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THE EFFECTS OF ACETYLCHOLINE AND METHACHOLINE UPON THE HUMAN COLON [1]

By FRED KERN, JR.,[2] and THOMAS P. ALMY

(From the Department of Medicine, the New York Hospital-Cornell Medical Center, New York, N. Y.)

INTRODUCTION

The association of life stress, emotional conflict, and disordered function of the colon has often been observed clinically and has recently been confirmed by experimental observation on man (1, 2). Because of the established importance of the autonomic nervous system in the integration of reactions to stress, it has been assumed that the disturbed activity of the colon is directly caused by autonomic stimulation. Yet little is known about the effects of sympathetic or parasympathetic stimulation on the human colon. Since the musculature of the colon is innervated by post-ganglionic parasympathetic fibers, the effect on the bowel of acetylcholine, the chemical mediator of these impulses, is of considerable interest. Numerous investigators have observed that acetylcholine enhances tone and peristaltic activity of the stomach and intestines in experimental animals both *in vitro* and *in vivo* (3–5). Nothing is known of its effect on coordinated motor activity of the human gastrointestinal tract. We have, therefore, studied its effect on the motility of the intact human colon. We have also used acetyl-beta-methyl choline, a choline ester, which, because of its slower hydrolysis by cholinesterase, is effective after subcutaneous injection. This drug also differs qualitatively from acetylcholine in that it possesses muscarinic action only, lacking the nicotinic action of acetylcholine (6).

MATERIALS AND METHODS

Eighteen paid volunteer college students and medical students were the subjects for the experiments in which acetylcholine was administered. All were male and they ranged in age from 18 to 32 years. Methacholine was given to medical students, patients with diseases unrelated to the bowel, and patients with the irritable colon syndrome. These subjects ranged in age from 16 to 55 years; 16 were male, eight were female. The nature of the procedure and the subjective effects of the drug to be used were carefully and reassuringly explained to each individual prior to the experiment.

Sigmoid motility was recorded by a simple balloon-kymograph technique previously described in detail (7). As preparation, each subject fasted six to 16 hours and the colon was emptied by one or two enemata of physiological saline two hours before the experiment. During a 30 to 60 minute control period, a sigmoid tracing was recorded and the blood pressure and pulse rate were measured by the usual clinical methods approximately every five minutes.

Methacholine [3] (acetyl-beta-methyl choline chloride) was administered subcutaneously, 2.5 to 10 mgm. It was usually repeated in a larger or smaller dose within this range at least once in each subject. After the injection, blood pressure and pulse rate were recorded each minute until all signs and symptoms of drug effect had disappeared. The subject was carefully observed for other systemic effects and their presence or absence was recorded. Each subject received one or more injections of physiological saline as control, after which similar observations were made.

Acetylcholine was administered by continuous infusion at accurately controlled rates. A sterile solution of acetylcholine chloride in saline containing 100 mgm. of acetylcholine per cc. was prepared and stored in the refrigerator. From this stock solution the final dilution (5 or 10 mgm. per cc.) was prepared just prior to its use. The infusion apparatus consisted of two 250 cc. burettes, one filled with physiological saline, the other with the acetylcholine solution. These led to a three way stop-cock bearing the intravenous needle. The rate of flow was controlled by a tunnel clamp and a glass infusion meter [4] placed in each system. A Murphy drip was also included in each system as an additional guide to the rate of flow. The actual amount of solution in-

fused each minute was read from the burette at intervals of one or two minutes.

Shortly after starting the sigmoid motility tracing, the infusion was initiated with saline and continued for at least 30 minutes before the acetylcholine was administered. During this control period, blood pressure and pulse rate were recorded every five minutes, and during the acetylcholine infusion at one minute intervals, while detailed notes were made of the rapidly changing systemic effects upon the subjects. The infusion was begun slowly and the rate of flow increased stepwise. Increases in rate were halted when the subject experienced a moderate degree of respiratory distress and tachypnea. The intensity of these respiratory symptoms was approximately the same in all subjects. The infusion rate was then maintained constant, usually for five to eight minutes. The entire procedure lasted 10–15 minutes. If the rate of flow was increased too rapidly, unpleasant or potentially dangerous side effects occasionally developed, at which time the infusion was immediately terminated.

Subcutaneous methacholine and intravenous acetylcholine were also given to a number of subjects while fluoroscopic observations of the barium filled colon were being made. "Spot" films were taken of the cecum and sigmoid before drug administration and several times during the period of drug effect.

RESULTS

Effect of acetylcholine on the colon. Eighteen subjects received 21 acetylcholine infusions. In 15 of these experiments there was complete or almost complete abolition of sigmoid contractions

(Figure 1); in two experiments, there was a definite increase in contractile activity, and no detectable change occurred in four.

Acetylcholine infusions were administered to three subjects during fluoroscopic observations of the colon after it had been cautiously filled, but not distended, with barium sulphate suspension by enema. In two of these experiments, the right half of the colon was seen to contract vigorously, with simultaneous shortening, widening and disappearance of segmental contractions in the sigmoid and distal descending colon (Figure 2).

The effect of acetylcholine on the colon became apparent only when the rate of infusion was such that the other systemic effects were fully established. These effects were no less pronounced in subjects whose colon motility pattern was not altered.

Other effects of acetylcholine. As the acetylcholine infusion was initiated, the patient usually experienced a burning sensation at the site of the needle, which extended along the course of the brachial veins into the shoulder. The superficial veins often became dilated and purplish red. This pain became very severe at times, particularly when a drug concentration of 10 mgm. per cc. was used, but it always disappeared after two to three minutes, despite an increasing rate of infusion.
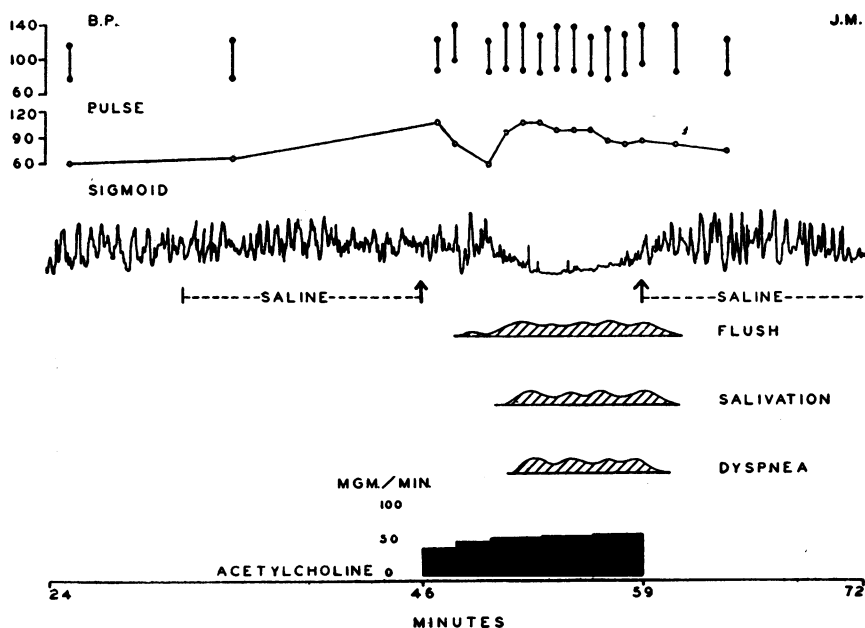

Fig. 1. Changes in Sigmoid Motility During an Infusion of Acetylcholine in a Normal Subject

As the stepwise increases in rate continued, there developed a feeling of warmth over the face, and to a lesser extent elsewhere, associated with a flush limited to the face, the neck, and occasionally the chest. These were often, but not always, followed by variable amounts of visible sweating, and a slight increase in salivation. In some subjects there was slight lacrimation. As the rate was further increased respiratory difficulty, tachypnea, and often a desire to cough became manifest. It was at this rate of flow that the infusion was maintained. Despite the constant rate, there was considerable fluctuation of all signs and symptoms; the blood pressure and pulse rate varied unpredictably. There was an initial irregular rise in systolic and diastolic blood pressure in almost all subjects, followed by a fall below the control level in 13; often there was a fall in diastolic pressure only, with an increase in pulse pressure. In general the pulse rate varied directly with the diastolic blood pressure. In a few subjects there was no significant change in the blood pressure or pulse. If the rate of infusion was increased too rapidly, or if the level of tolerance was exceeded, hypotension, bradycardia, nausea, and occasionally uncontrollable coughing developed. A number of subjects experienced central nervous system effects, manifested by feelings described as "far away from everything" or "I am going to faint." These were not related to blood pressure or heart rate changes. After termination of the infusion all symptoms subsided abruptly and disappeared completely within two or three minutes.

The amount of acetylcholine necessary to achieve the desired level of drug effect varied from 40 to 120 mgm. per minute with an average of 72. The total amount of acetylcholine given during an infusion varied from 505 to 1,270 mgm., averaging 739 mgm. The effective amount was independent of the weight of the individual.

Comment. This wide variation in individual tolerance to acetylcholine is in accord with the experience of Ellis and Weiss (8, 9). These authors infused acetylcholine intravenously into normal men and recorded systemic effects similar to those observed in these experiments. Carmichael and Fraser (10) also administered acetylcholine intravenously to human beings, but because of a different technique of administration their results are not comparable.
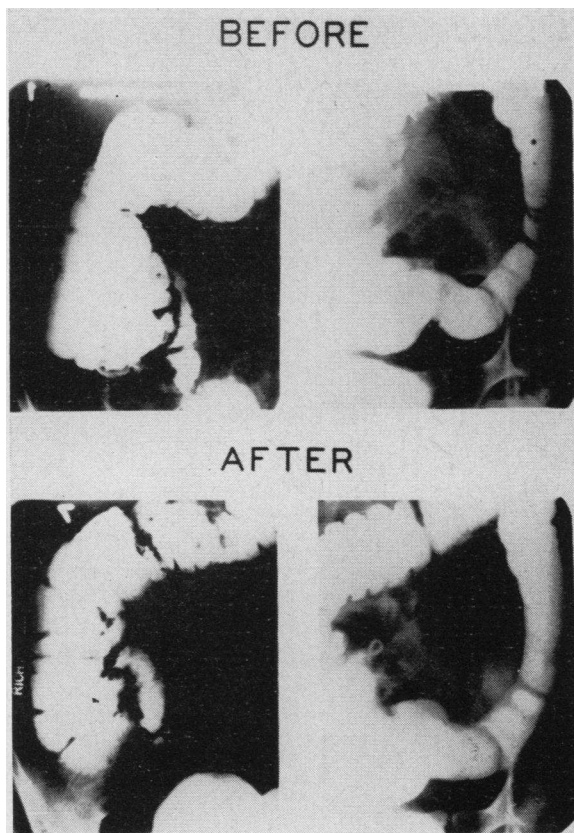

FIG. 2. ROENTGENOLOGIC APPEARANCE OF THE RIGHT AND LEFT PORTIONS OF THE COLON BEFORE INFUSION OF ACETYLCHOLINE AND AT THE HEIGHT OF THE EFFECT OF THIS AGENT

Effect of methacholine on the colon. Methacholine was administered 49 times to 24 subjects. In 20 of these experiments, there followed a marked diminution or complete absence of wavelike motility of the sigmoid (Figure 3). In six experiments the results were inconclusive, and in 23 experiments there was no significant change after methacholine. In no instance did methacholine produce augmentation of sigmoid motility.

In five of the subjects in whom methacholine produced abolition of contractions of the sigmoid, the injection of methacholine was followed by the intravenous administration of 0.6–1.0 mgm. of atropine sulphate. This caused only a brief interruption of sigmoid contractions, followed by a prompt return to the previous pattern. Thereupon the same or a larger amount of methacholine was again administered, and its effect upon sigmoid motility was blocked in each instance (Figure 4).

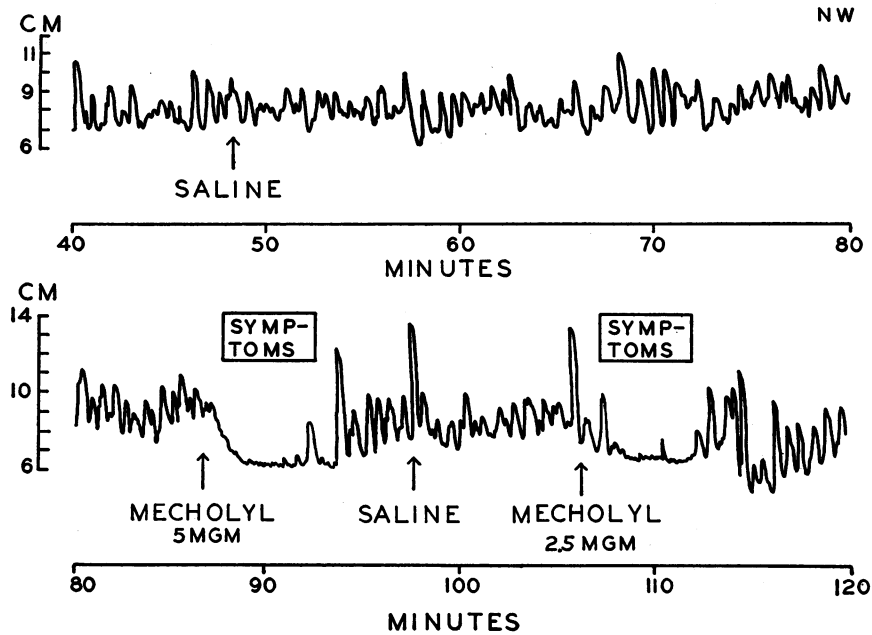One subject with a transverse colostomy re-

FIG. 3. TYPICAL EFFECT OF SUBCUTANEOUS METHACHOLINE (MECHOLYL®) UPON THE MOTILITY OF THE SIGMOID COLON

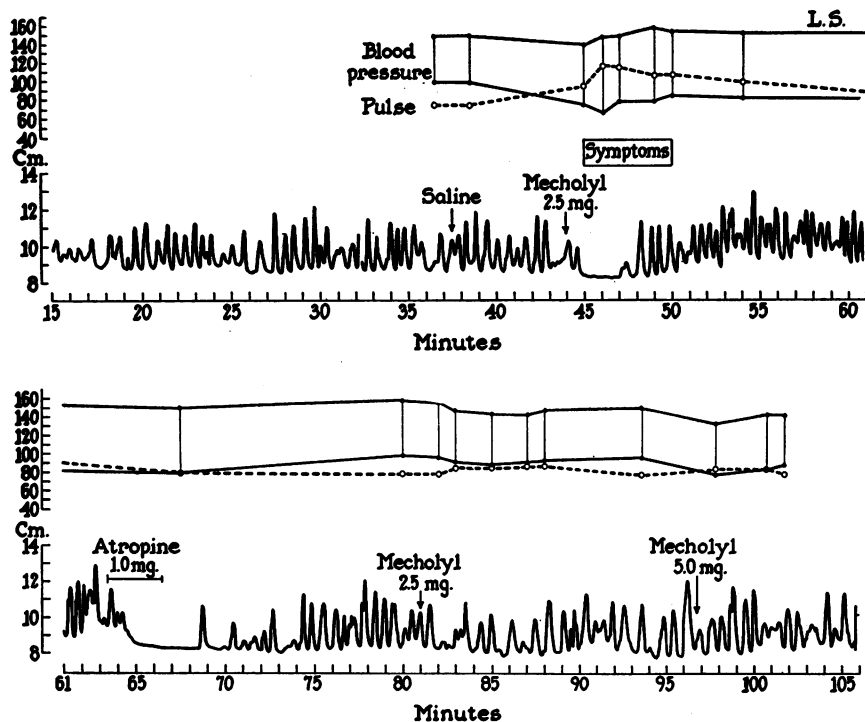Control injections of saline produce no effect.

FIG. 4. CONTINUOUS RECORD OF HUMAN SIGMOID MOTILITY, DEMONSTRATING THAT AFTER INTRAVENOUS ATROPINE, METHACHOLINE FAILS TO AFFECT THE SIGMOID MOTILITY, THE PULSE, OR THE BLOOD PRESSURE
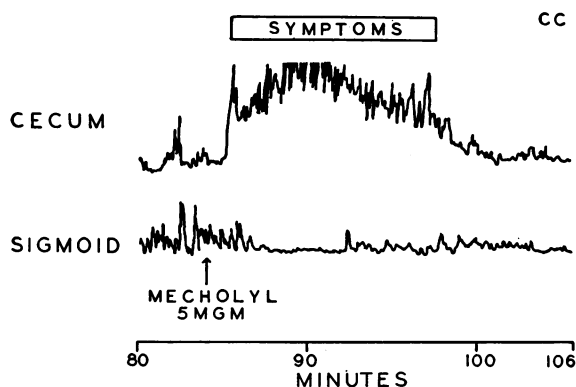
FIG. 5. BALLOON-KYMOGRAPHIC RECORDINGS OF MO-
TILITY OF THE CECUM AND SIGMOID COLON, SHOWING CO-
ORDINATE ACTION OF METHACHOLINE ON THESE REGIONS
OF THE BOWEL

ceived methacholine while motility tracings were
being recorded simultaneously from a balloon in
the sigmoid and a balloon in the cecum. There
was a pronounced increase in activity in the cecum,
resulting in the expulsion of feces from the colos-
tomy, coincident with the abolition of sigmoid con-
tractions (Figure 5).

Methacholine was administered subcutaneously
to six subjects while the barium filled colon was
observed fluoroscopically. In four of these, the
right half of the colon contracted forcefully, while
the distal colon shortened and widened. This re-
sponse was identical with that produced by acetyl-
choline.

Other systemic effects of methacholine. The ef-
fects of methacholine on other structures were
similar to those produced by acetylcholine. The
flush was usually more intense, lacrimation more
prominent, and respiratory embarrassment less
marked. The blood pressure and pulse rate al-
most invariably rose to some extent. These sys-
temic effects of subcutaneously administered
methacholine have been described repeatedly (3,
5, 6, 11), with a wide variation in individual sen-
sitivity to the drug. This individual difference in
intensity of effect, as well as the absence of effect
on the colon in 23 experiments, may have been
partly due to an irregular rate of absorption of the
subcutaneously injected drug.

The alteration in sigmoid motility was not re-
lated to the intensity of these phenomena, but it
was during their presence that the flattening of
the tracing occurred. The subjects were never
aware of abdominal cramps or intestinal activity.

DISCUSSION

In these experiments the usual effect of either
acetylcholine or methacholine on the human colon
was (1) abolition of phasic activity of the circular
muscle of the sigmoid, (2) shortening and widen-
ing of the same segment, and (3) increased pro-
pulsive activity of the more proximal portions of
the colon. These findings are compatible with
those of Abbott (11) who found an increase in the
overall pressure within the fluid-filled human colon
of three out of six subjects following the injec-
tion of 5 to 15 mgm. of methacholine. Yet, they
would seem to contradict extensive studies on the
actions of these drugs in animals, in which they
have augmented intestinal motility at all levels ex-
amined. This discrepancy can probably be ex-
plained by the difference in the anatomical and
functional organization of the colon in man and
in the usual herbivorous or carnivorous laboratory
animals (12).

The stimulation of the intestine produced by
acetylcholine in animals is considered a muscarinic
effect. When intestinal motility in the atropinized
animal is abolished by acetylcholine, the effect is
regarded as due to its synaptic (nicotinic) action,
with increased sympathetic stimulation of the gut.
In our observations on the human sigmoid, how-
ever, both acetylcholine and methacholine abolished
phasic activity. In the case of acetylcholine, this
effect could be due either to its synaptic or to its
muscarinic action, but since methacholine pos-
sesses only a muscarinic action, the response to
this drug probably represents direct cholinergic
stimulation of the smooth muscle. This conclu-
sion is strengthened by the fact that the response
was blocked by atropine. With both drugs, the
reduction of sigmoid motility coincided with force-
ful contractions in the right colon and with extra-
intestinal signs of muscarinic activity, such as
salivation, flushing of the skin, and usually a fall in
blood pressure.

These coordinate actions of acetylcholine and
methacholine on the proximal and distal colon
seem appropriate for the propulsion of fecal
masses and for the reception of these masses in
the lower portions of the bowel. Hurst (13), ob-
serving the propulsion of feces in man by fluoros-
copy, noted simultaneous abolition of circular mus-
cle activity of the distal colon, shortening of the
same segment, and massive contractions beginning

either in the right colon or in the region of the splenic flexure. Galapeaux, Templeton, and Borkon (14), in producing diarrhea in dogs by the instillation of bile into the colon, observed a reduction in phasic activity of the distal colon. The same phenomenon has been observed in kymographic studies on the human sigmoid in patients with functional diarrhea (15). Moreover, in a recent study of patients with ulcerative colitis (16), those patients with severe diarrhea were found to have an absence or marked reduction of sigmoid contractions, while those without diarrhea had normal sigmoid motility. The similarity of the sigmoid motility patterns in diarrheal diseases with those induced by cholinergic stimulation suggests that sustained parasympathetic activity may be involved in the pathogenesis of these conditions.

SUMMARY

The effect of acetylcholine and methacholine upon the colon of normal individuals has been studied, using a balloon-kymograph technique to record the motility of the sigmoid, and (in one experiment) of the cecum. Acetylcholine was administered intravenously 21 times to 18 subjects, and methacholine was injected subcutaneously 49 times in 24 subjects. In 20 experiments with methacholine, and in 15 experiments with acetylcholine, these drugs abolished the phasic contractions of the sigmoid. Acetylcholine augmented sigmoid contractions in two experiments, and methacholine in none.

In nine experiments, the entire colon was observed by fluoroscopy and spot roentgenograms. In these, at the time of disappearance of sigmoid contractions, the sigmoid appeared to shorten and the right colon contracted vigorously. This coordinate pattern of motor activity, produced by cholinergic drugs, is similar to that which occurs spontaneously during mass peristalsis.

The sigmoid motility response to acetylcholine and methacholine is identical with that observed in association with diarrhea in man and animals. This may help to define the role of the parasympathetic nervous system in the mechanism of functional diarrhea and of ulcerative colitis.

ACKNOWLEDGMENT

REFERENCES

1. Almy, T. P., Experimental studies on the irritable colon. Am. J. Med., 1951, 10, 60.
2. Almy, T. P., Kern, F., Jr., and Abbot, F. K., Constipation and diarrhea, as reactions to life stress. A. Res. Nerv. & Ment. Dis., Proc., 1950, 29, 724.
3. Molitor, H., A comparative study of the effects of five choline compounds used in therapeutics: acetylcholine chloride, acetyl beta-methylcholine chloride, carbaminoyl choline, ethyl ether beta-methylcholine chloride, carbaminoyl beta-methylcholine chloride. J. Pharmacol. & Exper. Therap., 1936, 58, 337.
4. Koppanyi, T., Acetylcholine as a pharmacological agent. Bull. Johns Hopkins Hosp., 1948, 83, 532.
5. Wolff, L. H., Effect of certain parenterally administered drugs on the colon of the dog. Am. J. Digest. Dis., 1939, 6, 243.
6. Simonart, A., On the action of certain derivatives of choline. J. Pharmacol. & Exper. Therap., 1932, 46, 157.
7. Kern, F., Jr., Almy, T. P., and Stolk, N. J., Effects of certain antispasmodic drugs on the intact human colon, with special reference to banthine (β-diethylaminoethyl xanthene-9-carboxylate methobromide). Am. J. Med., 1951, 11, 67.
8. Ellis, L. B., and Weiss, S., The study of the cardiovascular responses in man to the intravenous and intra-arterial injection of acetylcholine. J. Pharmacol. & Exper. Therap., 1932, 44, 235.
9. Weiss, S., and Ellis, L. B., The comparative effects of the intravenous administration to man of acetylcholine and acetyl-β-methylcholine. J. Pharmacol. & Exper. Therap., 1934, 52, 113.
10. Carmichael, E. A., and Fraser, F. R., The effects of acetylcholine in man. Heart, 1933, 16, 263.
11. Abbott, W. O., Acetyl-beta-methylcholine. II. The action on the gastro-intestinal tract of normal persons, in abdominal distention, and in certain other conditions. Am. J. M. Sc., 1933, 186, 323.
12. Alvarez, W. C., An Introduction to Gastro-Enterology. Paul B. Hoeber, Inc., New York, 1948, 4th ed., p. 570.
13. Hurst, A. F., Constipation and Allied Intestinal Disorders. H. Frowde, London, 1909.
14. Galapeaux, E. A., Templeton, R. D., and Borkon, E. L., The influence of bile on the motility of the dog's colon. Am. J. Physiol., 1938, 121, 130.
15. Almy, T. P., Abbot, F. K., and Hinkle, L. E., Jr., Alterations in colonic function in man under stress. IV. Hypomotility of the sigmoid colon, and its relationship to the mechanism of functional diarrhea. Gastroenterology, 1950, 15, 95.
16. Kern, F., Jr., Almy, T. P., Abbot, F. K., and Bogdonoff, M. D., The motility of the distal colon in non-specific ulcerative colitis. Gastroenterology, 1951, 19, 492.