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Action of Apomorphine Hydrochloride on the Intact Intestine in Unanesthetized Dogs.*

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Gruber and Brundage[1] published the results of 18 experiments performed on 8 dogs with Thiry-Vella loops of the small intestine using apomorphine hydrochloride. In these the drug produced an increase in general tonus in all of the observations made. In some, of which Fig. 1 in their article is an example, the sudden increase in the general tonus was followed by a rather prolonged decrease in the general tonus of the gut. This temporary increase, followed by a prolonged loss in general tonus was noted in the 8 experiments performed on the 3 animals in which the Thiry-Vella loops were of the jejunum, but was not observed in those experiments in which the ileum was used. Since their findings were reported, Slaughter and Gross[2] have presented the results of 10 similar experiments performed on 3 dogs with Thiry-Vella loops of the ileum. In these they observed only a decrease in the general tonus of the gut, whether the drug was injected intravenously or subcutaneously. In some of their experiments complete cessation of the contractions was noted. Because of the discrepancy between the results of the above investigators, additional observations seemed in order.

Six female dogs, weighing from 8.2 to 18.6 kg were used in this research. Except for the fact that in 5 of 6 animals, after the segment of intestine had been detached, the continuity of the alimentary canal was reëstablished by end to end anastomosis, the operation and experimental procedures were the same as those previously described by one of us.[3] In all cases the animals had been without food for 24 hours previous to the experiment, and a week was allowed to elapse between each 2 experiments on the same animal. The drug was administered intravenously to unanesthetized animals.

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1 Gruber and Brundage, PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 863.

2 Slaughter and Gross, *J. Pharm. and Exp. Therap.*, 1938, **63**, 289.

3 Gruber and Brundage, *J. Pharm. and Exp. Therap.*, 1935, **53**, 122.

The apomorphine hydrochloride employed in these experiments was the same as that used by one of us[1] in a previous report and complied with all of the purity tests given in the United States Pharmacopoea XI. In addition to this, through the generosity of Dr. O. H. Plant,‡ we were able to make observations with a sample of the same apomorphine as that employed by Slaughter and Gross[2] in their investigations.

Immediately before each injection, the drug was weighed and dissolved in distilled water so that each cubic centimeter contained 1 mg of apomorphine hydrochloride. The dose administered in each case was 0.02 mg per kg body weight.

Results. Twenty-two experiments were performed on the 6 animals used. In 10 experiments an unmistakable increase in the general tonus occurred and in some of these this increase lasted over 38 minutes. In 5 a decrease only in the general tonus was observed, and in the remaining 7 experiments the results were regarded as doubtful. In these doubtful cases usually an increase in general tonus occurred, which was followed shortly by a decrease which again changed to an increase in the general tonus, *e. g.,* in one experiment the increase in general tonus was of 5 minutes' duration, the subsequent decrease of 8, and the following increase of 21 minutes. In another instance the increase in the general tonus following the injection lasted 13 minutes and the subsequent decrease was 41 minutes long. From this investigation there seems to be a difference in the responses of dogs to apomorphine. Moreover, for no apparent cause, the same dog may respond differently to the drug on different days.†

In one of our animals 3 injections of the apomorphine were made and a decrease in the general tonus of the gut was noted in each instance, even though borborygmi were strongly audible. After 4 injections in each of 2 other animals, only once in each animal was an unmistakable increase in the general tonus of the gut recorded. These increases were obtained after the injection of the sample obtained from Dr. O. H. Plant. With the use of this sample of apomorphine, 4 of the 6 dogs showed increased tonus of the gut following its administration and one of the remaining was doubtful. (See Fig. 1.)

One dog responded invariably to apomorphine by contraction,

‡ The authors wish to thank Dr. O. H. Plant for his cooperation in supplying some of the apomorphine used in this investigation.

† Necropsies of these animals showed that (1) in 2 the loops were excised 10 cm and 35 cm above the ileocecal valve; (2) in 2 others, 91 and 96 cm above the ileocecal valve and 152 and 144 cm respectively from the stomach, and (3) in the remaining 2 animals the loops were removed 125 and 152 cm from the ileocecal valve and only 116 and 91 cm respectively from the stomach.

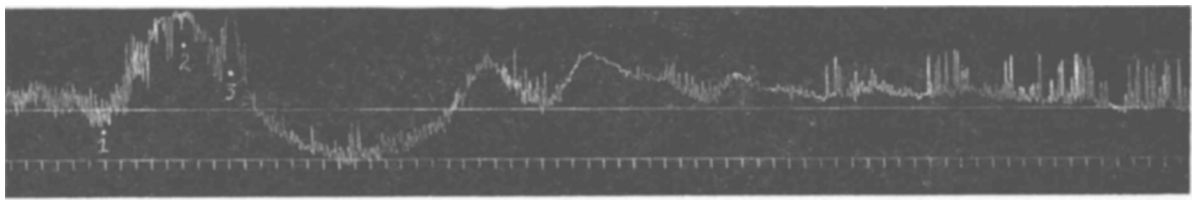

FIG. 1.

Unanesthetized dog. Weight 8.2 kg. Top curve is that of the contractions of the small intestine using a rubber balloon in the Thiry-Vella loop and 15 cm water pressure within the balloon. Bottom record the time in intervals of 30 sec. 1, Apomorphine hydrochloride (0.16 mg) injected into the saphena para vein. 2, Animal nauseated. 3, Animal vomited.

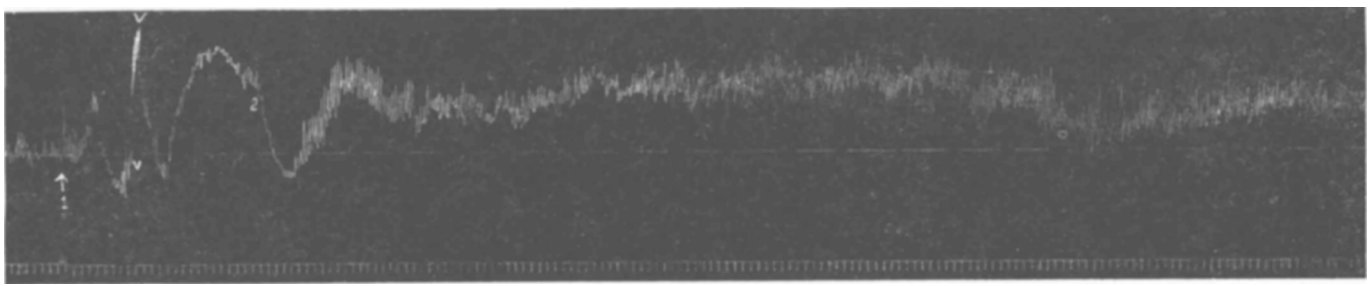

FIG. 2.

Unanesthetized dog. Weight 18.2 kg. Top curve, contractions of the small intestine (See Fig. 1) and the bottom record the time in intervals of 10 seconds. 1, Apomorphine hydrochloride (0.36 mg) injected intravenously. V, Animal vomited. 2, Animal again showed signs of nausea but neither retched nor vomited. A normal control record, showing no change in general tonus, of 45 min duration had been taken before the drug was injected.

and the remaining 2 usually responded by contraction, though in 3 experiments the results again were doubtful.

Fig. 1 illustrates what we regard as one of the doubtful findings. In this experiment the animal weighed 8.2 kg and received, at 1, 0.16 mg apomorphine hydrochloride intravenously. There is seen a sudden increase in the general tonus of the gut which requires approximately 4 minutes to return to the control level. At 2, in the figure, the animal first showed the central effects of apomorphine; nausea, salivation, swallowing and licking reflexes. At 3, the animal vomited. The sudden increase in the general tonus here is mechanical, due to the contractions of the abdominal muscles during retching. Following this, the animal continued to be nauseated. It is during this period that the general tonus of the gut falls below the control level. After the general tonus remains below the control level for 7 minutes it rises again and remains above normal level for about 20 minutes.

Fig. 2 is presented as typical of all the experiments in which an increase in the general tonus was produced by apomorphine. The animal used in this experiment weighed 18.2 kg. After a control record of 45 minutes' duration showed no fluctuation in general tonus of the gut, 0.36 mg of apomorphine hydrochloride were injected intravenously at 1. A sudden increase in the general tonus occurs during the next 20 seconds, which is followed by an equally rapid fall during the period of induced nausea, as shown by licking reflex, salivation, etc. At V the animal retched and vomited and the sudden increase in the general tonus is due to the contractions of the abdominal muscles. At 2, the animal again salivated excessively, and showed the licking and swallowing reflexes but did not vomit. In this, as in all of our experiments, the animal subsequently became depressed, drowsy and slept. In this animal the general tonus of the gut remained above the control level for over 16 minutes.

From the results of these experiments and those previously recorded it is apparent that apomorphine can cause an increase in the general tonus of the small intestine in some unanesthetized dogs. The action, though similar to that of morphine, is not as abrupt, pronounced nor as prolonged as that caused by morphine. These experiments also show that the small intestine of some unanesthetized animals may invariably respond to apomorphine by a loss in general tonus. However, even in some of these cases, the presence of borborygmi and the augmented peristaltic contractions of the segment would indicate that the activity of the gut had been increased.

Summary and Conclusions. 1. The results of these experiments

support the findings published by Gruber and Brundage[1] and by Slaughter and Gross.[2] 2. Apomorphine when injected intravenously may either increase or decrease the general tonus of the intact intestine, depending upon the animal and the condition of the animal at the time of the injection. Some animals respond to apomorphine only by increased tonus, others by decreased tonus, and still others by either or both responses. 3. The peristaltic contractions may be augmented by apomorphine especially when the general tonus is diminished. 4. Borborygmi are commonly noted following the intravenous injection of apomorphine.

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Hydrolysis of Acetycholine by Turtle Blood.*

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In connection with studies being conducted in this laboratory on the physiology of the turtle heart, it was of interest to know the choline-esterase activity of turtle blood. Work already done on the blood of other forms has revealed marked differences in the hydrolysis of acetylcholine between whole blood and serum and further variations depending upon the species. Galehr and Plattner[1, 2] found that human whole blood, shadow cells and washed corpuscles have a greater hydrolytic action on acetylcholine than the serum has. The filtrate from an acetylcholine solution treated with animal charcoal was from 78-100% physiologically inactive, but the total activity could usually be restored by acetylation. By analogy to the charcoal effects they concluded that the hydrolysis of acetylcholine by blood was due to surface catalysis. On the other hand, Engelhart and Loewi[3] repeated the charcoal experiments of Galehr and Plattner and found that partial inhibition of the destruction of acetylcholine could be obtained with a 1:5,000 dilution of physostigmine, which had been shown to be effective in preventing acetylcholine hydrolysis by extracts of frog hearts, and complete inhibition

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1 Galehr, O., and Plattner, F., *Pfluger's Arch.*, 1927, **218**, 488.

2 *Ibid.*, 1927, **218**, 506.

3 Engelhart, E., and Loewi, O., *Arch. exp. Path. u. Pharm.*, 1930, **150**, 1.