Fig 2 In vitro *response of tænia from the descending colon to 5HT.* Ac=*acetylcholine,* Ht=*5HT. Drug concentrations in μg/ml of Krebs in the organ bath. Contact times: 30 sec for acetylcholine, 60 sec for 5HT. Three-minute intervals between drugs with recorder stopped for two minutes*

Figs 1 and 2 are reproduced from Misiewicz et al. *(1966) by permission of the Editor and Publishers, BMA House, Tavistock Square, London, WC1*

In vitro, serotonin (0·04–5·0 μg/ml) inhibited all the muscle strips from the tranverse and descending colon (Fig 2) but cæcal muscle gave variable results (Table 2). Pharmacological analysis suggested that the site of action of 5HT was directly on the muscle cell. In contrast to the colon, upper and lower small intestine was consistently stimulated by serotonin *in vivo* (Table 1) and *in vitro* (Table 2). The site of action was again found to be directly on the smooth muscle cell.

In vivo, the same dose of 5HT given over the same period of time stimulated the small intestine, but inhibited the right and left colon, while *in vitro* pharmacological analysis suggested that the drug acted directly on the smooth muscle. The present *in vitro* results confirm the findings of Bennett (1965) and of Fishlock & Parks (1963). Inhibition by serotonin of the motor activity of the left colon is now generally accepted (Schmid & Kinzlmeier 1959, Fink & Friedman 1960, Ramorino *et al.* 1965), although some workers report contraction of the right colon (Ramorino *et al.* 1965). This variation in the response of the right colon may be due to differences in the rate of drug administration and different selection of subjects. Variations in the response of the colon to 5HT in the basal or stimulated state may also be important.

If the pharmacological effects of serotonin resemble the action of 5HT released in the body, then on the basis of the above results patients with the carcinoid syndrome who have diarrhœa and an elevated urinary 5HIAA should have hyperactivity of the small intestine and hypoactivity of the colon. This was so in a 56-year-old woman with carcinoid, facial flushing, diarrhœa and elevated urinary excretion of 5HIAA, whose motility record revealed gross small intestinal hyperactivity, while the colon was inactive.

The flush of carcinoid is now thought to be due to a release of a bradykinin (Robertson *et al.* 1962, Oates *et al.* 1966). Treatment with the serotonin antagonist methysergide relieves the diarrhœa while having no effect on the flush (Peart & Robertson 1961). It seems likely, therefore, that serotonin is a factor in the production of symptoms in the carcinoid syndrome.

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Mr N S Painter
(The Manor House Hospital, London)

The Effect of Neostigmine Methyl Sulphate on the Human Colon in Health and in Diverticulosis

Neostigmine has a parasympatheticomimetic action due to its ability to inhibit cholinesterase. It is a 'physiological' stimulus in so far as it probably accentuates the effect on the colon of naturally occurring stimuli. The intrasigmoid pressure patterns were measured for a period of one hour before and after the administration of 1 mg intramuscularly of neostigmine both in the healthy human subject and in patients with diverticulosis. These pressure patterns were

analysed to see if the drug caused diverticula-bearing segments of the sigmoid colon to produce a differential pressure response similar to that evoked by morphine (Painter 1962, 1964, Painter & Truelove 1964*a*). Cineradiography was used simultaneously to elucidate the mechanism by which the colon produced the localized high pressures which neostigmine was found to evoke (Painter *et al.* 1965).

The results of this investigation may be summarized as follows:

(1) Neostigmine caused an increase in the number of pressure waves occurring in the normal colon, in apparently normal segments of the sigmoid colon, in subjects with diverticulosis and in segments of the sigmoid which bore diverticula. When waves of greater pressure than 50 mmHg were considered the segments which bore diverticula were found to produce a greater number of these waves than the other types of segment. This differential response was not as marked as that seen after morphine (Painter & Truelove 1964*b*). When the duration of these waves was considered (in calculating the colonic motility index) it was found that the diverticula-bearing segments produced more pressure than the other types of segment.

(2) Combined cine-radiology and pressure recording showed that the colon generated and localized waves of pressure by segmenting in order to produce isolated pockets of pressure.

(3) Combined cine-radiology and pressure recording showed that neostigmine caused the colon to segment more markedly and that this resulted in the increased generation of pressure which was observed.

(4) Neostigmine caused the sigmoid which was beset with diverticula to segment to such an extent that segments were often isolated from their fellows by contraction rings which occluded the colonic lumen. Under these circumstances the colonic segments acted like 'little bladders' which each bore diverticula. These diverticula were distended when the pressure in their parent segment increased.

The finding that neostigmine evokes a different pressure response from diverticula-bearing segments, as does morphine, suggests that naturally occurring stimuli may also do so, which might be responsible for the progressive nature of diverticulosis and even for its appearance. Segmentation is concerned in the generation of intrasigmoid pressures and is almost certainly the mechanism by which the pulsion force responsible for diverticulosis is produced. Consequently, any knowledge obtained of the factors which cause excessive segmentation to occur may be relevant to the ætiology of diverticulosis.

Neostigmine exaggerates the colon's response to stimuli so that its normal behaviour is caricatured; it may be useful as an adjunct to barium enema examinations: if diverticulosis is suspected on clinical grounds, yet is not demonstrated by barium enema, the administration of neostigmine may cause diverticula to appear that were not previously demonstrated.

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