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THE ACTION OF POSTERIOR PITUITARY EXTRACTS UPON PROPULSION IN THE SMALL INTESTINE OF CONSCIOUS DOGS

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In 1909 Foderà and Pittau noted that injections of hypophysial extracts into dogs caused " la répétition de défécations ayant un caractère diarrhéique et suivies de tenesme." In the same year Dale independently reported that extracts of the posterior lobes of ox pituitaries, boiled in acetic acid, filtered, and neutralized before use, caused an isolated strip of dog intestine to contract; and Bell, working with pithed rabbits, observed defaecation and increased peristalsis after injections of similar extracts supplied by Dale. Bell also announced that he had employed the extracts, without a single failure, in the treatment of several patients suffering from post-operative paralytic ileus, and recorded the reports of some of his colleagues who had been persuaded to use the extracts in similar cases.

In the ensuing years numerous commercial preparations of pituitary extracts were put on the market, and much work was done in an attempt to throw the light of analytical experiment upon the empiricism of their use in clinical treatment. Although most authors were able to confirm that the extracts had a stimulating action upon various preparations of intestine, some, for example, Shamoff (1916), found them inhibitory. It was suggested by Roth (1917) that the differences in results could be attributed to the fact that insufficient attention had been paid to the presence of acid or preservative in many of the preparations. Detailed reviews of the early literature were made by Geiling (1926) and by Gruber and Robinson (1929).

In 1925, however, Macdonald, using carefully made, neutralized, and preservative-free extracts, could find no specific stimulating action upon cat intestine, and suggested that what action there was could be attributed to a non-specific " histamine-like " substance present in extracts of tissues other than the pituitary gland. Gaddum (1928) confirmed that cat intestine was insensitive to pituitary preparations, but showed that isolated rabbit gut was powerfully contracted by a substance in pituitary extracts which could not be histamine. He also demonstrated that the active substance was present mainly in the " pressor " fraction of the extract, and that the colon was contracted more forcibly that the jejunum. It thus appeared that, even after the elimination of unphysiological *p*H, preservative, and histamine, posterior pituitary extracts contained a substance which contracted the isolated intestine of all animals studied except the cat. (That cat intestine does, in fact, also respond to pitressin, though not to pitocin, was shown by Steggerda, Gianturco, and Essex, 1938.)

The defaecation produced in normal animals, and the stimulation of isolated pieces of gut, led to the expectation that injections of pituitary extracts could be shown to cause

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an increase in intestinal activity by methods which demonstrated intestinal motility *in vivo*. A contrary result was, however, obtained by McIntosh and Owings (1928), who found that pituitary extracts relaxed the tone and decreased the motility of segments of obstructed dog intestine *in vivo*, and by Gruber and Robinson (1929), who showed a similar inhibition of the movements (recorded by balloons) of Thiry-Vella loops in otherwise normal dogs. Quigley and Barnes (1930), also using balloon recorders, found relaxation and inhibition of the contractions of the stomach, small intestine, and colon after pituitary injections, and Quigley, Highstone, and Ivy (1934) showed that the extracts had a variable, but predominantly depressant, action upon the propulsion of boluses by Thiry-Vella loops. Wolff (1939), recording with balloons the activity of colonic fistulae *in vivo* in dogs, found regular inhibition with occasional subsequent stimulation after injection of pitressin and prolonged inhibition after pitocin ; and Larson (1941), recording with balloons inserted through the anus or an appendicostomy, also in dogs, showed that pitocin either had no effect or relaxed the bowel, that pituitrin both relaxed the tone and reduced the amplitude of contractions, while pitressin had no effect on tone but usually increased the contractions of the upper colon. Reagan, Harbor, and Puestow (1939), observing exposed segments of dog colon, thought the reverse, namely, that pituitrin had little effect on contractions, but somewhat increased the tone. Puestow (1942), observing by eye, in human subjects, the movements of various parts of the bowel in hernial sacs, was of the impression that the small intestine was relaxed and inhibited by pituitrin and pitressin, but that the colon was stimulated.

Other authors, however, have come to contrary conclusions. Melville and Stehle (1934) screened and took *x*-ray photographs of dogs given radio-opaque meals, and found that after injections of pitressin, but not of pitocin, the small intestine became constricted, and that the propulsion of the meal into the colon was hastened. Necheles, Maskin, Strauss, Strauss, and Taft (1935) and Macdonald and Settle (1936), recording with balloons from the small and large intestines of patients with fistulae, noted that " colicky " pain, increased contractions, and more rapid expulsion of contents followed injections of pitressin in nearly all of them. Comparable results were obtained by Carlson (1930) from three patients with colostomies and one with an ileostomy. Rundle (1935) reported a satisfactory response to pituitrin injections by three patients with paralytic ileus, but Seed, Falls, and Fantus (1937), recording that pitressin injections hastened bowel movements in uncomplicated post-operative cases, found them of no value in ileus. Larson and Bargen (1933), recording from various parts of colonic fistulae in dogs, were of the opinion that pituitrin contracted the middle but not the upper or lower parts of the colon, and Guthrie and Bargen (1936) confirmed Foderà and Pittau's original observation that pituitary injections caused defaecation in normal dogs, noting, in addition, that while pitocin and pitressin were both active the latter was much the more potent.

It is unfortunate that, so much work having been devoted to investigations of the actions of pituitary extracts, many of the conclusions reached have been contradictory. The very large number of papers at least pays tribute to the interest of the problem which, apart from its practical bearing upon the clinical use of pituitary preparations, concerns the question whether the gut-stimulating principle has any function in normal physiology. In 1940, Wang, Clark, Dey, and Ranson, in whose paper reference to previous work on the same subject may be found, demonstrated that stimulation of certain parts of the hypophysis resulted, after a delay, in hyperactivity of the intestines. The phenomena persisted after vagotomy, and they suggested that the effect might be due to the release of pituitary hormone. As they pointed out, however, the literature concerning the effect of pituitary hormones on

the intestine presents a picture which is far from clear, and their own attempts—on cats—to simulate the effects of hypophysial stimulation with pituitary injections led to different results in different animals. More recently Harris (1948), using rabbits, studied the effect of intracranial stimulation upon the motility of the intestines, as observed by eye through the shaved but unopened abdominal wall. His subjective impression was that, after electrical stimulation by an electrode implanted in or near the supraopticohypophysial tract, an increase of intestinal activity occurred similar to that provoked by injections of posterior lobe extracts.

It is possible that the action of pituitary extracts upon the intestines can be given a single interpretation which would reconcile all the evidence from which various authors have derived conflicting opinions. The problem is dealt with more fully in the discussion. Much of the disagreement arises from evidence obtained by means of balloons placed within the lumen of the gut. Apart from the fact that balloons are stimulating objects such as the intestine does not normally contain, the changes in their volume cannot reliably be interpreted in terms of "stimulation" or "inhibition" of the propulsive function of the bowel. Objections to the conclusions sometimes drawn from their use have been made in detail elsewhere (Vaughan Williams and Streeten, 1950). The results which follow were obtained by measuring simultaneously, but independently, the rates at which Tyrode solution flowed into and was expelled from cannulated loops of jejunum in unanaesthetized dogs.

Methods

The methods used have already been described (Vaughan Williams and Streeten, 1950 ; Vaughan Williams, 1951 ; Streeten and Vaughan Williams, 1951). Briefly, an operation was performed whereby a cannula was sewn into each end of a short intestinal segment which, with its pedicle of nerves and blood vessels intact, was left lying in the abdominal cavity, the continuity of the remainder of the gut being restored by anastomosis. The open ends of the two cannulae were exteriorized through separate stab incisions and gave permanent access to the oral and aboral ends of the loop. After the dog's recovery from the operation, an apparatus could be attached by water-tight joints to the two cannulae, and permitted the introduction of Tyrode solution under controlled conditions of temperature and pressure into the oral end of the loop. The contractions of the loop then transported the fluid and expelled it from the aboral end into an outflow recorder. The normal functioning of the apparatus can be seen in the first part of Fig. 1. From above downwards the four tracings represent (1) the excursions of a piston recorder from which may be inferred the amplitude of the contractions of the oral end of the loop ; (2) the movements of a float recorder which measures the rate at which fluid enters the oral end, each downward movement of the lever representing the entry of fluid ; (3) the amplitude of the contractions of the aboral end of the loop (piston recorder) ; (4) the rate at which fluid is expelled from the aboral end, each *upward* movement of the lever representing the expulsion of fluid (float recorder). The straight vertical lines in (4) and (2), respectively, represent the discharge, by a relay mechanism, of 10 ml. of fluid from the outflow recorder, and the simultaneous resetting of the inflow recorder by an equal volume of air.

Results

Five dogs were used, weighing between 9 kg. and 15 kg., two being males, three females. The animals were deprived of food, but not water, the night before an experiment, and were trained to lie for hours quietly on their sides. No soporific or

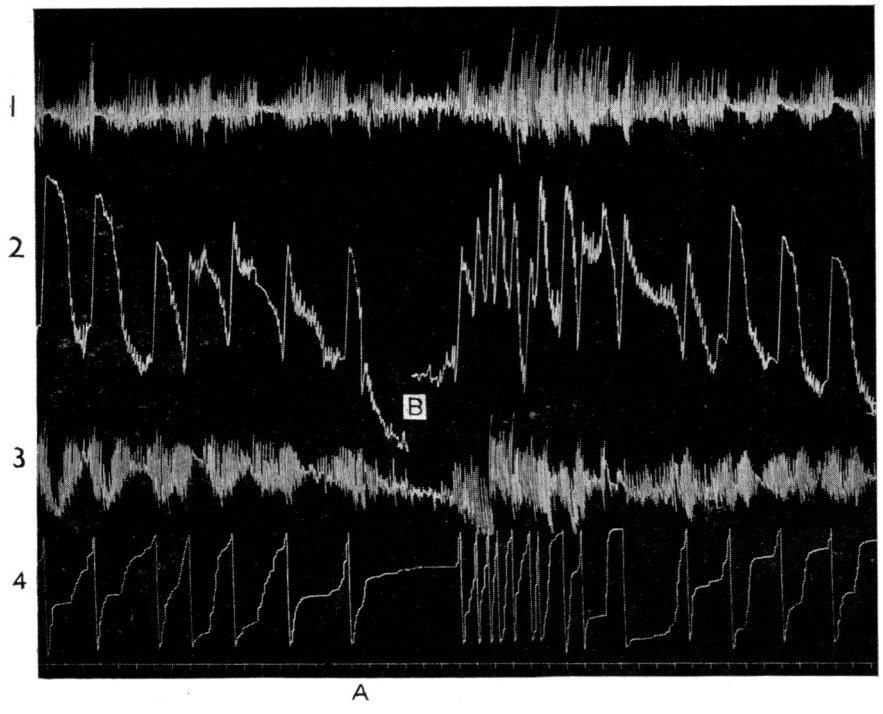

FIG. 1.—Effects of pituitrin on the motility of a loop of jejunum in a male dog. In this and subsequent tracings, the *first record* shows the amplitude of contractions at the oral end of the loop; the *second* indicates the rate at which fluid entered the oral end, each downward movement of the lever representing the entry of fluid; the *third* records the contractions at the aboral end of the loop; and the *fourth* measures the rate at which fluid was expelled from the aboral end of the loop, each upward movement of the lever indicating the expulsion of fluid. The straight vertical strokes, in the fourth and second tracings respectively, represent the automatic discharge, by a relay, of 10 ml. fluid from the outflow recorder and the simultaneous resetting of the inflow recorder by an equal volume of air. Time is marked in minutes. The inflow reservoir was 9 cm. above the cannulae, and the entrance to the outflow recorder 10 cm.; so that 1 g.cm. propulsive work was done for every ml. fluid expelled. At A, 0.5 U. pituitrin (45 mU./kg.) was injected intravenously. Contractions were diminished and fluid ran into the loop (fall in second lever) showing a dilatation. (At B, 7 ml. water was added to the system to reset the inflow recorder.) Before injection the mean rate of work was 3.9 g.cm./min. From the 5th to the 12th min. after the injection the mean rate increased to 12.2 g.cm./min. After 12 min. it had returned to 3.8 g.cm./min.

anaesthetic was used. The effects of normal respiration and slight movements of the dog could not be detected in the tracings. Subcutaneous injections of pituitrin were sometimes found painful, and occasionally gave rise to a sharp movement which could be seen as an artifact on the tracings. Such disturbances lasted only a few seconds; the effects of both subcutaneous and intravenous injections were similar, but all injections in the last three dogs were given intravenously. The doses given were small, ranging from 10 to 100 milliunits per kg.

At the left of Fig. 1 can be seen the normal activity of a loop in a male dog weighing 11.1 kg. At the oral end of the loop (top tracing) groups of large contrac-

tions alternated at fairly regular intervals with periods of relative quiescence. During the latter half of each group of large contractions and during the quiescence no fluid was admitted to the loop (second tracing). As the contractions grew gradually larger at the end of the quiescent period, fluid ran into the loop (indicated by a more rapid fall of second lever), and the whole cycle started again. A similar cycle existed at the aboral end, out of phase with the oral cycle. Periods of relaxation (third tracing), during which the outflow recording lever (fourth tracing) made a horizontal record showing that no fluid was expelled from the loop, alternated with groups of strong contractions during which fluid was pumped into the outflow recorder. The entry to the outflow recorder was fixed at a known level *above* the reservoir from which fluid entered the oral end of the loop so that work had to be done in order to transport fluid through the loop. The actual propulsive work done in transporting the fluid through the loop was thus easily measured.

At A, 45 milliunits per kg. of " Pituitrin " (Parke Davis) (diluted in saline immediately before use) was injected intravenously. Within a few seconds there was a large dilatation of the loop, resulting during the next two minutes in the admission of 12 ml. Tyrode from the inflow reservoir (fall of second lever). (At B, the inflow recorder was reset by 7 ml., to avoid overlapping of the second and third tracings.) For five minutes after the injection the relaxation persisted, the contractions at both ends of the loop remaining small and the outflow being very much reduced. Then a completely new phase of activity commenced, very large and powerful contractions occurring at both ends of the loop. The effect is demonstrated in the tracings, but it should, perhaps, be added that the great propulsive, almost " projectile," force of the contractions expelling the fluid was most striking to the eye.

The phase of increased activity lasted for seven minutes. During the 20 minutes before the injection the mean rate of work done by the loop was 3.9 g.cm. per min. During the seven minutes of the phase of increased activity the mean rate was 12.2 g.cm. per min. Even allowing for the five minutes of quiescence immediately after the injection, this represents an absolute increase of 38 g.cm. of additional propulsive work done during the 12 minutes after the injection, over and above what would have been expected had the loop continued to work throughout at the same rate as before the injection. The phase of relaxation was not always as marked as that shown in Fig. 1. In Fig. 2 some relaxation does occur, but is much smaller ; on the other hand, the stimulation in this tracing is also smaller than that of Fig. 1. Nevertheless, this difference suggests that the threshold dose for the phase of stimulation is lower than that for the phase of relaxation. The suggestion is supported by two other tracings in which there is an increase in the rate of propulsion in response to small doses preceded by an insignificant relaxation.

In Figs. 2, 3, and 4 are shown the results of intravenous injections, into another dog, of 36 milliunits/kg. pituitrin, 36 milliunits/kg. pitocin, and 18 milliunits/kg. pitressin respectively. The tracings show that pituitrin increased the rate of propulsion (Fig. 2) but that an equivalent dose of pitocin had no significant effect (Fig. 3). Half the dose of pitressin, on the other hand, caused a substantial increase (Fig. 4). Fig. 2 shows, also, an artifact caused by a sudden attempt by the dog to get up from the bench. Similar attempts to rise were occasionally made by other dogs after pituitary injections, and were probably the result of an impulse to defaecate.

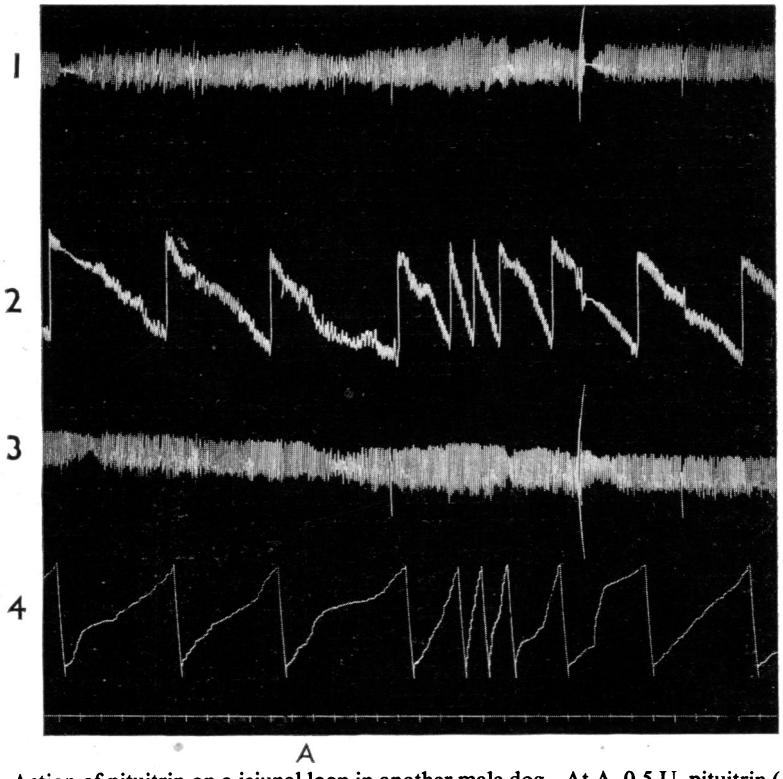

FIG. 2.—Action of pituitrin on a jejunal loop in another male dog. At A, 0.5 U. pituitrin (=36 mU./kg.) was injected i.v., causing an increase in the amplitude of contractions and the rate of propulsive work, which lasted from the 5th to the 12th min. after the injection. The phase of increased activity was preceded by a slight reduction in amplitude and propulsive rate. The inflow reservoir was 9 cm., the outflow recorder 10 cm., above the cannulae. Mean rate of propulsive work (g.cm./min.) for the 12 min. before injection, 1.9; for the 12 min. after injection, 3.9; and from the 13th to the 23rd min. after injection, 2.2.

The action of pituitrin was compared with that of physostigmine on intestinal propulsion. The effect of a small dose of physostigmine is shown in Fig. 5. At A, 6.8 μg./kg. was injected intravenously. There followed an immediate expulsion of fluid from *both* ends of the loop, as shown by the rise of the second lever indicating a regurgitation of fluid from the oral end of the loop back into the inflow reservoir. The period of increased tone lasted for 15 min. and was followed by a phase of greatly increased propulsive activity, lasting 37 min. The rate of work for the 15 min. before the injection was 4.6 g.cm. per min. During the phase of increased propulsion the rate was 9.7 g.cm. per min. From the 70th to the 82nd minute the rate was 5.5 g.cm. per min.—i.e., approximately the same as before the injection. Subtracting from the total propulsive work done during the 70 min. after the injection, the amount of work which would have been expected if the "control" level had persisted throughout, there was an absolute increase of 98 g.cm. propulsive work done as a consequence of the action of the drug.

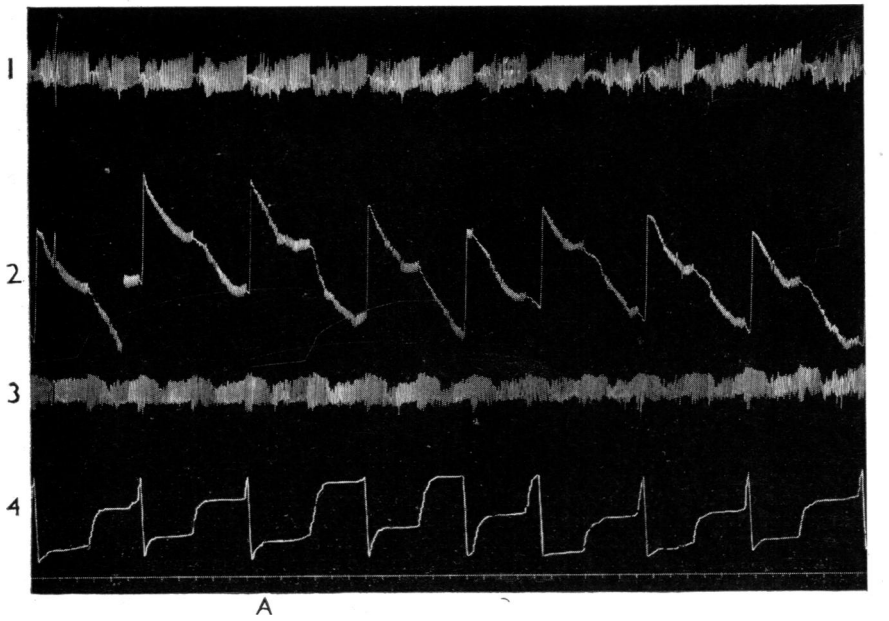

FIG. 3.—Pitocin, 0.5 U. (=36 mU./kg.) was injected intravenously at A into the same dog used for the experiments recorded in Figs. 2 and 4. No effect on the motility of the loop was detectable. The inflow reservoir was 8.5 cm., the outflow recorder 10 cm., above the cannulae.

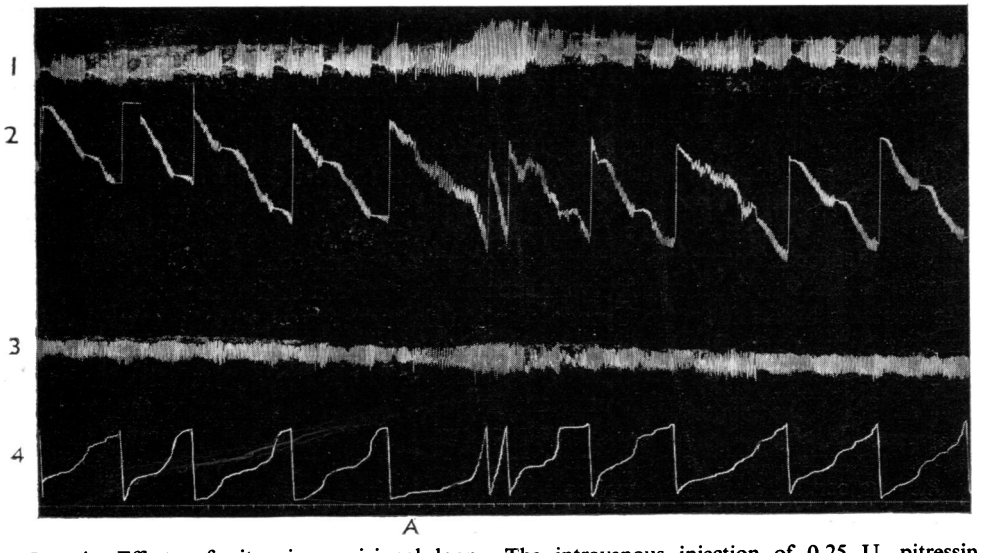

FIG. 4.—Effects of pitressin on jejunal loop. The intravenous injection of 0.25 U. pitressin (= 18 mU./kg.) at A caused a preliminary relaxation of the loop lasting 4 min., which was followed by a phase (also lasting 4 min.) of contractions of far greater amplitude and a higher rate of fluid propulsion. The inflow reservoir was 8.5 cm., the outflow recorder 10 cm., above the cannulae. Mean rate of propulsive work (g.cm./min.), for the 24 min. before injection, 2.6; for the 8 min. after injection, 4.4; and from the 9th to the 37th min. after injection, 2.4.

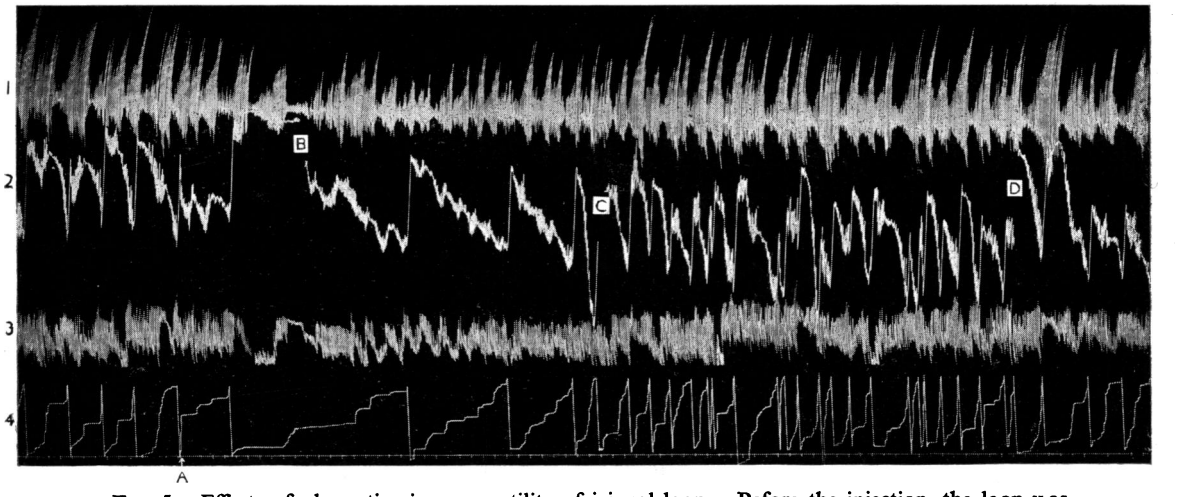

FIG. 5.—Effects of physostigmine on motility of jejunal loop. Before the injection, the loop was doing propulsive work at a mean rate of 4.6 g.cm./min. At A, 75 μg. of physostigmine sulphate (= 6.8 μg./kg.) was injected subcutaneously. After a delay of 4 min., the rhythmical contractions became reduced in amplitude and the rate of propulsion much diminished (lowest tracing) as the result of an *increase* in the tone of the loop, fluid being regurgitated from the oral end of the loop into the inflow reservoir, and causing the second tracing to run into the first. At B, the inflow recorder was readjusted by removing 5 ml. fluid. The phase of increased tone and reduced propulsion lasted 29 min. and was followed by a great increase in the rate of propulsive work to 9.7 g.cm./min. for 40 min. The inflow recorder was reset by the addition of 5 ml. at C and 3 ml. at D.

DISCUSSION

The results show that the pressor fraction of extracts of the posterior lobe of the pituitary contains a substance which causes the small intestine of the dog to perform more propulsive work than it was doing before injections of the drug. The intestinal preparations used are admittedly abnormal in that the segment performing work has been separated from continuity with the rest of the alimentary canal, and such a separation has been shown by Douglas (1949) to reduce the frequency of contractions, probably by the interruption of descending " pace-maker " impulses. In other respects the preparations approach physiological conditions. The dogs are unanaesthetized ; the blood supply and central innervation of the loop are intact, and the contents of the loop are Tyrode solution at body temperature, admitted under moderate pressure. Preparations of this kind have been studied in more than 20 dogs over the past two years, and have been found to work rhythmically for hours at a rate which is remarkably constant from day to day. Increasing the pressure of the entering fluid increases the rate of work (Streeten and Vaughan Williams, 1951), and the actual rate and rhythm adopted are presumably the resultant of numerous central and peripheral self-adjusting mechanisms, any of which might be altered in one direction or another by the injection of a drug, the others then accommodating themselves to the alteration.

A strip of muscle contracting in an isolated organ bath is liberated from influences normally reaching it from other parts of the body, and its behaviour in response to a drug *in vitro* may be different from that which would result if the other influences

were still present. For example, it is well known that the effectiveness of physostigmine as a stimulant of intestinal propulsion *in vivo* is extremely disappointing when judged from what might have been expected from its action *in vitro*. It may, therefore, have an action elsewhere in the body, for instance upon an automatic centre in the brain, which is relayed to the intestine by other mechanisms in part or temporarily cancelling its direct effect as observed *in vitro*. Thus a drug which predominantly " stimulates " *in vitro* could be " inhibitory " via different mechanisms *in vivo*.

There is a second difficulty in applying the words " stimulating " or " inhibitory " to drugs. The terms can be particularly misleading when the activity stimulated or inhibited is measured by an apparatus such as a balloon within the lumen of the bowel. For example, an immediate relaxation after the injection of a drug (= inhibition) could well be an instance of *reculer pour mieux sauter*, to be followed by contractions which, even if in life they possessed greater propulsive force, could not be distinguished by the balloon from other sorts of contraction.

Physostigmine, like pituitrin, also increases the absolute amount of work done by intestinal segments *in vivo*. Like pituitrin, also, its injection is followed by an immediate but temporary phase of " inhibition." The interesting point is that, during this temporary phase of reduced propulsion, the state of the gut is the exact opposite to that which exists after pituitrin. For whereas, after pituitrin, the loop dilates and fills during the phase of quiescence, after physostigmine it at first constricts and empties, for a length of time which depends both upon the amount of drug given and upon the pressure of the inflowing fluid.

The disagreements about the action of pituitary preparations upon intestinal motility can now be discussed in the context of the results presented here. There has been general agreement that in dogs, in rabbits, and in man injections of pituitrin and pitressin are often followed by defaecation. Melville (1936) reported defaecation by dogs after pitocin also. The first point of controversy which arose concerned the action of the extracts *in vitro*. It was shown that, when the complicating factors of unphysiological *p*H and adulteration by preservatives were controlled and eliminated, there was still present a substance which increased the amplitude of contractions of intestinal segments *in vitro*, contained mainly in the pressor fraction.

The second question concerned species differences. In man, dogs, and rabbits there was no doubt of the increased size of contractions, but cats were less sensitive. That cat gut also would, in fact, contract in response to pituitary extract was shown by Steggerda *et al.* (1938).

Thirdly, there was some disagreement about the sensitivity of different parts of the bowel. Most observers found some increase in activity by various methods of recording in some part of the colon, but many failed to demonstrate any such effect in the small intestine. It would, *a priori*, require convincing evidence that the reaction of the intestine on the near side of the ileocaecal valve was different from its reaction on the far side. On the other hand, it is well known that there is a gradual change from the oral to the aboral end of the intestine in certain physiological activities, for example, in the natural frequency of contractions (Alvarez, 1914) from 17.5–21 per minute in the duodenum to 10–12 per minute in the lower ileum. Elsom, Glenn, and Drossner (1939), recording contractions of different parts

of the bowel by means of Miller–Abbott tubes swallowed by human subjects, did in fact find a progressive increase in sensitivity to pituitary preparations as they proceeded from the jejunum to the colon. Our own results show an unequivocal response by the jejunum of the dog.

Fourthly, the presence of a preliminary phase of relaxation probably accounts for the classification of pituitary extracts as having an "inhibitory" action on the bowel. Although Gruber and Pipkin (1930), quoting Gruber and Robinson (1929), state that these authors found pituitary extracts caused "a decrease in tone and general force of contractions in Thiry-Vella loops in dogs," examination of Gruber and Robinson's paper reveals that after pituitrin and pitressin the phase of relaxation was often followed by "tonus waves" and contractions of increased amplitude. Similarly, although Quigley and Barnes (1930) emphasize that injections of pituitrin reduced the size of bowel contractions (measured with balloons), their tracing depicting the activity of the gut after "recovery" from the inhibition shows contractions which are larger than those in the control section before the injection.

The actual rate of propulsive work rhythmically maintained by a segment of intestine, although it remains remarkably constant for hours at a time, is the resultant of stimulation and inhibition by numerous agencies, known and unknown. Among the known factors which influence activity are the pressure and the temperature of the admitted fluid; the oxygenation of the blood; the concentrations of electrolytes in the plasma; the intrinsic activity of the muscle itself; impulses from the vagi and sympathetic nerves, which are themselves controlled by emotional influences as well as functional reflexes; the activity of the network of ganglia in the intestinal wall itself. It must, therefore, be by a continual adjustment of interacting influences that so constant a level of activity is maintained. The rhythmicity, of course, suggests the regular growth and decay of metabolic processes which influence one another. If one of these is interrupted or accelerated by the action of a drug, the others accommodate themselves to the changed situation, and the rate of work at which activity is "reset" in response to the new conditions may be greater or may be less than before the intervention. Thus, after pituitrin, a period of *dilatation* is followed by an absolute increase in the amount of propulsive work done; after physostigmine, a period of *constriction* is followed by an increase in the amount of work; and after morphine (Vaughan Williams and Streeten, 1951) a period of *constriction* is followed by a *decrease* in the propulsive work done. Thus the immediate response of the intestine to a drug, during the period in which the organism as a whole is adjusting itself to the changes produced by it, is not correlated to its ultimate response in terms of the amount of propulsive work finally produced.

Summary

1. An anomaly has long existed in that posterior pituitary extracts, which had been shown to cause defaecation in rabbits, dogs, and man, and to hasten the propulsion by the small intestine of radio-opaque meals, had been found by many workers, mainly using methods employing intraluminal balloons, to have a predominantly relaxant action on the intestine.

2. A recently described method has been employed to demonstrate the mode of action of pituitrin, pitocin, pitressin, and physostigmine upon the propulsive efficiency

of segments of jejunum in conscious dogs. The method makes use of cannulated Thiry-Vella loops, and permits the simultaneous measurement of the amplitude of contractions at both ends of the loop, the state of constriction or relaxation of the loop, and the rate of transport of Tyrode solution against a known pressure. From these measurements the actual amount of propulsive work done by the loop can be calculated.

3. Pituitrin and pitressin both caused absolute increases in the amount of propulsive work done. Equivalent doses of pitocin had no effect.

4. Pituitrin and physostigmine both caused an absolute increase in propulsive work done, but in each case the phase of increased activity was preceded by a period of reduced propulsion. Whereas, however, after pituitrin the loop was in a state of dilatation during the quiescent phase, after physostigmine it was in a state of constriction.

5. Past work concerning the effects of these drugs upon the intestine is discussed, and an interpretation of their mode of action is offered which would be consistent with all the evidence from which conflicting conclusions have sometimes previously been drawn.

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