SECTION II—*Experimental Physiology*

V. The Effects of Drugs on the Motility of Isolated Segments of the Intestine of Man*

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IN recent years, this Clinic has offered a unique opportunity for intensive study of functions of the large intestine. Patients who have had various kinds of intestinal disorders have been segregated on one floor of a hospital, under combined medical and surgical management. In this way, fifty to seventy-five patients, most of whom had disease of the colon, have been under observation the year around. Some of them consented to the performance of certain harmless, painless investigations, by which we hoped to learn facts which would be of benefit to them and to others. Consequently, many problems for clinical research have suggested themselves.

These patients were under the care of specially trained nurses and workers. This fact has been of great help in the execution of our research. This is the fifth report of a series of problems. The next study, now well under way, concerns the functions of the small intestine of colectomized patients. Colectomies have been done only for extensive polyposis or advanced chronic ulcerative colitis with serious complications. The results will be reported in the near future.

REVIEW OF PREVIOUS STUDIES

Members may recall that, at the meeting of this Association, in 1929, results of the first series of investigations were reported. These investigations were made on dogs. They established the fact that, in dogs, selective absorption and excretion of various drugs took place in the isolated colon. The colon of the dog was isolated by sectioning the distal part of the ileum, and the colon, as near to the anus as possible, and making end-to-end anastomosis of the proximal part of the ileum and the distal part of the colon. The distal end of the ileum was then brought to the outside of the abdominal wall, on the right side, and the proximal end of the colon was treated likewise on the left side, thus leaving the colon in the abdominal cavity, with nerve supply and blood supply intact.

The second and third studies concerned the motor and secretory activities of these isolated segments of colon. It was established that secretion of mucus is a normal function of the mucosa of the bowel and that mucus serves as a lubricant and protects against penetration of harmful bacteria. There was a strong suggestion that the mucus acted as a regulator of absorption. It was found that the amount of mucus secreted varies directly with the amount of colonic irritation; the source of irritation may be central as well as peripheral. Great loss of nitrogen occurs by excessive secretion of mucus. Mucus is not a product of inflammation.

The motor activity of segments of the colon varies. In the cecum, there is mixing and churning, and thus absorption is aided. In the distal portion of the dog's colon, the activity is largely one of propulsion.

With these studies on dogs as a background, similar studies on man have been undertaken. Some have been completed. The fourth study was reviewed in *"Surgery, Gynecology and Obstetrics,"* March, 1935. It concerned the absorption and excretion of various substances in isolated segments of the colon of man.

A surprising amount of conflicting experimental evidence exists concerning absorption of substances, other than water, by the large intestine. Colostomized patients are ideally suited to elimination of the usual fallacies inherent in investigations of colonic absorption. Instead of studying the colon of carnivorous or herbivorous animals, as has been done in the past, we could make observations on the isolated colon of omnivorous man. The divided colon has the added advantage of preventing error from regurgitation of the clysma into the absorbing ileum. Short distal segments can be thoroughly evacuated, thereby eliminating any errors attributable to failure to recover unabsorbed fractions, and finally, such segments can be cleansed, thus preventing error attributable to fermentation by bacteria.

By a study of such isolated portions of the colon of man, it was found that even in the distal seg-

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ments there is absorption of methylene blue, atropine, sucrose, arsenic as neoarsphenamine and glucose. Distal segments of the colon of man do not excrete methylene blue, glucose, or sucrose. Arsenic, as "treparsol," is excreted by the distal segments.

PRESENT STUDY CONCERNING THE EFFECTS OF DRUGS ON MOTILITY

Many drugs have been used in the past to combat and prevent postoperative intestinal distention, such as that which occurs with paralytic ileus from various causes. So far, knowledge regarding the ability of drugs, as extract of the posterior lobe of the pituitary body ("pituitrin"), physostigmine, acetylcholine, or "peristaltin," to influence intestinal tone and motility, has been founded principally on the results of experimentation with animals and on impressions acquired by clinical observations of the effects produced following administration of these drugs to patients affected with postoperative intestinal distention.

We undertook to evaluate the effects of these drugs on patients on whom colostomy had been performed. Patients who have undergone colostomy or ileostomy, at various levels, afford opportunities to study accurately the action of these drugs on intestinal segments. The intestinal stomas in the cases studied, had been made as steps preliminary to eradication of intestinal neoplasms, so that in each case ample normal colon was at hand after surgical resection.

For our experiments, patients were selected whose intestinal motility had been disturbed to the least possible extent. Hence, they were chosen with the thought that colostomy had not been performed longer than two weeks before the experiment was undertaken. The patients were all in excellent general condition and their bowels and colonic stomas were functioning well. No interference with intestinal function had taken place for several days before each experiment. During each experiment, the patient was supine on a couch, in a room that had been especially set aside for the carrying out of this study. Hence, the subject was free of extraneous influences which might cause reflex nervous irritation.

The apparatus used for these experiments was a closed air-balloon system, connected with a tambour and recording lever, this, in turn, writing with an ink point on smooth kymographic paper fastened to a revolving drum.

The drugs, whose action on the intestine of man we investigated, were (1) surgical pituitrin, (2) physostigmine sulphate, (3) "peristaltin" (Ciba), or soluble extract of cascara sagrada, grains 2½ (0.15 gm.) per ampoule, prepared for hypodermic use, and (4) acetylcholine. All the drugs were administered intramuscularly. The effect of each drug on various segments of the intestine was recorded.

THE TRANSVERSE COLON.—*Pituitrin:* After administration of pituitrin, powerful contractions of the transverse colon began within three to five minutes. These contractions occurred every three to five minutes, and the effect of the pituitrin lasted for forty-five to ninety minutes.

Physostigmine: Doses as large as 1/35 grain (0.0018 gm.) caused no effect on this segment of colon.

"Peristaltin": In some cases, 2½ grains (0.15 gm.) of this drug caused slight and irregular contractions. The contractions occurred every one and a half minutes to seven minutes, for an hour. At other times no effect from this drug was recorded.

Acetylcholine: Doses as large as 6 grains (0.4 gm.) caused no effect on this segment of colon.

THE SIGMOID COLON.—*Pituitrin:* This drug caused, on the sigmoid, reactions identical with those which it had exhibited on the transverse colon.

Physostigmine: Small to medium-sized contractions resulted from administration of this drug; the contractions occurred every one to eight minutes, for an hour.

"Peristaltin": A few small contractions occurred at irregular intervals.

Acetylcholine: Slight elevation of tone of the sigmoid occurred between six and nine minutes after administration of this drug, and small contractions occurred at irregular intervals for about forty-five minutes.

TERMINAL PART OF ILEUM AND SIGMOID COLON.—With balloons in the terminal part of the ileum and in the sigmoid colon of a single individual, simultaneous recording of contractions could be made.

Pituitrin: Contractions occurred simultaneously, in both sections of bowel, every one and a half to three minutes.

Physostigmine: On some occasions, no effect on the ileum could be recorded after administration of this drug; on others, increased ileal tone occurred, associated with small to medium-sized contractions every one and a half minutes to five minutes. The contractions occurred, although they gradually decreased in magnitude, for 105 minutes. In the sigmoid, slight contractions occurred every two to four minutes, beginning about ten minutes after administration of the drug.

"Peristaltin": On some occasions, no effect was observed on either the ileum or the sigmoid; on others, when administration of the drug was repeated, and in similar amounts, thirty minutes after the initial dose had been given slight increase in ileal tone occurred, but no effect on the sigmoid was noted.

Acetylcholine: Slight increase in tone of the ileum occurred for twenty minutes.

CONCLUSIONS

1. These experiments would compel the conclusions that pituitrin alone is a constant motor stimulant of the large and the small intestine of man. It increases motility without effect on intestinal tonus. Its action is rapid and powerful.

2. The action of the other three drugs is inconstant and uncertain, when amounts are given that will not cause other systemic effects.

3. These experiments open new avenues of valuable clinical physiologic research on man.

DISCUSSION:

DR. M. B. DREYER (Halifax, Nova Scotia): As a pharmacologist, I have to listen to a good many heresies. I don't want to take Dr. Bargen to task at all, but if one is going to use doses, use heroic doses. Secondly, "peristaltin," while it may be an excellent drug, should be considered from the point of view of kidney damage. Its indiscriminate use may lead to kidney damage.

I am more particularly interested in the use of pituitrin. The effect of it varies with the portion of the gastro-intestinal tract selected. The colon is particularly sensitive

to small doses, in that small doses of pituitrin (and I am speaking of the effects on cats) showed two effects: increase in tonus and increase in number of contractions per minute. All doses as I have used them were given intravenously.

Now, in the small intestine, strange as it may seem, in the cat and the dog (these results have been confirmed by Grüber), pituitrin causes relaxation of the small intestine. The effect of pituitrin varies on the pylorus and cardiac portions of the stomach. In the pylorus, pituitrin causes strong contractions, and at the cardia it causes a relaxation. To show that it is a real effect, one can compare that with the effect of histamine in the gastro-intestinal tract, where the histamine has a stimulating action on the colon but causes relaxation of the small intestine. Like pituitrin, it is followed by a period of increased activity. There is a well known tolerance produced by pituitrin, but it is less marked for the colon and most marked for the pylorus.

If one repeats the injections of pituitrin too rapidly, the pylorus will not respond and the large intestine will. That is similar in many respects to the effect of pituitrin on the uterus. The uterus is the organ in the body most tolerant to the action of pituitrin.

The fraction of pituitrin responsible for these motor effects on the intestine is "pitressin," and not "petressin" as such, but the interesting point is this, if you increase your dose of "pitocin," because it is 96 per cent pure, as you increase that, you eventually find that the large intestine will respond to pitocin but the small intestine will not respond at all.

Perhaps one should say there is some difference in the large intestine as compared with the small, which will make it respond to pitressin.

Another thing about the large intestine which might be considered is that it is an extremely sensitive portion of the intestine and its mucosa is considerably more sensitive to purgatives than is that of the small intestine, as shown by the recent work of Straub. He found that infusion of senna (10 per cent) will cause increased movements in the small intestine, whereas 0.1 per cent of infusion of senna will cause marked movement in the large intestine and will be ineffective on the small intestine.

Another point which perhaps might be stressed is this: Dr. Bargen said that bismuth is absorbed from the large intestine. Now, as a student, each of us was probably taught if there is one thing in which the large intestine differs from the small, it is that it acts as an excretory organ, and if you take bismuth and give it, you will get a blackening of the mucosa. One doesn't deny it might be absorbed from the large intestine.

Now, to utter one violent heresy, the large intestine, as you know, has three longitudinal bands and a lot of circular muscles. If you look at the large intestine when you produce a peristaltic wave, you find that the peristaltic wave confines itself almost exclusively to the circular coat and that the longitudinal bands are there merely for support of the circular coat; and, secondly, produce retraction to allow the circular muscle in contracting to pass the movements on better.

I should like to ask Dr. Bargen to observe when he gives morphine to a human being, say with the barium, in the large intestine, whether there are any increased reversed peristaltic waves following the use of morphine and some of the other drugs he uses.

DR. WALTER A. BASTEDO (New York, N. Y.): We like to see experiments such as these made on the human animal because, in the last analysis, that is our guide for the use of drugs in medicine. I have done animal experiments on the bowel with some of these drugs, particularly physostigmine, but also with pituitrin and atropine.

As to the four drugs mentioned, we have to think of pituitrin as acting on the muscle essentially. That puts it in quite a different category. Physostigmine, or eserine, acts essentially by enhancing and prolonging the influence of vagus stimulation. Acetylcholine has the effect of vagus stimulation if you can put it in the right place, but acetylcholine by hypo is very quickly destroyed by the tissues of the body or in the blood stream. Cascara, (represented by "peristaltin")—well, there isn't any active principle of cascara that has ever been isolated that will produce the same effect as cascara; and although you can get some action by hypodermic material made from cascara, unless one gives a great deal, much more than one would have to give by mouth, one can't get any effect on the bowels.

As far as the dose of eserine is concerned, a number of years ago I tested patients, post-operative, with physostigmine by hypo in doses of 1 milligram and two milligrams, and found it very inefficient. Sometimes we would get a little action and sometimes we wouldn't get any, even from two milligrams, that is, a thirtieth of a grain.

Martin and Weiss obtained very good results from double that dose, four milligrams, a fifteenth of a grain, but when one reaches that point of dosage, as Dr. Bargen has pointed out, one begins to get the toxic symptoms of physostigmine, which, as you know, are nausea and salivation, and, very strikingly, cramps in the bowel.

We found that physostigmine tends to increase peristalsis in the small intestine and to increase the tone waves into spasm or cramp. This effect can be completely overcome by atropine. We don't want cramps, and cramps result from physostigmine in dosage just a little larger than that which tends to stimulate peristalsis.

Of course, when we talk about peristalsis in the large bowel, I don't think we know much about it. We know a lot about the small bowel because that organ is so much more easy to work with, as its actions are rapid. We must think of the large bowel as an organ that holds back material instead of pushing it on, the small bowel emptying liquid into the large bowel all day long, and the large bowel expelling solid material only once or twice a day. The colon's job is to hold things back, not to push them along, except at very rare intervals; therefore, we have to be careful not to transfer the results of experiments on the small intestine to the large.

Just one more point: Drugs that stimulate the vagus—I mean that enhance the action from vagus stimulation—depend for their action, as vagus stimulation does also, on the state of the bowel at the time. If the bowel is contracted, if it is hypertonic, stimulation of the vagus causes it to relax—again I have made a mistake—we shouldn't say "vagus," but rather parasympathetic, for the vagus does not supply the colon in man. If the colon is in a relaxed state, parasympathetic stimulation tends to cause its contraction. This apparently contrary action, according to whether the bowel is in hypertone or hypotone, is a new idea to us medical men, but a fact established by a great many experimenters at the present time.

DR. J. ARNOLD BARGEN (closing the discussion): The suggestions of Professor Dreyer and Dr. Bastedo are very much appreciated. The opportunity for further intensive study of other drugs is constantly at hand. We chose the four drugs mentioned because they are the ones in common usage among surgeons and clinicians in the control of paralytic ileus of various kinds. We realize that the work of the last few years has but opened the field. We hope that these discussions will stimulate others sufficiently so that more intensive studies of this type will be undertaken.