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THE EFFECTS OF DRUGS USED IN ANESTHESIOLOGY ON THE TONE AND MOTILITY OF THE SMALL INTESTINE: AN EXPERIMENTAL STUDY *

ROBERT F. GOLDEN, M.D., AND FRANK C. MANN, M.D. †

Rochester, Minn.

POSTOPERATIVE alterations of tone and activity of the small intestine are common surgical complications. Fortunately the patient usually recovers from these irregularities of intestinal motility regardless of treatment given. They nevertheless cause considerable distress and their elimination would add much to the comfort of both patient and surgeon. The most important of these postoperative complications which involve the small intestine are commonly known as "gas pains," "distention" and "adynamic or paralytic ileus."

It is generally agreed that trauma plays the major role in their production; yet these complications are encountered following operations which do not involve the abdominal cavity (1). Everything occurring in the preoperative, operative and postoperative routine has been considered at some time or another an etiologic factor in their production. Anesthetic agents have long been charged with partial responsibility for these complications. Experimental work and clinical observations have been too few and inconclusive to evaluate properly these agents as etiologic factors. In order more properly to do so, it was decided to make a comparative experimental study of the effects of anesthetic agents, including some of the newer agents and combinations of agents, on the tone and motility of the small intestine.

Several investigators have studied the effects of various drugs and anesthetic agents on the tone and motility of the alimentary canal. Most of these experiments were not carried out under ideal conditions.

* Abridgment of thesis submitted by Dr. Golden to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M. S. in Surgery.

† From the Department of Surgery and the Division of Experimental Medicine, Mayo Foundation, Rochester, Minn.

It has been demonstrated (2) that a balloon under pressure of only 2 mm. of mercury, when placed within the lumen of the small bowel, can cause changes of the character of the motility. One must therefore judge with reservation any conclusions from experiments employing any intraluminal apparatus which exerts pressure (3). Observations on isolated loops of intestine not in continuity are also of limited value since continuity and the presence of normal intestinal contents may play an important role in maintaining intestinal motility.

With the development of a technic (4) for exteriorizing loops of small intestine in continuity, enclosed in bipedicled tubes of skin, it became possible for investigators to observe the bowel in a practically normal state. Recordings of the motility could be made with apparatus which exerted little more pressure on the bowel than was normally present. Several investigators (5, 6, 7, 8, 9, 10) have employed this method in studies of various phases of intestinal activity and their results support the belief that this is a satisfactory method for studying intestinal motility.

A considerable difference of opinion exists in the literature on the experimental effects of anesthetic agents and preanesthetic medication on the intestinal tone and motility. This is true even in instances in which the same technic and general problems were investigated. However, none of these studies has been made employing the exteriorized loop. This method was ideal for other investigations of the small bowel, and it was felt best to employ this same technic in these proposed studies. The dog was the logical experimental animal.

Because of demonstrated differences of normal intestinal activity of the dog at various periods after feeding, it was felt advisable to investigate the effects of anesthetics under the following conditions: (1) shortly after feeding, (2) after eighteen hours' fast and (3) after forty-eight hours' fast. Since it has been demonstrated (7, 8, 11, 12) that a so-called feeding reaction is a definite characteristic of the activity of the small bowel, it was decided to include a study of the presence or absence of this reaction after anesthetic agents had been administered.

Some investigators found different responses to the same stimulus in the two portions of the small bowel. Because of this and the normal difference in rate of contraction between the jejunum and ileum (13, 14, 15), it was felt advisable to use both portions of the small intestine in this study.

METHOD

The effects of anesthetic and preanesthetic drugs on the motor activity of both portions of the small intestine were studied in dogs that had permanent exteriorized loops of bowel in continuity, sheathed in a sleeve skin graft. Young healthy animals weighing from 7 to 14 kg. were used. Jejunal loops were established as close as possible to the duodenum and those of the ileum were made as near as possible to the ileocecal valve.

The high or jejunal loops were exteriorized on the animal's right upper quadrant and the low or ileal loops were brought out on the lower left quadrant. The animals were trained to lie on the side which was free from the exteriorized loop. This latter step was found to be an important procedure from the standpoint of preventing respiratory activity from being recorded on the kymograph. If the loop and its associated recording apparatus were permitted to lie between the animal and the padded animal board, respiratory excursions were recorded along with intestinal motility. If on the other hand the loop and apparatus were permitted to ride free on the abdomen and superior lateral wall, only the most violent respiratory activity was recorded. Intestinal motility did not change under the same conditions, regardless of which side the animal was allowed to lie on.

The loops were established as an aseptic surgical procedure with the animal under ether anesthesia in single stage operations. Two parallel incisions about 2 inches (5 cm.) apart are made through the skin of the abdomen for a length of about 6 inches (15 cm.). These are made so far as possible in the right upper or left lower quadrants depending on which region of the bowel is to be exteriorized. The skin is freed from its underlying tissue between the incisions, wrapped in a saline pack and pulled to one side. The remaining layers of the abdominal wall are opened by an incision running parallel to the first incisions and about midway between them. A loop of intestine from the desired region is selected and its mesentery is split in a bloodless area and opened as wide as possible without injuring vessels and nerves. This loop is then exteriorized and included with the skin flap in a saline pack.

The peritoneal and fascial layers of the abdominal wall are then sutured in layers with linen, an adequate opening being allowed to remain at each end of the incision. This opening is for the limbs of the exteriorized loop and its associated mesentery and necessarily must not be tight enough to compress the intestinal lumen. The loop and its mesentery are then enclosed in the skin which is sewed about them as a sleeve graft with linen sutures.

The skin lateral to the covered loop is then undermined to each side and brought together beneath the loop. The resultant loop, which resembles the handle of a suitcase, is completely enclosed in skin, as is the abdominal wall beneath, leaving no open wounds.

Experimental observations were not made for at least two weeks after operation, the animals being trained during this period. They were conditioned to the apparatus and the noise made by the running kymograph and were taught to eat solid and semisolid food while lying on their sides on a padded board with minimal restraint.

The apparatus used to record the motor activity of these loops of intestine was somewhat different from that previously described by Douglas and one of us (Mann) (6) and others. These investigators attached a tambour to the loop by means of an inelastic clip. Oppenheimer and one of us (9, 10) (Mann), working on different problems,

devised a method of enclosing the loop in a rigid cuff of heavy pressure tubing of large diameter. This diameter was held constant by taping the entire circumference securely. The loop as a result was enclosed for from 1 to 2 inches (2.5 to 5 cm.) within a tube or shell. Several different sized cuffs were made so that each loop had a properly fitted tube. These cuffs were removed after each experiment.

The pressure tubing cuff when properly applied to the loop surrounded it much as a tire and rim would surround an underinflated inner tube and allowed adequate room for the insertion of a small rubber condom balloon. This balloon was attached to small gage pressure tubing by an airtight connection. This tube was in turn attached to a tambour arm recording apparatus for tracing on a moving kymograph. A clamped T tube was placed in this air displacement system for the purpose of inserting sufficient air pressure.

With this method, it is important to manipulate the condom balloon considerably to be sure it is distended and fits snugly so that all changes of pressure will be related to intestinal activity and not to the balloon's assuming a new position. Once properly assembled, such an apparatus will maintain pressure relationships for several hours of constant use unless an air leak is present in the system.

Twenty-two animals were used in these studies in order that each animal might have adequate rest on a normal routine between experiments. Two of these animals had both jejunal and ileal exteriorized loops and were used chiefly for the purpose of establishing relationships between the responses of the two loops to the same stimulus. They were not used otherwise because of the technical difficulties of operating two separate recording units simultaneously while administering anesthetic agents.

More than two hundred hours of observations were devoted to the study of normal intestinal activity in order to obtain adequate controls. In the course of these observations, each animal was tested for the presence and character of the "feeding reaction" several times.

In these normal observations, four types of intestinal motility were observed: namely, irregular segmentation, regular segmentation, tonus waves and peristaltic waves. Irregular segmentation was the predominant type of activity; regular segmentation occurred for brief intervals, especially after the stimulus of feeding. Peristaltic waves occurred much less frequently than the other types of activity but exhibited the characteristic dilatation followed by a wave of contraction. These findings were in agreement with those of Castleton (5) and Douglas and one of us (Mann) (6).

One characteristic of intestinal motility was noted which has not been discussed much in the literature. This was the amplitude of contractions. This amplitude varied from time to time and appeared to be an index of the forcefulness of contractions. As would be expected

if this were true, the amplitude was increased with any stimulation and decreased with the length of fast or any depressant.

The response to feeding a fasted animal was so constant that it is believed to be a definitive characteristic of the musculature of the small bowel. Soft, semisolid and solid meals all produced the same reaction, but that produced by the latter type of meal was more definite and lasting in character. This was also demonstrated by Grindlay and one of us (Mann) (16) in a more extensive study of this relationship between type of meal and the resulting feeding reaction. Because of this more pronounced reaction to solid food, it was decided to use 400 Gm. of minced cooked meat as a standard meal in all observations for the presence of this feeding reaction after anesthesia.

These reactions were all studied by first making a control record of the intestinal activity of a fasted animal and then feeding the animal while it was still lying on the table with the recording apparatus operating. It seems well to mention that in no instance was any reaction observed till after food had been consumed. This was first demonstrated by Hinrichsen and Ivy (12). Even when the animals had become educated to the fact that they were about to be fed and the meal was placed before them, no response was noted till they had actually ingested food. Activity following a meal appeared as soon as one minute in jejunal loops and as late as fifteen minutes in ileal loops. The general average was three minutes for the high loops and eight minutes for the low loops.

Segmental activity, whether regular or irregular in type, maintained a constant rate of contraction for each particular loop. These rates varied from 20 per minute in jejunal loops to 11 per minute in ileal loops. This is an agreement with the findings of Alvarez (13, 14).

Quiescent periods were noted at brief and widely spaced intervals during the first few hours after feeding. These periods gradually increased in frequency till they consumed at least half the record at observations after a forty-eight hour fast. They appeared a little more often in the ileal loops than in the jejunal loops.

In every experiment, control observations of from fifteen to thirty minutes were made before administration of the anesthetic agent to be studied. Observations were made continuously from the control period till the motility had resumed a more or less normal state. This included the induction and maintenance periods of anesthesia. After the motility had reached this more or less normal state after anesthesia, periodic observations were made up to twenty-four hours after anesthesia.

Recordings of the tone were of little value once it became necessary to remove the animals from the board and associated apparatus since in subsequent recordings it was necessary to assume that the same pressure existed within the recording system. However, no difficulty was encountered in recording motility proper, except for slight differences

of amplitude as a result of these differences of pressure within the system. All observations made within the first three to five hours were made without removing the animals from the apparatus and therefore these factors did not influence in any way the most important periods of observation. The periodic observations which were made up to twenty-four hours after anesthesia were evaluated with realization of these minor deficiencies. A satisfactory method could not be found for returning the animals to the apparatus, once removed, with the same pressure relationships. Because of this, the Delahanty table used by other investigators for spinal administration of anesthetic agents was not used in these studies (17). All spinal punctures were performed with the animals on the observation table and the recording apparatus attached and running throughout.

Anesthetic gases and combinations were administered by a standard clinical gas machine adapted for use on laboratory animals as described by Mousel and Seldon (18). Ether was administered by the open drop method. In all experiments, anesthesia was maintained at surgical levels, or as near there as possible, for a period of fifteen minutes. Surgical anesthesia of stage 3, plane 2, according to Guedel (19), was maintained whenever it was possible to do so with the particular anesthetic agent in question. This degree of anesthesia was possible in nearly every instance. It may be argued that the dog and human beings do not react alike for various planes and stages of anesthesia. However, complete skeletal muscular relaxation and absence of response to standard stimuli were present in every case in which the animal was assumed to be in surgical anesthesia. We feel certain that major surgical procedures could have been carried out on these animals in every instance.

Observations to determine the presence or absence of feeding reactions were made after a forty-eight hour fast. The animals were given anesthetic agents in the usual fashion and were fed a standard meal thirty minutes after administration of the anesthetic agent had been stopped or as soon thereafter as the animal was able to consume food. Artificial or forced feedings were never attempted. In most instances, the dogs were able to eat within forty-five minutes after anesthesia. Observations for feeding reactions were not made following administration of combinations of anesthetic agents.

There was so little difference between the results obtained with combinations of anesthetic agents and with the principal agent contained therein, that studies were made on these combinations at the eighteen hour postfeeding interval only.

RESULTS

As stated previously, the effect of each agent or group of agents was studied on both jejunal and ileal loops. In the case of all major agents, these studies were carried out after feeding, after eighteen

hours' fast and after forty-eight hours' fast. In general, so little difference was found between the results of the two loops, even at different periods after feeding, that they do not warrant individual discussion in most instances. Where significant, these differences will be described. As a general rule, the longer the fast, the longer the recovery period regardless of the agent being studied.

I. Morphine.—In all experiments with this drug, the animals were given subcutaneously a dose of 1 mg. of morphine sulfate per kilogram of body weight. This dose was sufficient in every instance to produce vomiting shortly after administration. In many cases, defecation also occurred after administration of morphine.

In 18 experiments performed on both high and low loops, administration of morphine was followed by slight increases of tone and segmental activity for from twenty to forty minutes. These were followed by a sharp decrease of tone and a cessation of all motility for from one and a half to two and a half hours. Recovery after this depression was gradual and progressive over thirty to forty-five minute periods and all records beyond this stage were essentially normal (fig. 1).

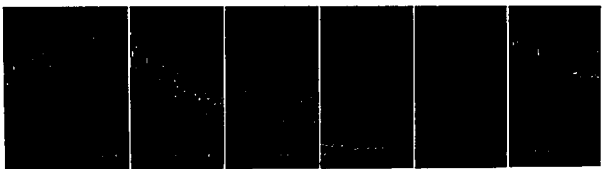

FIG. 1. Effect of morphine on activity of loop of jejunum. *a.* Normal control; *b*, five minutes; *c*, fifteen minutes; *d*, twenty-five minutes; *e*, one and a half hours and *f*, two hours after administration of morphine sulfate. Time in five second intervals.

Fasted animals given the standard test meal one hour after administration of morphine did not exhibit any signs of feeding reaction. These results are in accord with those obtained by Oppenheimer and one of us (Mann).

II. Atropine.—In all experiments with this drug, the animals were given subcutaneously a dose of 1/100 grain (0.00065 Gm.) of atropine sulfate. In 18 experiments on both high and low loops administration was followed within three to ten minutes by marked reduction of tone and cessation of all motility. This paralysis persisted for from one to two hours and was followed by a slow progressive return to normal activity within another hour. All subsequent observations were essentially normal. In no instance was any sign of a feeding reaction noted when fasted animals were given the standard meal after administration of atropine.

III. Morphine and Atropine Combined.—In all experiments, the same doses were given as had been used in the previous separate studies: 1 mg. of morphine sulfate per kilogram of body weight and 1/100 grain (0.00065 Gm.) of atropine sulfate for each animal. These drugs were given in solution in the same subcutaneous injection. Observations were made only at the eighteen hour fast periods.

A. Jejunal loops.—In 3 experiments, vomiting was produced within five minutes. This was followed by a slow progressive reduction of tone and amplitude of segmental activity over a period of twenty to thirty minutes, terminating in a complete cessation of motility. As in the case of these drugs when used separately, atypical contractions appeared and normal rates and levels were reached only in about two hours. Records taken at periodic intervals thereafter were essentially normal.

B. Ileal loops.—In 3 experiments, vomiting was produced within five minutes and this was followed by a short period of increased amplitude of contractions. Motility soon reached normal levels, however, and persisted in this manner. The presence of a stimulus was questionable but the absence of a depression was definite.

IV. Avertin.—Avertin (tribrom-ethyl-alcohol) was administered in combination with amylene hydrate in solution by rectum in the usual manner. A dose of 100 mg. per kilogram of body weight was used as it was the smallest dose which would produce definite drowsiness and a tendency to sleep. Any significant stimulation of the animals, however, produced alertness even with this dose. In every case, the insertion of the rectal tube caused a cessation of motility and a loss of tone for short periods. Injection of the solution caused this period to be lengthened slightly. It could also be lengthened by inserting warm water. This depression was obviously not related to the avertin proper. Three experiments with jejunal loops and three with ileal loops were observed at the standard periods of fast. In no instance was any depression or stimulation observed. Feeding reactions were present in all instances so studied.

V. Pentothal Sodium.—This agent was given intravenously in 2.5 per cent solution in amounts sufficient to produce satisfactory third stage anesthesia according to the criteria of Lundy (20). The dose naturally varied for different animals but averaged from 20 to 25 mg. per kilogram of body weight. It was noted that the fasted animal apparently required less pentothal sodium for the same degree of anesthesia than the same animal required when recently fed. Actually, about 60 experiments were made using this drug, but only representative cases are reported herein.

It was observed that the rate or speed of administration of this agent was the most important factor in determining the end result. When administered rapidly, a marked loss of tone and cessation of all motility were noted which persisted as long as twelve minutes. The

duration of this depression seemed related to the total dose given in this single dose technic for producing anesthesia. Anesthesia in these cases lasted usually twice as long as this depression, however. If the drug was administered slowly, the same degree of anesthesia could be produced without appreciable change of the tone and motility in either the high or the low loops.

Thirty-six representative experiments, half with the slow and half with the rapid administration technic, were studied with this drug at the standard periods after feeding. In every instance of the slow administration group no change of tone or motility from normal was noted at any period during or after anesthesia (fig. 2). In those experiments

FIG. 2. Effect of pentothal sodium when given slowly on activity of loop of jejunum. *a*. Normal control; *b*, immediately after completion of injection; *c*, ten minutes and *d*, thirty minutes after injection. Compare with figure 3. Time in five second intervals.

in which administration was more rapid, loss of tone and cessation of motility were noted immediately and persisted from eight to twelve minutes. Motility and tone returned to normal levels shortly thereafter, however, and remained so in all subsequent observations (fig. 3). Typical feeding reactions were obtained in every animal so tested after anesthesia.

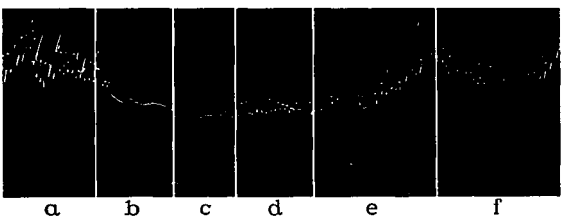

FIG. 3. Effect of pentothal sodium when given rapidly on activity of loop of jejunum. *a*. Normal control; *b*, during injection; *c*, five minutes; *d*, eight minutes; *e*, ten minutes and *f*, twenty minutes after injection. Compare with figure 2. Time in five second intervals.

VI. Ether.—This anesthetic agent was administered by the open drop method using a special fitted cone of metal which surrounded the animal's face. In all experiments, the animals were kept in plane 2 of third stage anesthesia, according to the criteria of Guedel (19), and

were maintained at this level for a period of fifteen minutes. This technic was followed in all inhalation anesthesia. A few animals were anesthetized as long as one hour at this level, but the results did not differ sufficiently from those instances in which the anesthesia was of fifteen minutes' duration to warrant extensive investigation.

In 18 experiments on both jejunal and ileal loops, tone was lowered and motility ceased with the onset of surgical anesthesia. When administration of ether was discontinued, tone and motility gradually returned to normal levels within ten to twenty-five minutes (fig. 4). No delayed changes were noted in any instance. In every case in which fasted animals were given a standard meal after anesthesia a typical feeding reaction resulted.

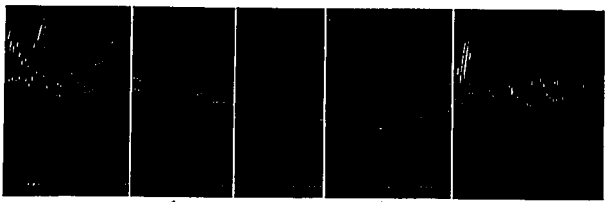

FIG. 4. Effect of ether on activity of loop of jejunum. *a*. Normal control; *b*, beginning third stage anesthesia; *c*, during surgical level of anesthesia; *d*, ten minutes and *e*, fifteen minutes after withdrawal of anesthetic agent. Time in five second intervals.

VII. Ether After Premedication with Morphine and Atropine.—Morphine and atropine were given in the same doses as used in the previous combined experiments. They were given subcutaneously thirty minutes before ether anesthesia was instituted. This combination was observed only at the eighteen hour fast period. As in previous ether experiments, anesthesia was maintained at surgical levels for a period of fifteen minutes.

A. Jejunal loops.—In 3 experiments there was a gradual progressive depression of tone and motility over a period of twenty-five minutes following administration of the morphine and atropine. With the onset of ether anesthesia motility ceased entirely. Tone and motility returned to normal levels within one and a quarter to one and a half hours after administration of ether was discontinued.

B. Ileal loops.—In 3 experiments there was a very slight reduction of tone and amplitude of contractions. With the onset of ether anesthesia, the tone was depressed and motility ceased. Within five minutes after ether was withdrawn, tone and motility had returned to normal levels. No delayed changes were recorded.

VIII. Ethylene.—Ethylene-oxygen anesthesia was maintained for fifteen minute periods in third stage levels. If this level could not be maintained without producing cyanosis the experiment was discontinued. It was important to note that in the few instances in which for some reason satisfactory anesthesia could not be maintained, no depression of the tone or motility was observed. With this anesthetic agent, as with ether, any lightening of the depth of anesthesia was followed promptly by a return of motility. In such instances, however, only second stage anesthesia was being maintained.

In 18 experiments on loops of both levels, surgical anesthesia was accompanied by a reduction of tone and a cessation of all motility. Both returned to normal levels within five minutes after the anesthetic agent was withdrawn (fig. 5). In five of the six experiments in which the animals were given a test meal after anesthesia, there was a typical feeding reaction. The other animal did not show any response within the first hour but did subsequently.

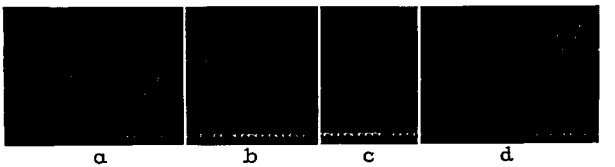

FIG. 5. Effect of ethylene-oxygen anesthesia on activity of loop of jejunum. *a*. Normal control; *b*, second stage anesthesia; *c*, third stage anesthesia; *d*, ten minutes after withdrawal of anesthetic agent. Time in five second intervals.

IX. Nitrous Oxide.—With nitrous oxide-oxygen anesthesia, a depth of anesthesia sufficient to produce relaxation of the skeletal muscles was always accompanied by cyanosis. The question may be quite properly asked whether the cyanosis and anoxemia or the nitrous oxide produced the results obtained. All experiments were necessarily carried to the point of cyanosis and in all there was depression of tone and motility at this level. Several animals showed temporary periods of increased amplitude of contractions immediately after administration of the anesthetic agent was discontinued. Anesthesia carried as deep as possible without causing cyanosis produced very little relaxation of the skeletal muscles and in turn no demonstrable changes of the tone and motility of the small intestine. Nine experiments on jejunal and nine on ileal loops were performed at the usual periods after feeding. Definite feeding reactions were observed in every case in which a fasted animal was given a standard meal after anesthesia.

X. Cyclopropane.—Cyclopropane-oxygen anesthesia was carried to plane 2 of the third stage and maintained at this level for periods of fifteen minutes. Cyanosis was never observed and relaxation of the

skeletal muscles was complete. In 18 experiments on both loops the tone was reduced and motility ceased during anesthesia. In every case but one they returned to normal levels almost immediately after the withdrawal of the agent. In this one case, recovery was not complete for one hour after anesthesia. It was, however, so atypical a response that it was deemed unworthy of further consideration. Short periods of slightly increased amplitude of contractions were observed in the records of the first ten minutes after anesthesia but the contractions were entirely normal thereafter. All animals exhibited typical feeding reactions when fed the standard meal after anesthesia.

XI. Spinal Anesthesia.—Procaine hydrochloride in doses of 2 cc. of a 2.5 per cent solution was used in each of these studies. This dose was found sufficient to produce complete paralysis of the hind quarters and a sensory loss to the upper thoracic levels for a period of forty-five minutes. A spinal puncture was considered successful only if spinal fluid could be aspirated freely before and after the injection of procaine. All animals became unusually nervous and irritable as the effects of anesthesia began to wear off. When this occurred, the amplitude of contractions was reduced and in some cases this persisted as long as one hour. Records beyond this time, when the animals had become more calm, were essentially normal. This depression may or may not have been related to the nervousness of the animals but we assumed that it was a direct result of this irritability. In no other group of experiments did the dogs exhibit such excitability. Because of this and the technical difficulty of making satisfactory spinal punctures, observations were not made for the presence of the feeding reaction following spinal anesthesia. All spinal punctures were made between the last thoracic and the first lumbar vertebra.

In 12 experiments on both high and low loops, injection of the procaine was followed almost immediately by defecation and a short period of reduced tone and depressed motility. Following this a very definite increase of motility, amplitude and tone was observed which persisted for an average of forty-five minutes. As the effects of the anesthetic agent began to wear off, the animals in all instances became much excited and the tone and motility were reduced during this period. This depression of the musculature of the small bowel lasted for as long as forty-five minutes. Normal activity was present in all subsequent records after the animals had reached a more or less rational state (fig. 6).

XII. Pentothal Sodium Supplemented with Ether.—Pentothal sodium was given intravenously after normal observation periods in doses of 20 mg. per kilogram of body weight, administered slowly. Following this, ether was given by the open drop method and the animals were maintained at surgical levels of anesthesia for fifteen minute periods. These observations were made only at the eighteen hour fast period.

In 6 experiments on low and high loops, injection of the pentothal

sodium by the slow method did not produce any demonstrable changes of tone or motility. With the onset of ether anesthesia, tone was reduced and motility ceased. Normal levels of activity were reached within fifteen minutes after ether was withdrawn. No delayed changes were observed.

XIII. Ethylene-Oxygen and Ether.—In these experiments, the animals were given ethylene-oxygen mixtures through the induction periods and then the gas mixture was given with ether (closed method) to produce surgical levels of anesthesia. The animals were maintained for fifteen minute periods as in other experiments. A standard clinical gas machine was used as with other combinations of anesthetic agents, the gas mixture being allowed to pass through ether. Observations were made at the eighteen hour fast periods only.

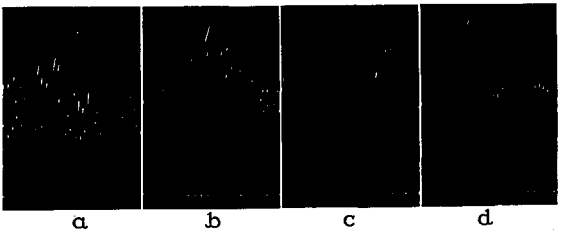

FIG. 6. Effect of spinal anesthesia on the activity of a loop of jejunum. *a*. Normal control; *b*, fifteen minutes; *c*, thirty minutes and *d*, two hours after injection. Time in five second intervals.

In 6 experiments, depression was not noted with induction but as surgical levels of anesthesia were reached, the tone was lowered and motility ceased. Both returned to normal levels within five to twenty minutes after anesthesia.

XIV. Pentothal Sodium Supplemented with Nitrous Oxide-oxygen.—The pentothal sodium was given intravenously, following normal observations, in doses of 20 mg. per kilogram of body weight. This agent was administered by the slow method. Following this, the animals were allowed to breathe a gas mixture of equal parts of nitrous oxide and oxygen for fifteen minutes. Surgical levels of anesthesia were present in the first portion of this period but not in the latter half. Six experiments with jejunal and ileal loops were performed at the eighteen hour fast period. No changes of the tone or motility were noted.

XV. Nitrous Oxide-Oxygen and Ether.—In these experiments, nitrous oxide-oxygen mixtures were given through induction, after which the gas was combined with ether (closed method) producing surgical levels of anesthesia. Six experiments with high and low loops at the

eighteen hour fast period were similar in every respect to those of the ethylene-oxygen and ether anesthesia group.

XVI. Avertin Before Ethylene-Oxygen.—Avertin in solution in doses of 100 mg. per kilogram of body weight was given by rectum after normal observations. In thirty minutes, ethylene-oxygen gas mixtures were given, producing third stage anesthesia for fifteen minutes. Observations were made only at the eighteen hour fast period with 6 experiments on both high and low loops. The results were identical with those obtained in the ethylene-oxygen group without basal anesthesia. Apparently little if any effect could be attributed to the use of avertin other than to bring about a more rapid induction.

XVII. Avertin Before Cyclopropane-Oxygen.—Observations were made at the eighteen hour fast period only with 6 experiments on jejunal and ileal loops. Results were identical with those obtained with cyclopropane-oxygen anesthesia alone.

General.—Under the heading of each specific agent or combination of agents studied, the observations made are listed briefly, but in order to prevent unnecessary repetition, some general observations are here reported which were more or less common to all groups.

With the exception of the studies on morphine and atropine, alone or in combination, and on these drugs and ether in combination, the rate of contraction for any particular loop of bowel remained constant. Whenever, as a result of some depressing effect, there were no contractions, there was naturally no rate present, but as soon as motility returned, the characteristic rate was noted in every study except with the agents listed in the first part of this paragraph. In the case of these exceptions, the rates were atypical only during the recovery periods.

During recovery in these exceptions, the rates varied from 3 to 6 contractions per minute and their character was that of a fatigued or depressed musculature. There were numerous short periods of quiescence which became less frequent as the effects of the drugs gradually wore off. In the later stages of this recovery, the rates fairly rapidly changed to the normal rate for the loop in question and remained constant thereafter.

In every observation reported, the statement is made that the tone and motility returned to normal levels within certain periods. This is not entirely true, for with the exception of avertin, careful study revealed a change of the relative type of motility which remained present for about twelve hours. The change consisted in a relative increase of the occurrence of peristaltic waves. The irregular type of segmentation was still the predominant type of activity. Actual percentage computations are of no value since they would necessitate a steady type of observation and the animals were too nervous and irritable after three to five hours' study to permit this.

COMMENT

Administration of morphine usually was followed by increased motility which persisted as long as forty minutes in one instance but was usually present for much shorter periods. It is believed that this stimulation is not as important in the species of animal studied as the depression which follows. Gruber and Robinson (21) illustrated the confusion which has existed on the effects of morphine on the intestines by reviewing the works of nearly thirty authors who have studied this problem in detail. They fall nearly equally into two schools, one concluding that morphine stimulates and the other that the drug depresses intestinal motility. The results of the earlier investigators in general support the hypothesis that morphine has a depressing effect but the results of the more recent studies indicate that it has a stimulating effect. These studies have been made with nearly every technic so far devised except the one we used. Some of the contradictory results may also be owing to differences of response in different species. After study of the results herein reported, it is believed that all of the investigators were observing true effects of morphine, but that none of the studies, including the present, is thorough enough to solve the problem properly.

Quigley, Highstone and Ivy (22), working with Thiry-Vella loops of jejunum, studied the propulsion time under the effects of morphine, and their results were similar to those obtained in this investigation. In fact, their observations suggest a longer depression than was noted here. Childrey, Alvarez and one of us (Mann) (23) observed the effects of morphine in dogs whose colons had been removed and ileorectal anastomosis performed. They noted a definite constipating effect for an end result. It is interesting to note that in their study, the administration of morphine was followed almost immediately by increased intestinal activity and defecation. In our study, defecation was also observed frequently in the early stages when stimulation was present. In a recently reported study on the human being, Puestow (24) observed a gradual increase of tone and motility of the terminal segment of the ileum without any secondary depression following the administration of morphine.

Atropine, when used alone, is considered a depressant by nearly all investigators. Results obtained in this study agree with this view. Bisgard and Johnson (25) were the only investigators not reporting any change of the tone or motility of the intestines of dogs after administration of atropine. They did, however, note depression when the drug was given to human subjects. There is little evidence to support any result other than depression after administration of atropine alone regardless of animal or technic used.

In these studies, atropine and morphine were administered together in a single injection in an attempt to simulate clinical preoperative

routines. Bisgard and Johnson (25) expressed the belief that the effects of morphine and atropine neutralize each other, resulting, when given together, in essentially no change. With this same belief in mind, many studies made with these drugs in combination have been done by first administering one drug and then the other after an interval. Other doses were given in an attempt to establish a balance between the depressing effects of atropine and the so-called stimulating effects of morphine.

The results obtained in this study on the effect of morphine and atropine combined on loops of jejunum are similar to the results noted by Carlson (26), and our observations on loops of ileum compare favorably with those made by Plant and Miller (27). There was no special difference observed when ether was given after the combination of morphine and atropine.

In general, more depression resulted from the use of preanesthetic drugs than from any anesthetic agent regardless of the depth or duration of anesthesia. The only exception to this was the use of morphine and atropine in combination on low ileal loops.

The use of avertin alone or as a basal anesthetic agent did not produce any change of intestinal activity, apart from the depression of activity which followed insertion of the rectal tube and/or the warm solution of avertin. This effect was also produced by an enema of warm water (28).

One of the most interesting findings of this study was the relationship between rate of administration of pentothal sodium and the depression produced. Rapid administration invariably produced a profound and immediate loss of tone and cessation of muscular activity. Except in instances in which very large doses were given, tone and motility returned to normal levels within a short period, usually within fifteen minutes. On the other hand, slow administration of the drug in the same doses produced essentially no change of the tone or motility, yet gave the same degree of anesthesia. Lundy (29) expressed the belief that this and other depressions following administration of pentothal sodium are due to rapid administration.

With ether, as with nearly all inhalation anesthetic agents, definite depression of tone and motility was observed in third stage anesthesia. Any lightening of the depth of anesthesia to less than this level usually resulted in slight elevation of tone and a return of segmental activity on a very limited scale as long as some anesthesia was maintained. Increasing the depth to surgical levels again would always result in depression of tone and motility. Recovery was fairly rapid with these anesthetic agents and no delayed effects were observed other than the relative increase of regular segmentation and the infrequency of peristaltic waves.

Bisgard and Johnson (25) with avertin before cyclopropane anes-

thesia, using ileal loops, produced surgical anesthesia without depression of activity of the small intestine. In our investigation, a depression was produced with this combination at surgical levels of anesthesia. Miller (30), using ethylene-oxygen in what he termed "depths corresponding to clinical levels," did not obtain any depression. When he used this combination in levels of anesthesia permitting relaxation of skeletal musculature, he noted a depression similar to that obtained with ether, but also observed respiratory depression. In the present study, this anesthetic combination was given cautiously and relaxation of the skeletal muscles was produced without respiratory depression. Loss of tone and muscular activity of the small bowel was characteristic of such anesthesia but the recovery was a little more rapid than that following administration of ether.

Spinal anesthesia has been advocated (31, 32, 33) for the relief of ileus because of the increased tone and motility resulting from its use. The results of our study are similar to those already reported. It is believed that with spinal anesthesia the inhibitory influence mediated through the splanchnic nerves is abolished by blocking the rami communicantes. In these observations, the effects persisted as long as the anesthetic agent was effective. When the effects began to wear off and anesthesia was no longer present, the animals exhibited marked nervousness which was not observed with any other agent. During this recovery period, the motility was slightly depressed but it assumed a normal character as the animals became rational.

The feeding reaction as observed in the small bowel appears characteristic of that organ. This reaction was observed after anesthesia in every instance with the exception of those cases in which morphine or atropine was employed. This observation lends support to the belief that these drugs are more depressing than the anesthetic agents proper. It also gives support to the observation that any depression resulting from anesthesia without premedication is of relatively short duration. This ability to obtain a record of a feeding reaction often came before the animals had fully reacted from the anesthetic agent.

Depth of anesthesia is probably more important than duration in the production of any depression of intestinal activity. In a few experiments, ether anesthesia was carried for more than one hour at surgical levels with no more depression after withdrawal than was found with fifteen minute periods of anesthesia. Cannon and Murphy (34) showed depth to be more important in experiments on cats in which the gastric emptying time and the progress of food through the small bowel were visualized by means of roentgenoscopic studies. These same experimenters showed that trauma plays a more important role than any other specific factor in the production of depressions of these functions.

SUMMARY AND CONCLUSIONS

The effects of preanesthetic and anesthetic agents in general on intestinal activity were studied in order to attempt to evaluate the significance of these agents in the production of postoperative complications associated with alteration of intestinal motility. These studies were made on trained dogs that had loops of small intestine in continuity enclosed in bipedicled tubes of skin. Both jejunal and ileal loops were studied.

All anesthetic agents used, except for spinal anesthesia, were found to have either a depressing effect or no effect on the tone and motility of the loops of intestine observed. No definite stimulation was observed. Intestinal activity after anesthesia was characterized by a relative increase of segmentation and decrease of peristalsis. Spinal anesthesia produced increased activity as long as the anesthetic substance was effective.

Morphine produced a transitory increase of intestinal activity followed by a depression which was more extensive than that produced by any other agent studied.

The depth of anesthesia appeared to be more significant in producing a decrease of intestinal motility than the length of anesthesia.

The rate of administration of pentothal sodium was found to be an important factor in regard to the amount of depression of intestinal motility produced by this substance.

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COMING EXAMINATIONS

The Part I (Written) Examinations for certification by the American Board of Anesthesiology, Inc., will be held at various places throughout the country on January 21, 1944.

The Part II (Oral) Examinations of the Board probably will be held in June, 1944, at the place and just prior to the time of the meetings of the American Medical Association. Applications must be filed 90 days before date of examination. Sec., Paul M. Wood, M.D., 745 Fifth Avenue, New York 22, New York.