUS COPPLESON, F.R.C.S.	,,
JOHN HENRY GADDUM, M.R.C.S.	,,
HERBERT JOHN SEDDON, C.M.G., F.R.C.S.	,,
IAN WILLIAM HUGH ROSE CRAN, M.R.C.S.	C.B.E. (Military)
ALWYN JAMES ARNOTT, F.D.S.R.C.S.	C.B.E. (Civil)
WILLIAM COOPER GISSANE, F.R.C.S.	,, ,,
LINLEY HENZELL, M.R.C.S.	,, ,,
THOMAS CECIL HUNT, M.R.C.S.	,, ,,
ROBERT GYWN MACFARLANE, M.R.C.S.	,, ,,
HAROLD JORDAN MALKIN, M.R.C.S.	,, ,,
FREDERICK HERMAN AITKEN WALKER, F.R.C.S.	,, ,,
IAN HARRIS COLLEY, M.R.C.S.	O.B.E. (Military)
PETER FRANCIS KING, M.R.C.S.	,, ,,
CYRIL LAWSON MCCLINTOCK, M.R.C.S.	,, ,,
DOUGLAS WILLIAM COWLEY GAWNE, F.R.C.S.	O.B.E. (Civil)
JOHN CHIVERS GRAVES, M.R.C.S.	,, ,,
HARRY HALL-TOMKIN, M.R.C.S.	,, ,,
MAURICE JOHN O'DONNELL, M.R.C.S., F.D.S.R.C.S.	,, ,,
JOHN MALCOLM BOLTON, M.R.C.S.	M.B.E. (Civil)