The intraluminal pressure patterns in diverticulosis of the colon¹

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Part III The effect of prostigmine

THE REASON FOR STUDYING PROSTIGMINE

Prostigmine (neostigmine methylsulphate) was introduced in 1931 as a gastrointestinal stimulant. Its parasympatheticomimetic actions are due to its ability to inhibit cholinesterase, but it may have a direct effect on the autonomic ganglia. It has less effect on gastric motility after vagal section, and it is believed that an intact nerve supply to the gut is necessary for it to exert its full effect, which is greatest on the colon (Goodman and Gilman, 1955).

Prostigmine may be considered to be a 'physiological' type of stimulus in so far as it possibly enhances the effects of any impulses that activate the colon, and in this manner it may accentuate the motor activity induced by naturally occurring stimuli. Its effect on the intrasigmoid pressures was studied to see whether it produced an exaggerated response of the diverticula-bearing segments of the sigmoid colon similar to that which we observed after morphine (Painter and Truelove, 1964).

METHOD OF STUDY

The apparatus, method of investigation, and analysis of the pressure tracings thus obtained were identical with those described in the first part of this study.

After the resting pressure pattern had been recorded for one hour, prostigmine (1 mg.) was given intramuscularly and the next hour's recording yielded the 'prostigmine pattern'. This hour was measured from the time of injection of prostigmine and so our results in the normal patients are not strictly comparable with those of Chaudhary and Truelove (1961a), who allowed an interval to elapse after the injection before recording the 'prostigmine pattern'.

RESULTS

EFFECT OF PROSTIGMINE ON THE PRESSURE PATTERNS IN THE NORMAL SIGMOID COLON The effect of the drug was apparent about 15 minutes after its injection and often began to wane by the end of one hour. The

number of waves was generally increased and high waves of long duration were more frequently seen. The form of these waves differed from those seen under basal conditions and after morphine in that their outline was sometimes less smooth and complex waves were more commonly seen. These complex waves consisted of several peaks whose descending strokes did not return to the base line (Fig. 1).

Sometimes a short succession of waves was recorded on one or more leads and their occurrence might appear to be rhythmic at times, but this phenomenon was less common than after morphine. Whereas after morphine it was almost possible to predict the onset of the next bout of activity, after prostigmine isolated waves of higher pressure were recorded at irregular intervals. The duration of the majority of these waves did not appear to be very different from those seen after morphine, but long waves were seen a little more commonly.

EFFECT OF PROSTIGMINE ON THE PRESSURE PATTERNS IN THE SIGMOID COLON IN DIVERTICULOSIS The pressure tracings derived from leads that were related to diverticula were not obviously different from tracings belonging to leads that were recording pressures from unaffected segments. Waves of all sizes were generally increased in number and complex waves consisting of several peaks were more frequent. The form of these waves differed little from those seen after prostigmine in normal patients.

QUANTITATIVE ASPECTS OF PRESSURE WAVES IN THE SIGMOID COLON IN NORMAL SUBJECTS AND THOSE WITH DIVERTICULOSIS AFTER ADMINISTRATION OF PROSTIGMINE Table I shows the number of patients studied; Tables II and III give the mean values of the waves by amplitude and duration, both before and after prostigmine. The mean resting values in this series differ slightly from those given in the first part of this study, which were derived from a larger number

¹Parts I and II of this study may be found in the previous issue of this Journal (*Gut*, 5, 201-213).

FIG. 1. Pressure patterns after neostigmine methylsulphate (prostigmine). Two tracings, each representing three minutes of recording time, in which the top pressure-recording channel had been modified to record the exposure of a simultaneously-exposed cineradiographic film. The upper tracing shows pressure waves recorded from a normal sigmoid colon after prostigmine. The lower tracing was obtained from two leads in the sigmoid colon of a man of 46 with diverticulosis who had been given prostigmine. Such multi-peaked and complex waves were seen after prostigmine both in health and in diverticulosis.

TABLE I
NO. OF SUBJECTS STUDIED AND LEADS FROM WHICH PRESSURE TRACINGS WERE OBTAINED IN THE STUDY OF NEOSTIGMINE METHYLSULPHATE (PROSTIGMINE)

	Number of Subjects (Each Studied Once)	Leads in Sigmoid
Normal subjects	12	26
Subjects with diverticulosis	12	9 (related to diverticula) 11 (not related to diverticula)

of observations. Such a discrepancy is not surprising when the wide variation in activity that is seen in the resting colon is taken into account.

Waves of less than 10 mm. Hg were increased by about a third after prostigmine except in the affected segments. Waves over 20 mm. Hg were at least four times as common. The very high waves that exceeded 50 mm. Hg occurred between four and five times as often, except on leads not related to diverticula where they were seven times more frequent. The reason for these variations is unknown.

TABLE II
NO. OF WAVES BY AMPLITUDE OF WAVE IN SIGMOID COLON BEFORE AND AFTER ADMINISTRATION OF NEOSTIGMINE METHYLSULPHATE (PROSTIGMINE)¹

Amplitude of Wave (mm. Hg)	Resting Values			Post-prostigmine Values		
	Normal	Diverticulosis		Normal	Diverticulosis	
		Not Related	Related		Not Related	Related
1-9	29.00	33.09	30.33	39.42	45.73	33.78
10-19	3.23	3.64	4.89	12.96	19.18	15.22
20-29	1.58	0.91	1.78	6.23	5.91	6.78
30-39	0.54	0.64	1.11	2.88	2.55	5.33
40-49	0.50	0.18	0.67	2.15	2.64	1.33
50-59	0.38	0.09	0.56	1.15	0.82	1.22
60+	0.19	0.09	0.11	1.12	0.45	2.46
Total	35.42	38.64	39.45	65.91	77.28	66.12

Mean values per lead per 60 minutes' recording time

TABLE III

NO. OF WAVES BY DURATION OF WAVE IN SIGMOID COLON BEFORE AND AFTER
ADMINISTRATION OF NEOSTIGMINE METHYLSULPHATE (PROSTIGMINE)¹

Duration of Wave (mm. Hg)	Resting Values			Post-prostigmine Values		
	Normal	Diverticulosis		Normal	Diverticulosis	
		Not Related	Related		Not Related	Related
1-9	8.42	13.75	12.33	10.50	20.00	10.11
10-19	18.08	16.27	16.67	34.23	37.73	22.11
20-29	6.15	5.91	6.44	13.73	12.73	14.33
30-39	1.58	1.55	1.89	3.53	3.64	7.78
40-49	0.65	0.82	1.22	1.92	1.55	4.56
50-59	0.23	0.18	0.56	0.96	0.73	3.11
60+	0.31	0.18	0.33	1.23	0.91	4.11
Total	35.42	38.64	39.44	65.92	77.29	66.11

¹Mean values per lead per 60 minutes' recording time

The segments that actually bore diverticula produced the greatest number of waves over 20 mm. in height after prostigmine (Fig. 2), but the number of such waves in these segments did not exceed the number of similar waves in the other types of segment to the same extent as was seen after morphine. Thus prostigmine did not elicit the same excess of waves of high pressure from the affected segments as did morphine, either when waves greater than 20 mm. Hg or greater than 50 mm. Hg were considered (Fig. 3). It appears that the two drugs evoke different responses from the colon.

This difference was apparent when the duration of the pressure waves was considered, as prostigmine caused the affected segments to generate pressures of longer duration than the other segments to a greater extent than after morphine.

EFFECT OF PROSTIGMINE ON THE COLONIC MOTILITY INDEX The colonic motility indices for the three groups of leads before and after prostigmine are

FIG. 2. Average number of waves exceeding 20 mm. Hg in height (per lead per hour) in the sigmoid colon before and after neostigmine methylsulphate (prostigmine).

shown in Figure 4. These were calculated as described in Part 1 of this study. There was a considerable spread of values in any one group, but the averages of the resting values of these indices were very similar both with one another and with the average of the resting values obtained (Painter and Truelove, 1964). This suggests that this simple method of calculating an index of the sigmoid's pressure generation in one hour gives a value that, despite the approximations inherent in its definition, is sufficiently reliable to justify its use as a measure for comparing the activity of two groups of colons.

Prostigmine increased the colonic motility indices in the three types of segments. The greatest values were obtained from leads related to diverticula, and these were far greater than those calculated after morphine. The highest value was more than twice that seen in the morphine study, and, after prostigmine, even some normal colons produced higher indices than were obtained from diverticula-bearing segments after morphine.

The average colonic motility indices of the three types of segment after prostigmine indicate that

FIG. 3. Average number of waves exceeding 50 mm. Hg in height (per lead per hour) in the sigmoid before and after neostigmine methylsulphate (prostigmine).

FIG. 4. Colonic motility index: resting and post-prostigmine values. The horizontal lines represent the mean values of the indices in each column.

segments which bore diverticula were subjected to twice the 'total pressure' experienced by the other types of segment, despite the finding that these latter segments harboured more waves of high pressure after prostigmine than they did after morphine.

DISCUSSION

Stimulation of the sigmoid colon in normal subjects and those with diverticulosis by prostigmine shows that when the colonic motility indices are considered, those segments that bear diverticula react excessively to this drug. Thus these segments can react differently from their fellows, a finding that demonstrates that their differential behaviour after morphine is not an effect peculiar to this drug.

Nevertheless, the actions of prostigmine are not identical with those of morphine when judged by detailed analysis of the pressure tracings. Whereas morphine only evokes an excessive number of waves

of high pressure in the neighbourhood of diverticula, prostigmine causes such pressures to be more uniformly increased in frequency both in the healthy colon and in all segments of the colon affected by diverticulosis. Prostigmine is more potent than morphine when judged by the colonic motility index and influences the affected segments so that they produce more pressure in a given time than the other segments.

Hence both drugs cause the sigmoid to generate an excessive number of pressure waves in the neighbourhood of diverticula, but the patterns of these pressure waves are different with the two drugs. One possible explanation for this finding is that the two drugs activate different groups of colonic muscle fibres to different degrees. It is already known that parts of the colon's muscle coat can contract differentially; the very existence of the interhaustral rings and the variation in 'haustration' that occurs are evidence of this. At present, our knowledge of colonic physiology is too limited to explain the different pressure patterns that are produced by morphine and prostigmine.

However, it has now been shown that two unrelated drugs, morphine and prostigmine, both elicit a differential effect from the affected segments in diverticulosis. This finding suggests the possibility that naturally occurring stimuli may also evoke an enhanced pressure response from those segments that bear diverticula. Lloyd-Davies (1953) has tentatively suggested that a psychosomatic factor might play a part in the causation of diverticulosis. Emotion has been shown to increase colonic motility as demonstrated by balloons (Almy, Kern, and Tullin, 1949; Almy, Hinkle, Berle, and Kern, 1949; Almy, Abbot, and Hinkle, 1950), and also to be capable of eliciting very high pressures (Chaudhary and Truelove, 1961b). There is consequently the possibility that emotional stress may generate sufficiently high pressures to initiate the herniation of the colonic mucosa or to aggravate established diverticulosis.

SUMMARY

Prostigmine (neostigmine methylsulphate) increases the frequency and the amplitude of pressure waves in the normal sigmoid colon. It also increases the frequency and amplitude of the pressure waves in diverticulosis coli. The response is greater in the affected segments than in unaffected segments.

Although prostigmine resembles morphine in provoking a greater response from affected than unaffected segments, the actions of the two drugs do not appear to be identical when the pressure tracings are analysed in detail.

The main interest in these findings is the discovery that two unrelated drugs each elicit an excessive motor response in those segments of the sigmoid that bear diverticula.

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Part IV The effect of pethidine and probanthine

THE EFFECT OF PETHIDINE

Once it was realized that morphine caused the sigmoid colon to generate high pressures that might be dangerous if the drugs were used as an analgesic in acute diverticulitis (Painter and Truelove, 1964b), it was decided to study the effect of pethidine (Demerol) on the intrasigmoid pressures. The drug is said to relax smooth muscle and it seemed likely that it might not increase these pressures.

METHOD OF STUDY

Pethidine (100 mg.) was given intramuscularly to a small series of patients (Table I), who were studied in the same manner as those who received morphine. The 'post-pethidine' pattern of pressures was analysed as described in the first part of this study.

The resting patterns of pressures of the subjects who received pethidine were essentially similar to those already described (Painter and Truelove, 1964a) and will not be referred to again.

TABLE I

NO. OF SUBJECTS STUDIED AND LEADS FROM WHICH PRESSURE TRACINGS WERE OBTAINED IN THE STUDY OF PETHIDINE

	Number of Subjects (Each Studied Once)	Leads in Sigmoid
Normal subjects	6	15
Subjects with diverticulosis	5	7 (related to diverticula) 3 (not related to diverticula)

RESULTS

EFFECT OF PETHIDINE ON THE PRESSURE PATTERNS IN HEALTH AND IN DIVERTICULOSIS Pethidine modified the resting pressure patterns so that waves of all sizes were diminished in frequency, both in health and in diverticulosis. The effect of the drug was seen on average within 12 minutes of its intramuscular injection. No dramatic change in the configuration of

FIG. 1. Effect of pethidine on pressure patterns in sigmoid colon. All three leads were in a normal sigmoid colon; the only changes of pressure recorded in six minutes were due to respiration. After pethidine, the pressure tracing frequently remained flat for several minutes.