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ON THE ABSENCE AND THE RETURN OF PENDULUM MOVEMENTS AFTER CONTRACTION

BY

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In the course of experiments concerning the origin of the rhythmic spontaneous movements (pendulum movements) of the surviving intestine, it was noted that they were absent or much reduced after large doses of acetylcholine.

Cantoni and Eastman (1946) found a similar decrease in the spontaneous activity (if present previously) of guinea-pig's ileum after large doses of some stimulating drugs (histamine, acetylcholine, mecholyl, pilocarpine, barium chloride), together with a decreased sensitivity to small doses of these drugs. The decrease in sensitivity was not specific for the drug by which the large contraction was elicited, i.e. the response to small doses of histamine was equally depressed by a previous large dose of histamine or pilocarpine. Repeated washings with fresh Tyrode did not shorten the period of decreased sensitivity. The effect of small histamine doses was, however, not diminished after a large contraction elicited by potassium chloride, and if the Tyrode solution contained twice the normal amount of potassium the depressant action of a large dose of histamine was prevented.

Feldberg and Schilf (1930) and Barsoum and Gaddum (1935) showed that small doses of histamine became ineffective after a large dose. Feldberg and Solandt (1942–3) also observed the reduced effect of acetylcholine on rabbit's intestine in glucose-free Tyrode after a large dose of acetylcholine, or if the interval between consecutive acetylcholine additions was shortened.

The depressant after-effect of acetylcholine on striated muscle was described by Gasser and Dale (1926), who found that after a large dose of acetylcholine denervated mammalian muscle may become completely inexcitable electrically. Brown (1937) obtained similar results both with denervated cat's gastrocnemius and with normal and denervated frog's muscle.

That acetylcholine itself can, according to circumstances and dose, produce both excitation and inhibition on the same preparation is also well known (McDowall, 1945, 1946 ; Hoffman, Hoffman, Middleton, and Talesnik, 1945 ; Burn and Bülbring, 1949 ; Burn and Vane, 1949). Burn and Vane (1949) showed on surviving rabbit's intestine that, whereas the usual acetylcholine doses had the well-known contracting effect, a very large dose (about 300 μg. per ml.) added at the height of such a contraction caused a relaxation. Of particular interest is their observation that on

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rat's uterus smaller doses of acetylcholine cause a contraction and large doses a relaxation. After repeated large doses of acetylcholine, however, a smaller dose, that previously caused excitation, causes an inhibition. This action is, however, different from the one studied in this paper. In the experiments to be described the inhibition appeared only after the removal of acetylcholine from the bath, and the dose of acetylcholine given was well within the range causing contraction of the intestine (1–10 μg. per ml.).

METHODS

The lowest part of rabbits' ileum was used throughout these experiments, as this shows the most regular pendulum movements when suspended in Tyrode solution *in vitro*. The intestine was removed and used immediately after killing the rabbit by a blow on the head, no experiment being made on stored preparations. Each ileum preparation was 2–4 cm. long and was suspended in a 50 ml. bath containing freshly made Tyrode solution (0.8 g. NaCl, 0.02 g. KCl, 0.02 g. $CaCl_2$, 0.01 g. $MgCl_2$, 0.05 g. NaH_2PO_4, 0.1 g. glucose, 0.1 g. $NaHCO_3$ per 100 ml.) aerated with a mixture of 95% O_2 + 5% CO_2. The temperature of the bath was kept constant at 38.5° C. The contractions of four such preparations were recorded simultaneously, representing thus about 10–15 cm. of the rabbit ileum from the ileocolic sphincter upwards. All preparations immediately showed vigorous and regular pendulum movements, but 20–30 minutes were always allowed (the Tyrode being exchanged three times) before the first addition of drugs. Acetylcholine was usually used. The dose was always given in a volume of 1 ml. by means of a syringe and was left in the bath for different lengths of time. The Tyrode containing this acetylcholine was then let out and the intestine washed twice in quick succession so as to ensure complete removal of the drug.

EXPERIMENTAL RESULTS

Examples of the inhibition following an acetylcholine (ACh) contraction are given in Figs. 1, 2, 4, and 5. The removal of the acetylcholine was followed by an "inhibition," by which term the complete cessation or decreased size of the pendulum movements is meant. In Fig. 1, for instance, 500 μg. acetylcholine was left on the intestine for ten minutes. When the drug was washed out hardly any pendulum movements occurred for about three minutes and then they gradually increased in size. The length of the inhibition varied a great deal with preparations from different rabbits and, to a smaller extent, with the four preparations coming

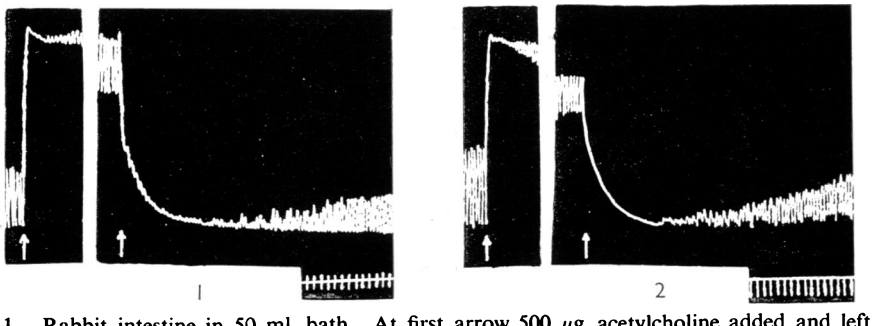

FIG. 1.—Rabbit intestine in 50 ml. bath. At first arrow 500 μg. acetylcholine added and left for 10 min. At second arrow intestine washed with fresh Tyrode. First tracing: at the beginning of the experiment. Second tracing: 4.5 hr. later. Time: 10 sec.

from the same rabbit. On the same intestinal preparation 4–5 consecutive acetylcholine contractions and inhibitions can well be compared with each other and show a remarkable consistency ; e.g. in Fig. 1 the second inhibition shown occurred 4.5 hours after the first, various drugs having been added in between and the acetylcholine addition repeated seven times. On other occasions a gradual lengthening of the inhibition took place, as for instance in the example given in Fig. 2. Two hours elapsed between the different parts of the Figure, and during that time the same dose of acetylcholine was repeated four times (not shown in the Figure).

The inhibition is longer after the removal of larger doses of acetylcholine than after smaller doses. This point is illustrated in Table I. The dose of acetylcholine

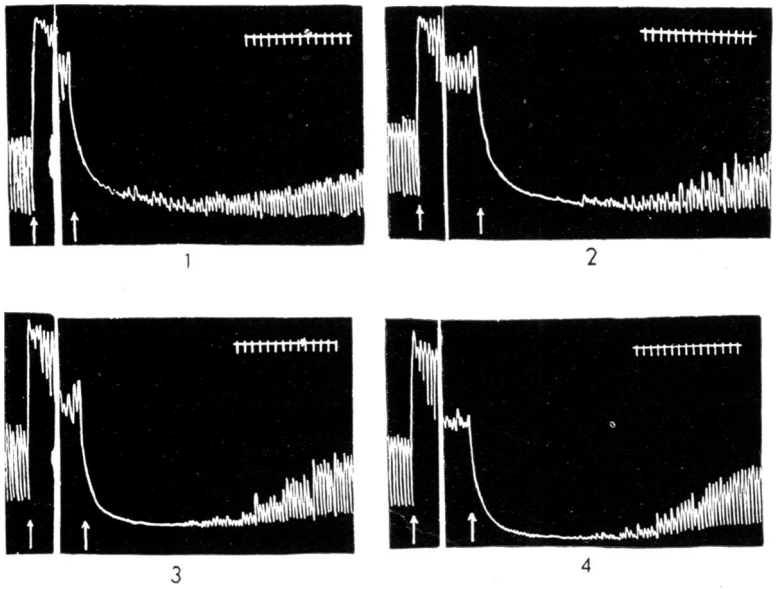

FIG. 2.—Rabbit intestine in 50 ml. bath. At first arrow: 100 μg. acetylcholine for 10 min.; washed at second arrow. First tracing: 0 hr.; second tracing: 2 hr. later; third tracing: 4 hr. later; fourth tracing: 6 hr. later. Time : 10 sec.

TABLE I

THE LENGTH OF THE INHIBITION AS A FUNCTION OF THE ACETYLCHOLINE DOSE

Dose of ACh in μg.	Length of inhibition in minutes and seconds. ACh was left on the intestine for				
	10 min.	10 min.	10 min.	10 min.	5 min.
1	30 sec.				0 sec.
5	2 min. 30 sec.	2 min. 10 sec.			15 sec.
10	3 min. 0 sec.	3 min. 45 sec.			30 sec.
50	4 min. 0 sec.	5 min. 15 sec.	1 min. 15 sec.	4 min. 0 sec.	1 min. 0 sec.
100	4 min. 0 sec.	6 min. 0 sec.	1 min. 40 sec.		1 min. 40 sec.
200			3 min. 20 sec.		
500			5 min. 35 sec.	6 min. 50 sec.	
1,000			5 min. 30 sec.		

was varied from 1 μg. to 1,000 μg. The five columns represent results from intestines of different rabbits. Each dose of acetylcholine was left on the intestine for ten minutes in the first four sets of results and for five minutes in the last. The length of the inhibition is expressed by measuring the time from the washing off of the acetylcholine to the point at which the pendulum movements regained their original size (i.e. that before the acetylcholine addition). It can be seen from the Table that the time taken by the pendulum movements to regain this original size is longer after larger doses of acetylcholine. It can also be seen that there is a great difference between individual rabbits, e.g. the inhibition after ten minutes of 100 μg. acetylcholine varies from 1 min. 40 sec. to 6 min.

TABLE II

THE LENGTH OF THE INHIBITION AS A FUNCTION OF THE LENGTH OF THE ACETYLCHOLINE ACTION

Time of ACh action in minutes	Length of inhibition in minutes and seconds Dose of acetylcholine				
	50 μg.	50 μg.	100 μg.	100 μg.	1,000 μg.
1		45 sec.	20 sec.	30 sec.	25 sec.
2	1 min. 15 sec.				
3		1 min. 45 sec.	1 min. 15 sec.	1 min. 0 sec.	1 min. 0 sec.
4	2 min. 55 sec.				
6		2 min. 15 sec.	1 min. 50 sec.	3 min. 25 sec.	3 min. 45 sec.
8	3 min. 35 sec.				
10		4 min. 15 sec.	2 min. 0 sec.	6 min. 0 sec.	5 min. 50 sec.
16	4 min. 30 sec.		1 min. 50 sec.		
20					5 min. 40 sec.

Table II shows that after a fixed dose of acetylcholine the inhibition lasts longer, the longer the drug has been in contact with the intestine. There are again great individual variations in different rabbits ; for instance, in one rabbit a dose of 100 μg. acetylcholine was not followed by a longer inhibition than two minutes, however long it had been left on the intestine, whereas in other rabbits 50 μg. acetylcholine, acting for 2–4 min., caused an inhibition of similar length.

The absence or decrease in pendulum movements after a large dose of acetylcholine is accompanied by a decreased sensitivity to small doses of other drugs. Shortly after a large dose of acetylcholine the effect of a small dose (e.g. 1 μg.) is much reduced and becomes progressively larger as the pendulum movements reappear and increase in size. This is in agreement with the results of earlier investigators.

As stated by Cantoni and Eastman (1946), the decrease in sensitivity is not specific, i.e. during the inhibition following an acetylcholine contraction the effects of small doses of acetylcholine, histamine, barium chloride, etc., are equally reduced. The lack of pendulum movements and decreased sensitivity to other drugs is, however, not due to the intestine being exhausted at this stage. This was proved in two ways : (1) If the same large dose of acetylcholine (e.g. 100 or 500 μg.) that caused an inhibition is re-added several times during the inhibition, the same contraction is obtained as on the first addition. (2) When, for instance, a dose of 100 μg. acetylcholine is allowed to act for 10 min. and then washed off inhibition appears. If,

however, the same dose of acetylcholine is left on the same intestine for 30–50 min. the intestine goes on showing rhythmic contractions and relaxations, on a higher tone level, without any signs of fatigue and the inhibition only appears when the acetylcholine is exchanged for fresh Tyrode.

The inhibition of the pendulum movements can be observed after all large and lasting contractions that are followed by a sharp relaxation. Thus it was noted after choline (5–100 mg. per 50 ml.), histamine (5–100 mg. per 50 ml.), barium chloride (about 10 mg. per 50 ml.), pilocarpine (10–100 μg. per 50 ml.), and probably even after potassium chloride (1–100 mg. per 50 ml.). Frequently, however, when these drugs are removed there is no immediate relaxation, but only a gradual return to the original relaxed level; this was noted after barium chloride, pilocarpine, and particularly after potassium chloride. Therefore, especially with the last-named drug, it is difficult to say whether there is any inhibition and even more difficult to measure its length. On the other hand, the removal of acetylcholine, however large the dose and however long it has acted on the intestine, is always followed by an immediate and sharp relaxation to the base line. Therefore, acetylcholine has been our drug of preference and was used throughout in attempts to discover the nature of this secondary inhibition.

The inhibition appearing after a large dose of acetylcholine is not due to the liberation into the bath of effective concentrations of some inhibitory humoral agent (e.g. adrenaline). This is shown by the following experiments.

(1) The inhibition is not shortened by exchanging the Tyrode several times during this period, as also observed by Cantoni and Eastman (1946).

(2) The inhibition cannot be transmitted. When one intestinal preparation was completely quiescent after the removal of a large dose of acetylcholine, i.e. while there were no pendulum movements, the Tyrode was sucked off and transferred to another preparation showing normal pendulum movements. The pendulum movements of this second preparation went on uninfluenced by the fluid in which the first preparation had shown no movements at all.

(3) The inhibitions after different doses of acetylcholine were matched with known concentrations of adrenaline and noradrenaline. Ergotoxine, in doses that completely abolished the effect of fifty times these adrenaline or noradrenaline concentrations, had no influence on the inhibition after acetylcholine.

The depression caused by the presence of small doses of acetylcholine on the rat's denervated diaphragm preparation may be relieved by sympathomimetic drugs (adrenaline, ephedrine) and by *d*-tubocurarine (McDowell and Watson, 1951). It seemed interesting to see whether the presence of adrenaline during the contraction would influence the inhibition. It was found that it did not do so as long as it did not alter the acetylcholine contraction itself. It may be mentioned here that the dose of adrenaline that leaves the acetylcholine contraction uninfluenced differs greatly between preparations coming from the ileum and those from the duodenum. The threshold concentrations for both adrenaline and acetylcholine in the duodenum and the ileum of the same rabbit were identical. When the two drugs were mixed, however, an entirely different response was obtained, as seen in Fig. 3. In the duodenum ten times (sometimes even a hundred times) as much adrenaline as acetylcholine can be given together and the result is still a contraction, similar to the one caused by the same dose of acetylcholine alone. In the ileum, on the other hand, the maximal

amount of adrenaline that can be mixed with the acetylcholine without altering the contraction is about a tenth of the acetylcholine dose. If the adrenaline concentration in the mixture is further increased, e.g. adrenaline and acetylcholine are mixed in equal amounts, there is only an inhibition (see Fig. 3).

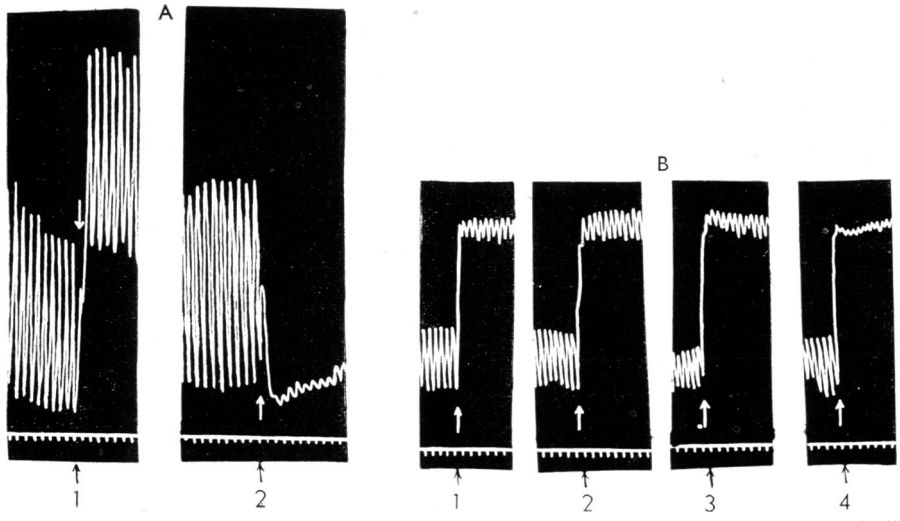

FIG. 3.—Rabbit intestine in 50 ml. bath. A: lower ileum. First arrow: 10 μg. acetylcholine; second arrow: 10 μg. acetylcholine + 10 μg. adrenaline. B: duodenum from same rabbit. First arrow: 10 μg. acetylcholine; second arrow: 10 μg. acetylcholine + 10 μg. adrenaline; third arrow: 10 μg. acetylcholine + 100 μg. adrenaline; fourth arrow: 10 μg. acetylcholine + 1,000 μg. adrenaline. Time: 5 sec.

Drugs which paralyse ganglionic and nervous structures have very little influence on the inhibition following an acetylcholine contraction as long as they do not interfere with the contraction itself.

(1) Hexamethonium, in concentrations of 10^{-7} to 2×10^{-4} has no, or very little, influence either on the pendulum movements, or on the acetylcholine contraction (Feldberg, 1951), or on the inhibition which follows.

(2) *d*-Tubocurarine up to a concentration of 2×10^{-4} does not alter the acetylcholine contraction (Feldberg and Lin, 1949) or the inhibition.

(3) While nicotine (10^{-7} to 2×10^{-4}) hardly alters the contraction (Emmelin and Feldberg, 1947), there may be a slight tendency of the inhibition to become longer; 2×10^{-3} nicotine completely paralyses the intestine, i.e. the pendulum movements disappear and acetylcholine produces no contraction.

(4) The acetylcholine contraction takes place in the presence of cocaine, until the concentration of the latter reaches 2×10^{-3}, when complete paralysis occurs. Below a cocaine concentration of 2×10^{-3} the height of the acetylcholine contraction is hardly altered and the inhibition following the contraction is also unchanged, though there is a tendency for the pendulum movements to become smaller and more irregular with increasing cocaine concentrations (Feldberg and Lin, 1949).

(5) Proguanil acts like nicotine, complete paralysis taking place when its concentration in the Tyrode reaches 2×10^{-4} (Vane, 1949).

The inhibition after an acetylcholine contraction becomes longer if the glucose content of the Tyrode is reduced. After 30 min. in Tyrode containing only half the normal amount of glucose (0.05 g./100 ml.), the pendulum movements and the acetylcholine contraction remained unchanged, but after the acetylcholine contraction, the pendulum movements returned to normal much more slowly, i.e. the inhibition was prolonged; 30 min. in normal Tyrode completely restored the inhibition to its normal length. The pendulum movements decrease in size during 30 min. in glucose-free Tyrode, the acetylcholine contraction is much reduced, the tone of the contraction not being maintained (Feldberg and Solandt, 1942–3), and when the acetylcholine is removed the pendulum movements do not reappear. When the bath fluid is replaced by normal Tyrode, however, complete recovery takes place.

As a next step the effect of alterations in the ionic composition of the Tyrode was investigated; that this might influence the inhibition after acetylcholine was indicated by the experiments of Cantoni and Eastman (1946), who found that the inhibition disappeared if the potassium content of the Tyrode was increased to twice its normal value.

After the inhibition following a suitable dose of acetylcholine had been established in normal Tyrode, the bath fluid was replaced by Tyrode solutions containing two, three, or four times (in the case of Mg up to six times) the normal amount of

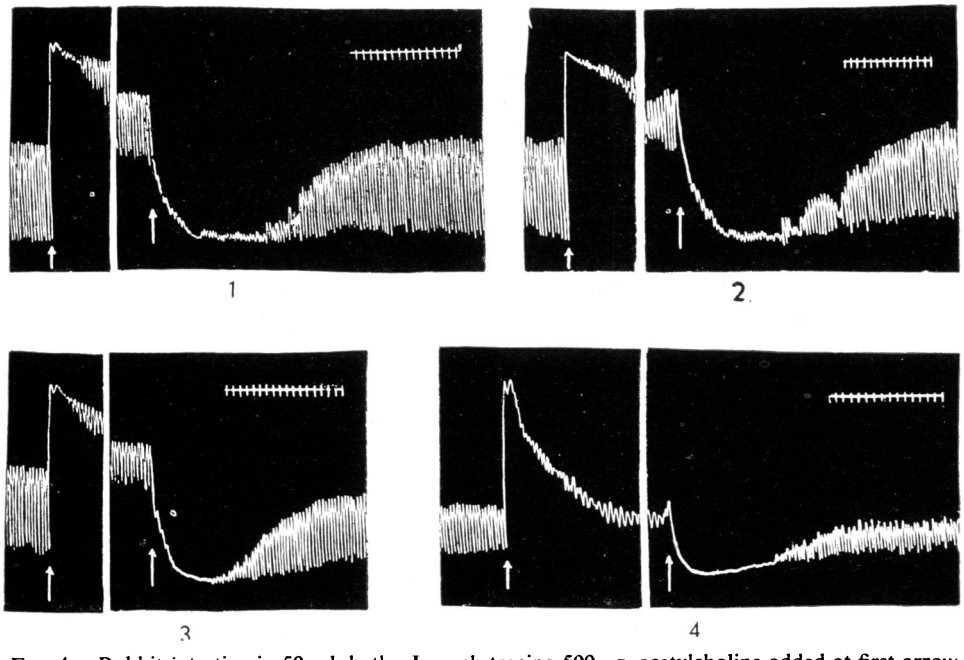

FIG. 4.—Rabbit intestine in 50 ml. bath. In each tracing 500 μg. acetylcholine added at first arrow left for 10 min., and washed out with fresh Tyrode at second arrow. (1) In normal Tyrode. (2) In Tyrode with twice the normal amount of potassium (0.04% KCl). (3) In Tyrode with three times the normal amount of potassium (0.06% KCl). (4) In Tyrode with four times the normal amount of potassium (0.08% KCl). Time: 10 sec.

potassium or calcium or magnesium. The same dose of acetylcholine as before was then added and the intestine was washed with Tyrode of the same increased ionic content as that in which the contraction had occurred. The inhibition after acetylcholine occurred in all solutions tried. Fig. 4 shows the inhibition in Tyrode containing an increased potassium content.

The same experiment was then repeated with Tyrode solutions in which the concentrations of K, Ca, or Mg was reduced to $\frac{1}{2}$, $\frac{1}{3}$, or $\frac{1}{4}$ of the normal. A few experiments were also made with one ion missing altogether from the Tyrode. The inhibition was present in every solution and there was no unequivocal change in its duration, though the inhibition seemed to be somewhat shorter in Tyrode solutions with a reduced potassium content.

The experiment was then varied in such a way that five consecutive acetylcholine contractions and inhibitions formed one set of experiments: (1) Acetylcholine contraction and inhibition in normal Tyrode. (2) Acetylcholine contraction in normal Tyrode, inhibition in Tyrode with altered ionic composition. (3) Both acetylcholine contraction and inhibition in Tyrode with altered ionic composition. (4) Acetylcholine contraction in Tyrode with altered ionic composition, inhibition in normal Tyrode. (5) Both acetylcholine contraction and inhibition in normal Tyrode, i.e. repetition of (1) in order to show that no change had occurred in the meanwhile in the length and strength of the inhibition. If in the above set of experiments the Tyrode with altered ionic composition is Tyrode with increased potassium content, there is no change in the inhibition. If, however, it is Tyrode with reduced ($\frac{1}{2}$, $\frac{1}{3}$, $\frac{1}{4}$

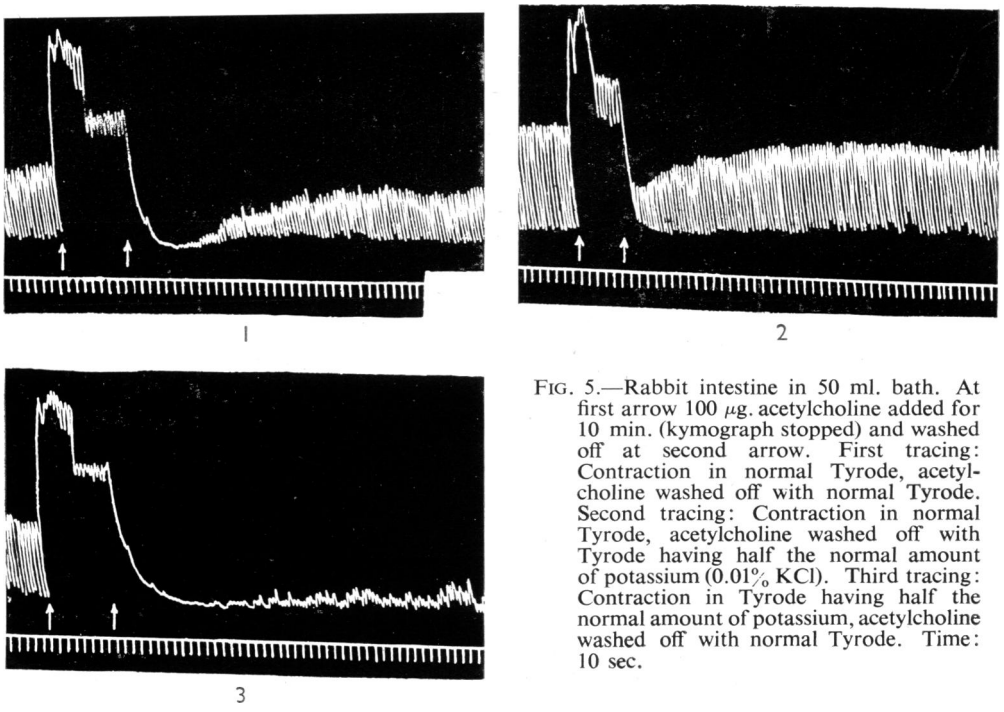

FIG. 5.—Rabbit intestine in 50 ml. bath. At first arrow 100 μg. acetylcholine added for 10 min. (kymograph stopped) and washed off at second arrow. First tracing: Contraction in normal Tyrode, acetylcholine washed off with normal Tyrode. Second tracing: Contraction in normal Tyrode, acetylcholine washed off with Tyrode having half the normal amount of potassium (0.01% KCl). Third tracing: Contraction in Tyrode having half the normal amount of potassium, acetylcholine washed off with normal Tyrode. Time: 10 sec.

normal) potassium content, the inhibition is practically abolished when the acetylcholine is applied in normal Tyrode, but washed out with Tyrode containing a reduced potassium content (Exp. 2 above). On the other hand, the inhibition is much prolonged if the order of the solutions is reversed, i.e. if the acetylcholine is applied in Tyrode with reduced potassium content, but washed out with normal Tyrode (Fig. 5). If, instead of the potassium, the calcium content of the Tyrode is altered, the following results are obtained. When acetylcholine is applied in normal Tyrode, but washed out with Tyrode containing an *increased* calcium content (Exp. 2 above), the inhibition is much prolonged. When acetylcholine is applied in normal Tyrode and washed out with Tyrode containing a *reduced* calcium content, the results are not so unequivocal. In one rabbit we saw an actual shortening of the inhibition ; in all other rabbits, however (8 in all), the inhibition was unaltered or prolonged. Other possible combinations with increased or decreased calcium content had no influence on the inhibition.

Lastly the effects on the pendulum movements of all the above alterations in the ionic composition of the Tyrode were observed in the absence of acetylcholine. The only regular changes observed were the following : There is an inhibition of the pendulum movements (similar to the one seen after an acetylcholine contraction) if normal Tyrode is exchanged for one having an increased calcium content (Fig. 6). An even more pronounced and long-lasting inhibition is observed if the intestine is in Tyrode with reduced potassium content and this is exchanged for normal Tyrode (Fig. 7). No other alteration in the ionic composition of the Tyrode had

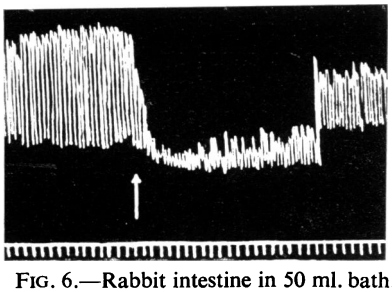

FIG. 6.—Rabbit intestine in 50 ml. bath. At arrow: Normal Tyrode replaced by Tyrode with twice the normal amount of calcium (0.04% $CaCl_2$). Time: 10 sec.

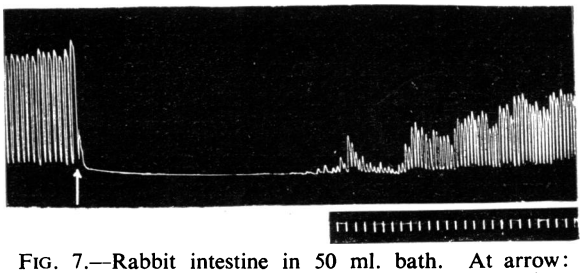

FIG. 7.—Rabbit intestine in 50 ml. bath. At arrow: Tyrode containing one-third the normal potassium content replaced by normal Tyrode. Time: 10 sec.

any marked effect on the pendulum movements. Alterations in the first few beats after the change may occur, but some irregularities also occur when normal Tyrode is simply replaced by fresh normal Tyrode. The one further change that may be mentioned here is that the frequency of the pendulum movements decreased if the calcium content of the Tyrode was decreased.

DISCUSSION

It seems to be well established that, on a surviving intestinal preparation, a period of decreased sensitivity and an inhibition of the pendulum movements follow any large contraction. It also seems to be certain that this inhibition is not specific

to any one drug and is not due to fatigue of the preparation or to the accumulation of some inhibitory substance. So far the results here presented are in agreement with those in the literature.

Cantoni and Eastman (1946) found, however, on the guinea-pig's ileum that if the Tyrode contained twice the normal amount of potassium a large dose of histamine was not followed by a period of decreased sensitivity to small histamine doses. In our experiments on the rabbit's ileum, the inhibition after a large acetylcholine contraction occurred whether the Tyrode contained normal or twice, three, or four times the normal amount of potassium. The cause of this discrepancy is not known. It has to be pointed out, however, that Cantoni and Eastman's results were obtained on the guinea-pig's ileum and the sensitivity was tested after a large histamine dose by the contractions given to small doses of histamine. In the present experiments rabbit's ileum was used and the inhibition of the pendulum movements was determined after a large acetylcholine contraction.

A decrease in the potassium content or any change in the calcium or magnesium content of the Tyrode have likewise no definite influence on the inhibition, if contraction and relaxation occur in a Tyrode having a similar composition.

The following changes in the length of the inhibition after the same large acetylcholine contraction have been regularly observed.

(1) The inhibition is much prolonged if (*a*) the acetylcholine is applied in Tyrode with reduced potassium content and removed with normal Tyrode, or if (*b*) the acetylcholine is applied in normal Tyrode and removed with Tyrode containing an increased calcium content. These same changes, i.e. changing from Tyrode with decreased potassium content to normal Tyrode or changing from normal Tyrode to one with increased calcium content, also cause an inhibition of the pendulum movements themselves, when no acetylcholine has been added. Therefore, it seems likely that the inhibition occurring after an acetylcholine contraction alone and the inhibition caused by these ionic changes simply summate.

(2) The inhibition is much shortened or altogether absent if the acetylcholine contraction takes place in normal Tyrode and the acetylcholine is removed with Tyrode containing reduced potassium content. The picture would be similar, if in some way an acetylcholine contraction reduced the amount of potassium in the Tyrode ; washing with normal Tyrode would then cause an inhibition, even in the absence of any previous contraction.

Decreasing the glucose content of the Tyrode prolongs the inhibition, but this only happens if the intestine has been for some time in the reduced-glucose-Tyrode. Reduction of the glucose content of the Tyrode, i.e. exhaustion of the carbohydrate reserve during a normal acetylcholine contraction, cannot, however, be the cause of the inhibition, because (*a*) the inhibition itself occurs in fresh Tyrode, (*b*) as long as the acetylcholine is left on the intestine, no inhibition appears, and (*c*) there is no inhibition if relaxation takes place in Tyrode with a reduced potassium content.

SUMMARY

1. An acetylcholine contraction of the surviving rabbit's intestine is followed by an inhibition after the removal of the acetylcholine. The length of the inhibition increases with the size and duration of the preceding acetylcholine contraction.

2. The absence or decrease of the pendulum movements during this inhibition runs parallel with a decreased sensitivity of the preparation to other chemical stimuli.

3. The inhibition is not specific to acetylcholine; it is present after all prolonged contractions which are followed by a sharp relaxation.

4. The inhibition is not due to fatigue of the preparation, nor to the liberation of some inhibitory chemical agent. It is uninfluenced by nicotine, hexamethonium, *d*-tubocurarine, cocaine, and proguanil. It is present in Tyrode solution with increased or decreased potassium, calcium, or magnesium content, if both contraction and relaxation take place in identical solutions.

5. The presence of adrenaline during the contraction does not influence the subsequent inhibition as long as it does not alter the contraction itself. The admixture of much more adrenaline is needed to change an acetylcholine contraction into relaxation in the duodenum than in the ileum of the same rabbit.

6. An acetylcholine contraction is not followed by an inhibition if the acetylcholine contraction takes place in normal Tyrode and the acetylcholine is removed with Tyrode containing a reduced potassium content.

7. The inhibition is prolonged (*a*) if the glucose content of the Tyrode is reduced, (*b*) if the acetylcholine contraction takes place in Tyrode with reduced potassium content and the inhibition in normal Tyrode, and (*c*) if the acetylcholine contraction takes place in normal Tyrode and the inhibition in Tyrode with increased calcium content.

8. In the absence of acetylcholine, the pendulum movements are inhibited by (*a*) changing from reduced potassium Tyrode to normal Tyrode and (*b*) changing from normal Tyrode to Tyrode with increased calcium content.

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