and all except 5 patients gained weight. The patients showed greater frequency of folic-acid deficiency than a group of aged control subjects, and their diets contained, prior to admission to the home, less folic acid, iron, protein, and total calories. The implications of these studies are discussed.

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Physiological and Clinical Assessment of the Effect of the Musculotropic Agent Mebeverine on the Human Colon

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It is possible to achieve smooth muscle spasmolysis by two methods which are pharmacologically distinct. Anticholinergic drugs, such as belladonna, act by blocking cholinergic fibres, while other preparations, such as papaverine, have a direct effect on smooth muscle. Anticholinergic preparations have been widely used as smooth-muscle relaxants. Success in this respect has been limited on account of their widespread effect through the organism. In order to achieve a therapeutic result at one site it is usually necessary to administer doses likely to produce effects elsewhere in the body, with resulting undesirable side-effects. On the other hand, a direct musculotropic drug such as papaverine does not have these effects (Goodman and Gilman, 1955). Unfortunately, papaverine has not been shown to be effective in the treatment of bowel disorders. Kralt *et al.* (1960) showed that in animals phenylethylamine derivatives of resperine had little or none of the central nervous effect of the parent compound but did have strong papaverine-like spasmolytic effects with less marked atropine-like effects. One of these compounds, Mebeverine,† has been shown to have virtually no atropine-like action as tested by the lacrimation response, the sialogic response, and the inhibition of gastric secretion in cats. Dose for dose it was three times as potent as papaverine in inhibiting the peristaltic reflex of the guinea-pig ileum and 20 to 40 times more powerful in inhibiting the sphincter of Oddi (Lindner *et al.*, 1963). The pharmacological properties of this compound have been extensively studied by Lindner *et al.* (1963), who have shown it to be remarkably free of untoward effects. In man no atropine-like effects could be established.

This paper assesses Mebeverine physiologically with regard to its affect on the motility of the colon and small intestine in man and clinically by a double-blind controlled trial of its effect on the irritable colon syndrome.

1. Effect on Motility of Colon and Small Intestine in Man

The patients were studied using either miniature balloons or a pressure-sensitive radio telemetering device of high sensitivity. The tubes were inserted into the colon through a sigmoidoscope, which was then withdrawn, and manœuvred until the miniature balloons lay at approximately 25, 20, and 15 cm. from the anus respectively. Subsequently the patient was allowed to rest for at least 30 minutes before a recording was begun. Full details of the method and procedure have been described elsewhere (Connell, 1961). This method was used to study the pelvic colon.

The pressures in the small intestine and the proximal colon were studied, using a miniature ingestable radio transmitter whose frequency of oscillation is altered by external pressure. These changes are detected by an external aerial and receiver system and displayed on a suitable recorder (Connell and Rowlands, 1960). Full details of the technique and its application to the study of the small intestine and ascending colon have been described elsewhere (Connell *et al.*, 1963).

Subjects and Procedure

The effect of Mebeverine on the sigmoid colon was studied during the course of routine motility studies in patients suffering from the irritable colon syndrome. In 10 patients Mebeverine was administered by a slow intravenous injection of 50 mg., and in one by an intramuscular injection of 75 mg. The effect of a slow intravenous injection of 50 mg. was tested in the small intestine (ileum) in two normal subjects and on the caecum in two subjects, one normal and one suffering from the Zollinger-Ellison syndrome. In all cases a basal recording lasting from 30 minutes to one hour was obtained, after which the patient received a control injection of intravenous saline. Thirty minutes later the Mebeverine was given and the recording continued for at least 30 minutes. Records were analysed over the 15-minute period following the control injection and the 15-minute period following the injection of Mebeverine. This analysis was made in respect of (1) the percentage of the term of analysis in which activity was present (percentage

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† Not yet available in the United Kingdom, but is marketed in certain European countries.

D.A.); (2) the mean amplitude of the waves (M.A.); (3) the product (duration of activity × mean amplitude) is an estimate of total activity. A discussion of the rationale and accuracy of this analysis has been presented elsewhere (Connell, 1961).

Results

Pelvic Colon.—Fig. 1 illustrates a typical record. At the first arrow an intravenous injection of saline was given which resulted in a slight increase in motility. The second arrow indicates the occasion of an intravenous injection of Mebeverine which resulted in a diminution of motility, though a few waves persisted.

Table I summarizes the analysis of the motility of the 10 patients who received an intravenous injection of 50 mg. of Mebeverine and compares it with the motility following a saline injection. In four of the patients the resting motility was in excess of normal, in four it was normal, and in two it was in the low normal range. The effect of an intravenous injection of Mebeverine is to decrease all motility, and there is a suggestion that this preparation has a greater proportional effect on hyperactive subjects and less or no effect on hypoactive subjects. The time taken for a return to normal motility was from 10 minutes to more than 35 minutes, with a mean of 19 minutes. The subject who had an intramuscular injection of 75 mg. of Mebeverine showed no significant decrease in motility.

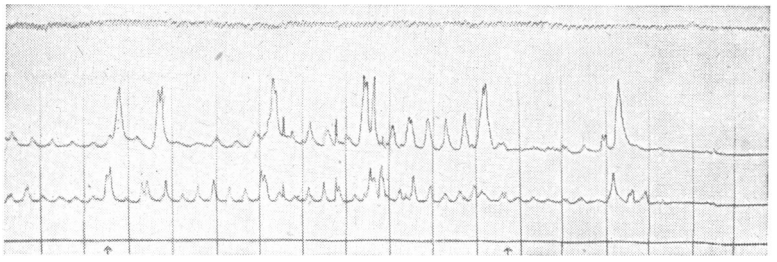

FIG. 1.—Effect of Mebeverine on sigmoid colon during routine motility studies. The first arrow marks an intravenous injection of saline leading to a slight increase in motility. The second arrow marks an intravenous injection of Mebeverine causing a diminution of motility.

Small Intestine and Proximal Colon.—The effect of a slow intravenous injection of Mebeverine on the small intestine was slight and temporary, and the only change observed was that the amplitude of the segmenting waves of the small intestine was reduced for five minutes. Of the two records from the proximal colon there was no change in one, and in the other the record was vitiated by artifacts caused by the patient's restlessness.

Side-effects

Side-effects were studied in 15 patients. In 11 patients in whom pulse rates were taken before and after injection there was a decrease in rate in all but one. This decrease varied from 5% to 33% of the resting pulse rate. There was no effect on the blood-pressure in any patient, and no change was seen in the E.C.G. of one patient in whom it was studied (Table II). Four of the patients complained of side-effects. In three this amounted to no more than a slight feeling of faintness after injection, but a fourth, who suffered from severe vomiting due to a Zollinger tumour, vomited after injection.

2. Controlled Clinical Trial of Mebeverine in Irritable Colon Syndrome

Subjects and Procedure

Selection of Patients.—Out-patients of both sexes between the ages of 16 and 70 years with a history of low abdominal pain and abnormality of bowel function were selected for the trial. All patients had symptoms either continuously or intermittently for at least one year, and had at least one attack in the three months before starting treatment. None had symptoms relating to the genito-urinary tract. No abnormalities of the colon were detected by radiology or sigmoidoscopy, and no parasites were found in the stools. Where the symptoms indicated that they were needed a barium meal and cholecystogram were also performed.

Experimental Arrangement.—The patients were allocated in pairs at random to one or two groups. The first group was treated for 12 weeks with oral Mebeverine 100 mg. four times daily. The other group was given an identical inert preparation four times a day for 12 weeks. The treatments were allocated by the hospital pharmacist according to a prearranged schedule. The doctor in charge of the trial did not know the nature of the tablets being received by the patient.

The trial was carried out sequentially and stopped as soon as a decision was reached with regard to the effect of Mebeverine

TABLE II.—*Side-effects Observed after Intravenous Injection of Mebeverine*

	Mebeverine	Initial Pulse Rate	Side-effects: Lowest Pulse	Side-effects: Per Cent. Decrease	Subjective Effects
1.	50 mg. i.v.	78	52	33	None
2.	50 mg. i.v.	96	80	15	None
3.	50 mg. i.v.	64	72	+13	None
4.	50 mg. i.v.	68	60	12	None
5.	50 mg. i.v.	72	62	14	"Faintness" (2 min.)
6.	75 mg. i.v.	—	—	—	None
7.	50 mg. i.v.	70	64	8	None
8.	50 mg. i.v.	60	55	8	Slight "wooziness"
9.	50 mg. i.v.	80	64	20	None
10.	50 mg. i.v.	—	—	—	None
11.	(75 mg.) i.m.	—	—	—	None
12.	50 mg. i.v.	—	—	—	Vomited
13.	50 mg. i.v.	76	50	33	"Dizziness"
14.	50 mg. i.v.	70	66	5	None
15.	50 mg. i.v.	74	66	9	None
				15·7	

There was no significant effect on blood-pressure.

TABLE I.—*Comparison of Effect of Intravenous Mebeverine and of Intravenous Saline on Colonic Motility in Irritable Colon Syndrome*

	Irritable Colon Syndrome: Main Symptoms	Sex	Weight lb.	Weight Kg.	Duration of Effect (Minutes)	% Duration of Activity Before	% Duration of Activity After	Mean Amplitude cm. H_2O Before	Mean Amplitude cm. H_2O After	Product Before	Product After
1.	Nervous diarrhoea	F	134	60·8	31*	97	23	26	5	2,522	115
2.	Post-prandial pain and distension	M	189	85·7	22*	95	10	24	4	2,280	40
3.	Left iliac fossa pain constipation	M	168	76·2	10*	80	80	25	5	2,000	400
4.	Left iliac fossa pain. Vasomotor symptoms	M	196	88·9	14	90	0	20	0	1,800	0
5.	Post-prandial distension	M	154	69·8	> 35	90	0	14	0	1,260	0
6.	Right iliac fossa pain	M	182	82·5	15	56	0	20	0	1,120	0
7.	Post dysenteric constipation. Abdominal discomfort. Rectal prolapse	F	110	49·9	14*	54	18	6	7	324	126
8.	Right-sided abdominal pain. Constipation	F	126	57·2	10*	16	25	18	13	288	325
9.	Post-dysenteric irritable bowel	F	112	50·8	24	33	0	3	0	99	0
10.	Diverticulosis	F	—		13	16	10	4	3	64	30
	Average				19	62·7	16·6	16·0	3·7	1,176	104

* Occ waves occur in this time.

according to the doctor's assessment. The sequential scheme was of Armitage's restricted type (Armitage, 1960).

Recording of Data.—In a condition such as the irritable colon syndrome there are objective criteria of improvement, and the assessment of the patient's response to treatment was necessarily subjective. Patients were interviewed at four-weekly intervals for a period of three months after starting treatment, and the response to questioning was recorded on a special form. To assist in making this assessment each patient was given, for each period of treatment, a special record card, and requested to make daily entries with regard to stool frequency, the occurrence of abdominal cramps, the presence of symptoms after eating, the presence of any other symptoms, and the use of other treatments. On the basis of this and on the doctor's assessment of the patient by direct questioning at interview on each four-weekly occasion, a score (+, 0, or −) was given for each period according to whether the patient was considered better, unchanged, or worse.

Comparability of Treatment Groups.—Table III compares the patients in the active and placebo group with respect to age, sex, and the nature of symptoms experienced. It will be seen that no significant differences are present between the two groups of patients.

TABLE III.—*Comparison of Patients in Active and in Placebo Groups*

Criterion		Treatment		Total
		Mebeverine	Placebo	
		Number of Patients		
Age distribution	Age below 40 yr.	10	9	19
	Age above 40 yr.	10	11	21
	Total	20	20	40
Sex distribution	Males	7	8	15
	Females	13	12	25
	Total	20	20	40
Abdominal pain	One side (left or right)	12	10	22
	Both sides	8	10	18
	Total	20	20	40
Abnormal bowel function	Constipation	11	9	20
	Diarrhoea	6	8	14
	Alternating constipation and diarrhoea	3	3	6
	Total	20	20	40

Analysis of Results

The assessments of the doctor were the criterion of the analysis. Within each pair of patients a preference was derived as to which had benefited more by the treatment. Cases where no preference could be stated because both had responded similarly were not included in the sequential test of significance.

Because a number of patients did not complete the whole three-months period, the preferences were derived in two ways —either by comparing the doctor's assessment in equivalent intervals of treatment, the length of the interval being determined by the shorter of the two treatment periods within a pair, or by directly comparing the overall effect of treatment of both patients of a pair.

Altogether 44 patients were entered into the trial but four were subsequently withdrawn, two because of the finding of gall-stones shortly after starting treatment. After the trial was completed one patient was found to have terminal ileitis, and a fourth had to be admitted for treatment of an inguinal hernia during the course of the trial. Thirteen patients (six Mebeverine, seven placebo) did not take tablets regularly for the full three months. Each of these patients was seen and interviewed, and in each case admitted that they had defaulted, some because they felt cured and no longer needed tablets, and others because they did not feel that they were improving. In each case these were scored according to their condition at the time of stopping the tablets.

Results of Treatment

Figure 2, A and B, show the results of the sequential analysis with Mebeverine plotted against the placebo. Figure 2 (A) is scored according to the preference derived from the doctor's assessments for equivalent periods of treatment, while Fig. 2 (B) is scored according to the preferences established by direct comparison of the overall results. It will be seen that on either scoring Mebeverine is superior to the placebo in controlling the symptoms of the irritable colon syndrome.

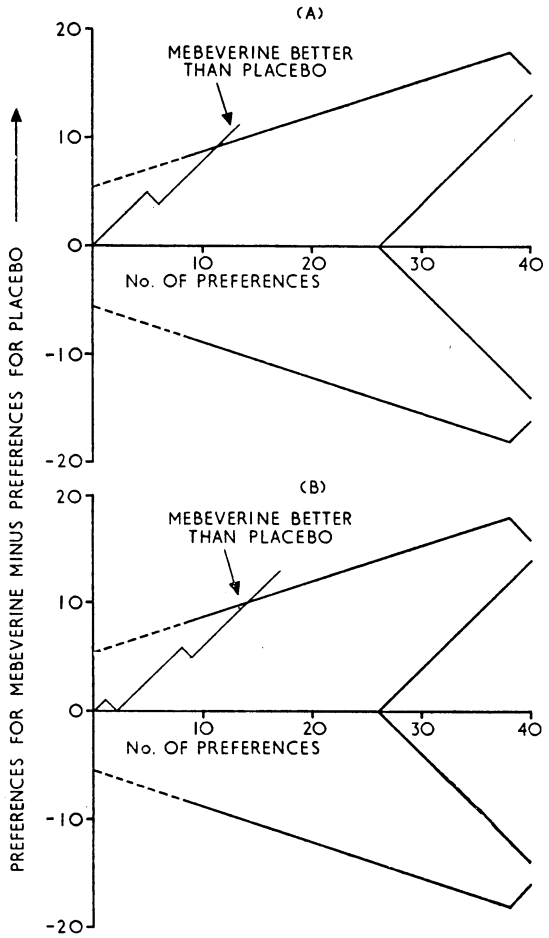

FIG. 2.—Plotted results of sequential clinical trial with Mebeverine against placebo: (A) according to preferences derived from doctor's assessments in equivalent intervals; (B) according to preferences established by direct (" blind ") comparison of the overall results.

Side-effects.—Five patients complained of side-effects during the course of the trial (Table IV). As complaints occurred with both placebo and active treatment it is probable that the effects complained of were related to the nature of the disorder rather than to the treatment.

TABLE IV.—*Side-effects Observed During Trial*

No. of Patients	Treated With	Side-effect
2	Placebo	Wind accumulating in epigastrium
10	Mebeverine	Depression, headache ("wanted to put teeth into someone")
31	Placebo	Headaches (occipital); loss of concentration; dizziness
36	Mebeverine	Depression, dizziness
38	,,	Headaches

Discussion

The demonstration of an effect of Mebeverine on intestinal motility marks a significant advance in smooth muscle spasmolysis in that it offers an alternative to anticholinergic preparations. Indeed, considering the widespread use of belladonna-like preparations in the treatment of abdominal discomfort and

colonic disorders their use rests on flimsy experimental evidence. In general the effect of atropine is to depress colonic motility (Jackman and Bargen, 1938), but results may be inconstant and variable. For example, in one study (Kern *et al.*, 1951) the normal therapeutic dose of 0.6 mg. of atropine given intravenously had no effect on one occasion, while on another occasion the same dose given subcutaneously resulted in a supression of motility. In general the effect of even larger doses (1 mg.) was slight and of short duration, usually less than 30 minutes.

This paper indicates a definite effect of Mebeverine on colonic motility. Of particular interest is the suggestion from these results that Mebeverine has a more marked proportional response in patients with colonic hypermotility than in patients with normal or diminished motility. This would be a useful quality, as the aim of therapy in a motility disorder is not to produce the abnormal state where all motility is abolished but to restore an abnormally active or incoordinate bowel to a more normal pattern of activity. To date the evidence for the effectiveness of Mebeverine has rested on animal experiments, and it is well known that such evidence may have only a limited significance in human therapeutics (Rowlands, 1959). This paper, however, demonstrates a definite effect on human motility of a musculotropic agent given intravenously. There are, however, differences in response—that of the small intestine and proximal colon being minimal, while the response of the sigmoid colon is distinct. It may be that the therapeutic effectiveness will be shown to reflect this specificity.

From time to time assessments have been made of the effect of anti-spasmodic preparations on the course of the irritable bowel syndrome, but as far as is known this is the first attempt to study the effect of an anti-spasmodic preparation in a double-blind controlled way. The difficulties in such an assessment are great, particularly as no objective criteria of effectiveness are available. Indeed, this fact would seem to underline the necessity of assessing symptomatic therapy in as unbiased a way as possible. One further difficulty in the way of such an investigation is the lack of any objective criteria of diagnosis. The diagnosis of an irritable colon is vague and at best is one of exclusion. The association of the symptoms of lower abdominal pain and disturbance of bowel habit with the colon rests on no secure basis and is only presumptive, and it is conceded that the symptom complex studied may be the end-result of a number of functional or pathological processes.

It is likely, however, that Mebeverine has an effect on the colon, and that, moreover, in these patients over a period of three months the abdominal cramps and disturbance of bowel habit improved to a greater degree using the active preparation Mebeverine than the identical inert control tablet. It would appear that it is a useful preparation in such patients. The usefulness is enhanced by the fact that there are virtually no side-effects. This is a considerable advantage over the standard anticholinergic preparations, where for therapeutic effectiveness it is usually necessary to give dosages which affect not only the target organ but also other sites in the body.

Summary

A new anti-spasmodic preparation which has a direct musculotropic effect has been studied.

Mebeverine results in a diminution of exaggerated colonic motility as tested by the measurement of intraluminal pressures in the sigmoid colon in man.

In a double-blind controlled trial assessed by sequential analysis Mebeverine was shown to be superior to a placebo preparation in relief of symptoms assumed to be arising from the irregular activity of the lower alimentary tract.

I am grateful to n.v. Philips-Duphar for supplies of Mebeverine and to Mr. W. Strik for the statistical analysis of the results, also to Dr. F. Avery Jones and Dr. T. D. Kellock for permission to study patients under their care.

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Recurrent Acute Renal Failure: Report of Two Cases

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Records of two separate episodes of acute renal failure in the same patient are extremely rare. This paper describes two cases in which a second episode of acute oliguric renal failure occurred during the recovering diuretic phase after the first attack.

In the first patient a Gram-negative septicaemia was implicated on both occasions. The second patient had initially acute renal failure after trauma, and the development of a Gram-negative septicaemia during his recovery caused a second episode of renal failure.

Case 1

First Episode : Renal Failure Due to Post-operative Septicaemia.—A man of 44 with a two-year history of dyspepsia from a chronic duodenal ulcer came to hospital with a history suggestive of acute appendicitis. A gangrenous retrocaecal appendix which had perforated at the base, with local peritonitis, was removed. The wound was drained. After operation he remained febrile, and by the second day abdominal distension and hypotension had developed. The wound was re-explored for suspected general peritonitis, but a paralytic ileus was the only finding. Blood culture before the second operation was positive for *Escherichia coli*. He was oliguric from the second day after appendicectomy (Fig. 1, a), and a diagnosis of acute renal failure due to post-operative septicaemia was made. Haematemesis began on the fifth day, and the urea level rapidly rose, to reach 500 mg./100 ml. by the seventh day, when haemodialysis was performed. He required haemodialysis again on the

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