Brit. J. Pharmacol. (1950), **5**, 584.

THE ACTION OF MORPHINE, PETHIDINE, AND AMIDONE UPON THE INTESTINAL MOTILITY OF CONSCIOUS DOGS

BY

E. M. VAUGHAN WILLIAMS* AND D. H. P. STREETEN†

From the Department of Pharmacology, University of Oxford

(Received September 20, 1950)

Morphine is still the most important analgesic in general use. Unfortunately, it has side-effects, such as its constipating action, which must be taken into consideration when it is used, for example, for the relief of pain after abdominal operations. It would therefore be an advantage in certain cases to have available an analgesic with relatively less effect than morphine upon intestinal motility. A new method of measuring the propulsive power of the intestine having been recently developed (Streeten and Vaughan Williams, 1950a), it was decided to take advantage of the opportunity it offered to make a comparison between the inhibitory effects of morphine and the two modern analgesics, pethidine and amidone (" Physeptone ").

The value of studying the activity in dogs of drugs intended for human use may be questioned. If, however, evidence from both human and other species is in agreement, objections based on the use of animals cannot reasonably be maintained. The interpretation, for example, of the adverse effects of a high venous pressure in accordance with Starling's law of the heart is not disputed, although a heart-lung preparation has never been made in man. A vast number of papers has been published concerning the action of morphine in a variety of tissues and species, including man. Although contradictory conclusions have in the past been drawn from various portions of the available evidence, the results obtained by the method described in this paper have suggested an interpretation of the effects of morphine with which none of the evidence is inconsistent.

Morphine has long been used in the treatment of paralytic ileus. The relief of the patient's anxiety may be an important factor in its efficacy, or the intestine may benefit from the depression of its activity induced by the drug. The explanation, however, of the reported beneficial effects of morphine in ileus as due to a stimulant action upon intestinal propulsion cannot be sustained by any published evidence. Whether morphine is, in fact, beneficial in cases of ileus is a problem quite distinct from that of its mode of action, and is not the concern of this paper.

Morphine

The controversy concerning the action of morphine on the bowel appears to have been the result partly of a failure to give a precise meaning to the word " stimulation," partly of an assumption that different methods of recording were measuring the same phenomena. The dispute began when Nothnagel (1882),

* Schorstein Research Fellow, Oxford University.
† Nuffield Demonstrator in Pharmacology, Oxford University.

failing to confirm Nasse's (1865) observation that morphine "stimulated" rabbit intestine *in situ*, described the drug as inhibitory. Of the very large number of observations made since that time, some have been taken to support Nothnagel, others to vindicate Nasse. The literature has been exhaustively reviewed by Krueger, Eddy, and Sumwalt (1941).

A great many investigators* have agreed that morphine increases the "tone" of the intestine. All these authors employed recording methods which necessitated the introduction of balloons into the intestinal lumen. The reaction of the intestine to an injection of morphine was to compress the balloon, with the result that its volume was reduced and its contents expelled. Unfortunately, this sustained reduction in volume and expulsion *from the balloon* (which formed a closed system with the recording apparatus) of the fluid or air contained inside it was sometimes taken to imply an increase in the propulsive power of the intestine itself, although the balloon, in fact, remained *in situ*. The objections to the interpretation of results obtained with balloons in terms of propulsive activity have been forcibly expounded by Adler, Atkinson, and Ivy (1942). When methods of studying intestinal motility were employed which were expressly designed to measure the effort made by the intestine to push along its contents within its own lumen, no evidence of a maintained increase of propulsive efficiency after morphine could be obtained. Three such methods of measuring intestinal propulsive power have been employed.

(*a*) *Timing the passage of a bolus through an intestinal segment* was originally described by Gottlieb (1910), who introduced a piece of cork into the proximal opening of a "Weller" (? Thiry-Vella) loop in a dog, and found that it passed through the loop in 35 minutes. When morphine had been sprayed into the lumen of the loop, the passage of the cork occupied two hours. After Reid's (1931) description of a similar technique in Thiry-Vella loops, the method was modified by Quigley, Highstone, and Ivy (1934a), who employed a sponge rubber bolus and lubricated the inside of the loop with liquid paraffin. They found (1934b) that at first, for 10–90 minutes after the injection of morphine, 0.25–1.5 mg./kg. subcutaneously, the bolus was expelled from the loop more quickly. When, however, this initial phase was over, there followed a pronounced reduction in the rate of passage of the bolus, lasting 4–5 hours or more. Similar results were reported by Kanan (1937), and by Weissel, Youmans, and Cassels (1938), on dogs with two intestinal fistulae, one of which was used for timing the passage of a rubber bolus, while the other was used to record contractions on a balloon within the lumen. Templeton and Adler (1940) recorded the tension developed by a dog's colon in its effort to expel an inflated balloon inserted through a caecostomy. Again morphine was found to cause a short period of more violent propulsion of the balloon, associated with an increase of intestinal tone, but followed by a prolonged reduction of propulsive effort. Thus the main effect of morphine exhibited by these methods is a prolonged decrease in intestinal propulsive power, and this is in agreement with the evidence obtained by all other methods of measuring propulsive efficiency. The only evidence which *appears* to contradict this finding is the initial and transitory phase of more vigorous propulsion of balloons and boluses which occurs immediately after an injection of morphine, and this will be discussed later.

* Abbott and Pendergrass, 1936; Adler, Atkinson, and Ivy, 1942; Adler and Ivy, 1940; Devine, 1946; Dvorak, Carlson, Erickson, Smith, and Wangensteen, 1931; Gruber, Brundage, DeNote, and Heiligman, 1935; Gruber, Greene, Drayer, and Crawford, 1930; Gruber and Robinson, 1929; Kanan, 1937; Krueger, Howes, and Gay, 1935; Ochsner and Gage, 1933; Oettel, 1935; Orr and Carlson, 1926; Plant and Miller, 1923 and 1926; Slaughter and Gross, 1940; and Weissel, Youmans, and Cassels, 1938.

(*b*) *Radiological methods* have been used extensively on cats, dogs, and man. Magnus (1908) studied the passage of a bismuth meal down the gastro-intestinal tract of cats with diarrhoea induced by an exclusively milk diet. He concluded that the observed constipating effect of morphine was largely due to a prolongation of the gastric emptying time resulting from a tonic contraction in the region of the pylorus, with relatively slight inhibition of small intestinal transport and no effect on the large bowel. Schwenter (1912–1913), also working with cats, found that the passage of the contrast medium through the small bowel was considerably retarded.

Human studies have all revealed a retardation of gastric emptying (von den Velden, 1909; Stierlin and Schapiro, 1912; Schapiro, 1913; Mahlo, 1913; Zehbe, 1913; Pancoast and Hopkins, 1915; Orr and Carlson, 1926; Abbott and Pendergrass, 1936; Myers and Davidson, 1938). This has been shown by Abbott and Pendergrass (1936) to be due not to pylorospasm but to spasm of the duodenum immediately distal to the duodenal cap. Most authors have found that, in addition to the retardation of gastric emptying, there is a slowing of the passage of the radio-opaque medium through the small bowel. That these two effects are distinct has been proved by observing the time taken, after complete emptying of the stomach, for the opaque medium to reach the caecum (Schapiro, 1913), and by timing the passage of barium through the small bowel when the injection of morphine has been delayed until the stomach is already empty (Stierlin and Schapiro, 1912). In the human bowel not all the evidence is in entire accord, for, while Mahlo (1913) and Zehbe (1913) considered an inhibition in the rate of large intestinal transport to be the predominant action of morphine on the gastro-intestinal tract, Stierlin and Schapiro (1912) could not demonstrate such an effect. There is, however, complete agreement that morphine does not increase propulsion.

X-ray studies in a dog with an ileostomy (Orr and Carlson, 1926) have confirmed the inhibitory effects of morphine, already noted in cats and in man, on the transport of opaque media through the stomach and the small intestine. Schapiro (1913) anastomosed the distal end of the upper half of the small bowel of dogs to the caecum, and made a fistula leading into the proximal end of the lower half. Timing the passage of bismuth inserted into such ileal fistulae, he found that morphine delayed its progress, which is in agreement with the other evidence obtained by radiological methods. If, during an experiment, the dog was fed, it was found that the conditions were somewhat different. The bismuth appeared to move more quickly after food and an injection of morphine, than after food alone. It is known, however, that feeding itself causes a prolonged delay in intestinal transport (Schapiro, 1913; Gregory, 1950). This delay has recently been shown (Vaughan Williams, unpublished experiments) to be due at least in part to emotional factors, and apparent quickening may result from a lessened emotional response to the meal. Whatever the explanation of this response to food, the effect of morphine in the absence of the complicating factor of feeding was to delay intestinal transport.

(*c*) The third method of study has been the measurement of the *rate at which intestinal contents were expelled from intestinal fistulae or per anum.* Forster (1938, 1940) found that a pronounced reduction in the volume of the faeces discharged from a human ileostomy occurred during the 90-minute period following the hypodermic injection of 7.5–22.5 mg. morphine. This result was confirmed in experiments on a human ileostomy and on four human colostomies by Adler, Atkinson, and Ivy (1942). These authors showed that the volume of faeces discharged from the ileostomy was reduced from an average of 90 ml. in 22 control periods of three hours each, to an average of 35.6 ml. in 18 periods of three hours following a morphine injection. In the subjects with colostomies the expulsion of faeces or gas, and the outward movement of the tubes attached to the balloon which was used to record contractions in the colon, were much reduced by morphine, 5–16 mg. intramuscularly. On nine occasions when the patients with colostomies were found to

have " hypermotility of the colon . . . the administration of morphine completely abolished the discharge " from the colostomy.

Working on rabbits, Sato (1935) found that an injection of morphine (2–20 mg./kg.) reduced the frequency of defaecation and the number of pellets passed during a 7-hour period following the injection. This was repeated under urethane anaesthesia when increased longitudinal and circular muscle tone could be recorded in the gut *in situ* by means of levers appropriately connected to the bowel wall. The constipating effect of morphine in rabbits has been confirmed by Scott, Chen, Kohlsteadt, Robbins, and Israel (1947). The passage of a carbon suspension through the gastro-intestinal tract of rats, killed 60 minutes after a test meal, was used by Karr (1947) to measure the propulsive rate. He found that morphine reduced the mean distance along the alimentary tract traversed by the carbon particles in 60 minutes.

In summary, it may be said that all the evidence adduced by radiological methods and by investigating the passage of fluid or semi-fluid intestinal contents through the alimentary tracts of cats, dogs (except when being fed), rabbits, rats, and man has indicated that morphine inhibits their active transport. The only results obtained from methods designed to measure propulsion which are in conflict with this conclusion are those which have involved the insertion of a solid bolus or an inflated balloon into a Thiry-Vella loop or a fistula of the colon. As already mentioned, records of the movements of fluid in and out of balloons remaining *in situ* in the intestinal lumen cannot be taken as evidence of intestinal propulsion. The same objections apply to the use of multiple balloon systems, spaced at intervals and supposed to record the passage of " peristaltic waves " from one balloon to the next. Morphine has been said to increase such waves. The danger of interpreting the contractions recorded by such a method as a measure of true intestinal propulsive efficiency has been demonstrated by Rowlands, Chapman, Taylor, and Jones (1950), who employed concurrently both a multiple balloon system, with four balloons, and a radiological method. They found in human subjects that only a special type of sustained contraction could be correlated with the passage of a barium suspension along the gut, and that these contractions were diminished and the movement of barium was delayed for at least four hours by an injection of 10 mg. morphine.

Pethidine and amidone

Previous investigations of the effects of pethidine and amidone have established a spasmolytic action on Magnus preparations of bowel from guinea-pigs, rabbits, and other animals (Schaumann, 1940; Gruber, Hart, and Gruber, 1941; Climenko, 1942; Uchiyama, Kirchhof, and David, 1947; Scott and Chen, 1946). Pethidine has been shown to produce severe constipation in an habituated subject (Curry, 1947) and to inhibit the contractions recorded from inflated balloons placed within the human large and small bowel, both through a colostomy opening and at the end of a Miller-Abbott tube passed through the mouth (Batterman, 1943; Yonkman, 1944; Yonkman, Noth, and Hecht, 1944). Work on amidone has established a constipating effect in rabbits (Karr, 1947; Scott, Chen, Kohlsteadt, Robbins, and Israel, 1947) and retardation of the passage of a carbon emulsion down the gastro-intestinal tracts of rats (Karr, 1947).

On the other hand, studies of intestinal motility recorded by means of balloons inserted into Thiry or Thiry-Vella loops in dogs have shown that both pethidine

(Gruber, Hart, and Gruber, 1941; Yonkman, Noth, and Hecht, 1944) and amidone (Scott, Chen, *et al.*, 1947) increase the tone and the amplitude of contractions. Here again, as with morphine, there is an apparent conflict between the inhibitory effects of the drugs demonstrated by one method, and the " stimulation " shown by another.

Solid boluses and balloons are highly abnormal objects for the small intestine to harbour, its contents being, under ordinary physiological conditions, fluid or semi-fluid. It was possible, therefore, that the apparent differences in drug activity already noted might, in fact, be artificial, and have resulted from the disparity in the methods used for recording intestinal motility, rather than from any species difference, or dual action on the part of the drugs. It was felt that the sort of evidence necessary to reconcile previous observations in apparent conflict could only be obtained from preparations from which the most likely sources of artefacts were eliminated; that is to say, by the use of conscious animals and by the measurement of the actual rate of propulsion of physiological fluid, under controlled conditions of temperature and pressure, by segments of intestine which retained their nerves and blood supply mainly intact. The results presented in this paper were obtained from preparations fulfilling these criteria.

Methods

The methods employed were substantially the same as those already described (Streeten and Vaughan Williams, 1950a). Briefly, a segment of intestine 4–6 inches long was resected, and cannulae were sewn into each end of it. A pedicle carrying the nerves and blood vessels was left intact. The continuity of the rest of the gut was restored by a side-to-side anastomosis. The cannulae were then brought out through separate small stab incisions in the abdominal wall, so that, after recovery, a recording apparatus could be attached by water-tight fittings to both cannulae, and the rate at which fluid was transported through the loop could be measured. Two piston recorders, writing on a smoked drum, recorded the contractions of the proximal and distal ends of the loop, and a float recorder, emptied at intervals by a relay, measured the rate at which fluid was expelled from the loop.

The following modifications were made to the method already described. The cannulae used in previous work were made of silver, and it was not found possible to prevent the ultimate development of leaks around them. Nearly all the work described in this paper was done on loops fitted with " perspex " plastic cannulae, which caused less tissue reaction and were simpler than the silver ones. The terminal flange was made separately, and was mounted on a collar whose position could be adjusted so that it could be made to press a perspex washer down upon the skin before the commencement of each experiment. The flange was returned to its original position, thus releasing the washer, when the day's experiments were finished. The operation in its present form has given satisfactory results for six months without further modification. A perspex cannula, and the method by which it is sewn into the loop and abdominal wall, is illustrated in Fig. 1.

A new method of fitting the recording apparatus to the cannulae has also been introduced. As originally described, the presence of a co-axial rubber collar, between the inner wall of the cannula and the tube leading to the apparatus, made it impossible for the internal diameter of the latter to be greater than 3/16th in. The method of attachment now used (Fig. 2) permits a tube (also of perspex) of bore 5/16th in. to be inserted into a cannula of external diameter $\frac{1}{2}$ in. No metal now comes into contact with the fluid passing through the loops, all parts through which it runs being made of perspex or rubber.

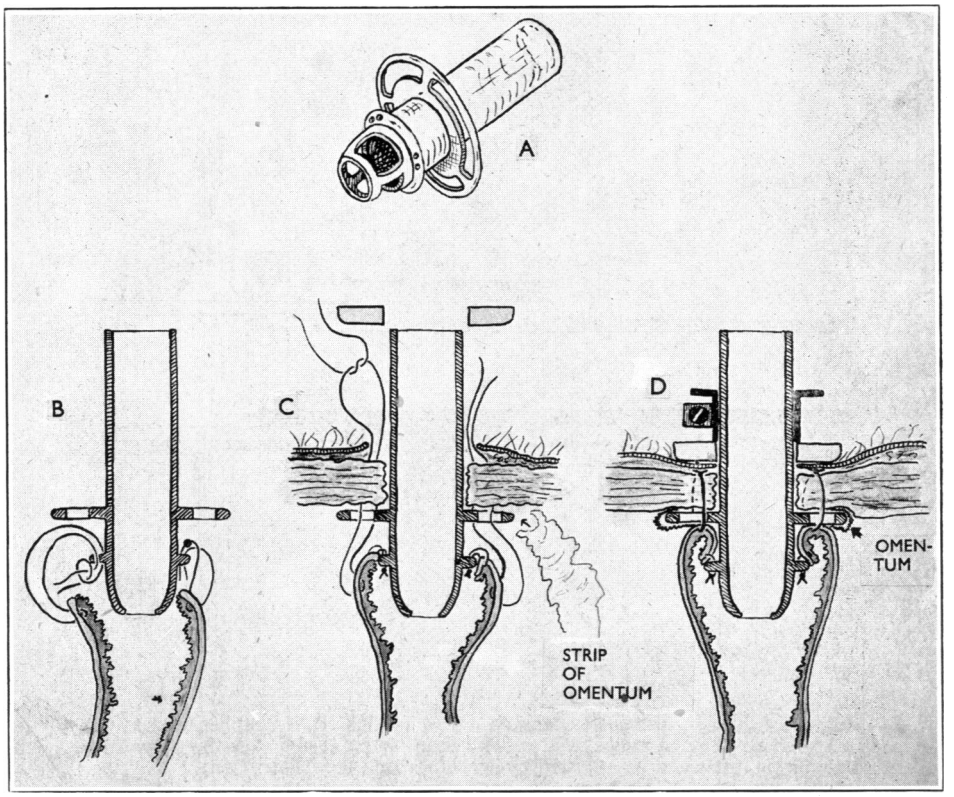

FIG. 1.—A, perspex cannula. B, cannula and gut sewn end to end. C, invagination of mucosa and fixation of cannula to abdominal wall. A strip of omentum covers over the inner flange. D, outer flange adjusted to press a perspex washer against the skin immediately before an experiment.

For some of the experiments designed to reveal the mode of action of morphine an additional recorder was fitted to the inflow reservoir. This involved the construction of fresh apparatus, which has been described elsewhere (Vaughan Williams, 1950).

RESULTS

Experiments performed on eight dogs are recorded in this paper. Assays of all three drugs were carried out on five of them. The animals were deprived of food overnight, and used to lie quietly on their sides while the experiment was in progress. The temperature and pressure of the fluid running into the loop were rigidly controlled, since they have a great influence on activity, which has already been the subject of detailed study (Streeten and Vaughan Williams, 1950a). Disturbing noises and intrusions were avoided by performing the experiments in a quiet basement. The pressures were adjusted to induce the loop to work at a suitable rate, usually about 2.0 g. cm. work/min. (method of calculation described below), and it was then allowed to function for a long control period before the injection of any drug, to give it an opportunity of establishing a steady rate of work.

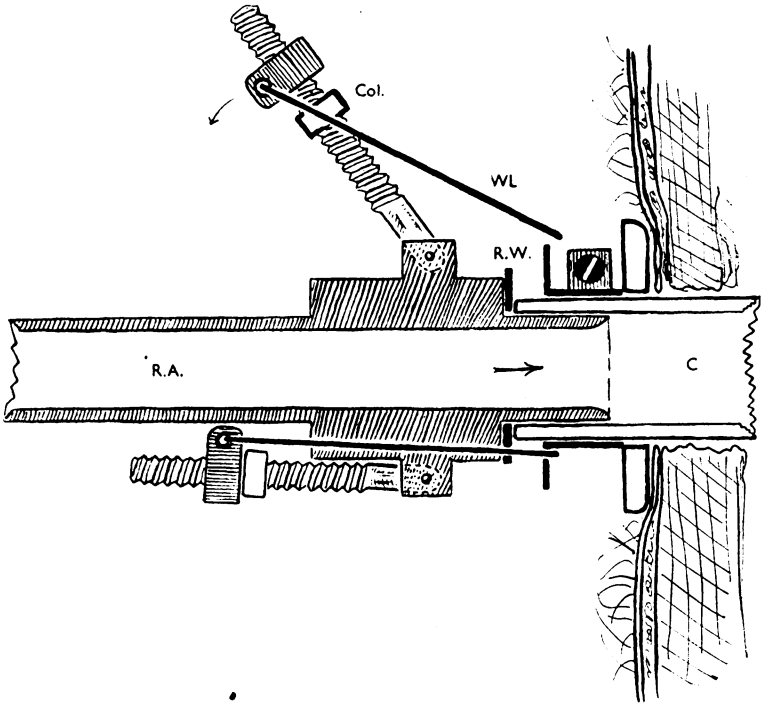

FIG. 2.—Method of fitting apparatus to cannula. C, cannula. R.W., rubber washer. R.A., tube leading to recording apparatus. A steel wire loop, W.L., drops over the outer flange on the cannula; its tightness can be adjusted by screwing back the collar, COL.

The injections themselves caused no disturbance in the motility of the loops in trained dogs, as was established on numerous occasions by injections of saline and even of locally irritant solutions, such as 0.5 per cent acetic acid.

A typical control tracing is shown in Fig. 3. The upper record depicts the contractions of the proximal end of the loop. The second tracing records the contractions of the distal end of the loop, and the third tracing registers the rate at which fluid is transported. Each upward movement of the third lever represents the expulsion of some fluid from the distal end of the loop, and it can be seen that the vertical parts of this tracing correspond with the groups of large contractions in the second tracing. The largest contractions on the upper tracing, on the other hand, coincide with the horizontal parts of the third tracing, when no fluid was being expelled, indicating that, although the groups overlap, the bursts of activity at the upper and lower ends of the loop are out of phase. The three long downward strokes of the third lever indicate the emptying of the outflow recorder by the relay.

In the experiment shown in Fig. 3 the fluid was running into the proximal cannula at a pressure of 6 cm. Tyrode. The side-arm on the outflow tube, however, was set at 8 cm. above the outflow cannula, so that every millilitre of fluid expelled from the loop had been raised through a height of 2 cm. By calibrating the tracing

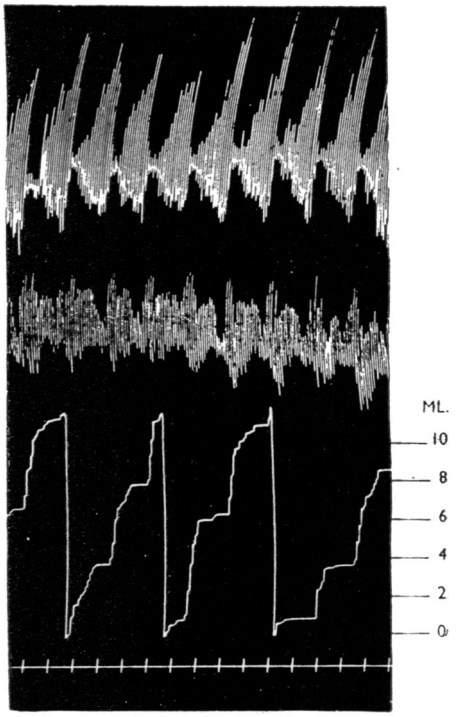

FIG. 3.—Upper tracing: contractions of the proximal end of the loop. Second tracing: contractions of the lower end of the loop. Third tracing: volume of fluid expelled from the loop, calibrated in millilitres. The three downward strokes indicate the emptying of the recorder by a relay. Lowest tracing: time in minutes.

of the outflow recorder in millilitres, the rate at which propulsive work was done by the loop could easily be calculated from the tracing in gramme-centimetres per minute. Time was marked in minutes at the foot of the tracing.

Morphine, pethidine, and amidone all reduced the rate at which fluid was transported by the loop. In Fig. 4 the effects of subcutaneous injections of 30, 70, and 140 μg./kg. of morphine are illustrated, all three experiments being on the same dog. The increase of effect with increase in the dose is obvious. Not only is transport completely abolished, but the amplitude of the contractions is depressed. The effects of approximately equipotent doses of morphine, pethidine, and amidone on another dog are shown in Fig. 5.

Qualitatively the effects of the three drugs are obvious from the tracings. How best to make a quantitative comparison between them was not immediately apparent, however, for recovery from the effects of the drug was gradual, and the rate of work done by the loop was in any case subject to spontaneous variations. Finally, two methods were adopted. The first was to determine the ratio between the doses of each drug just sufficient to cause a complete abolition of fluid transport for not less than five minutes. In order to do this a number of doses of each drug were given, increasing from below threshold, and the "threshold" dose was taken as the mean of the doses which just would, and just would not, cause abolition of transport for the stated interval.

The second method was to measure the work done every five minutes for a control period of about thirty minutes after a reasonably steady rate had been

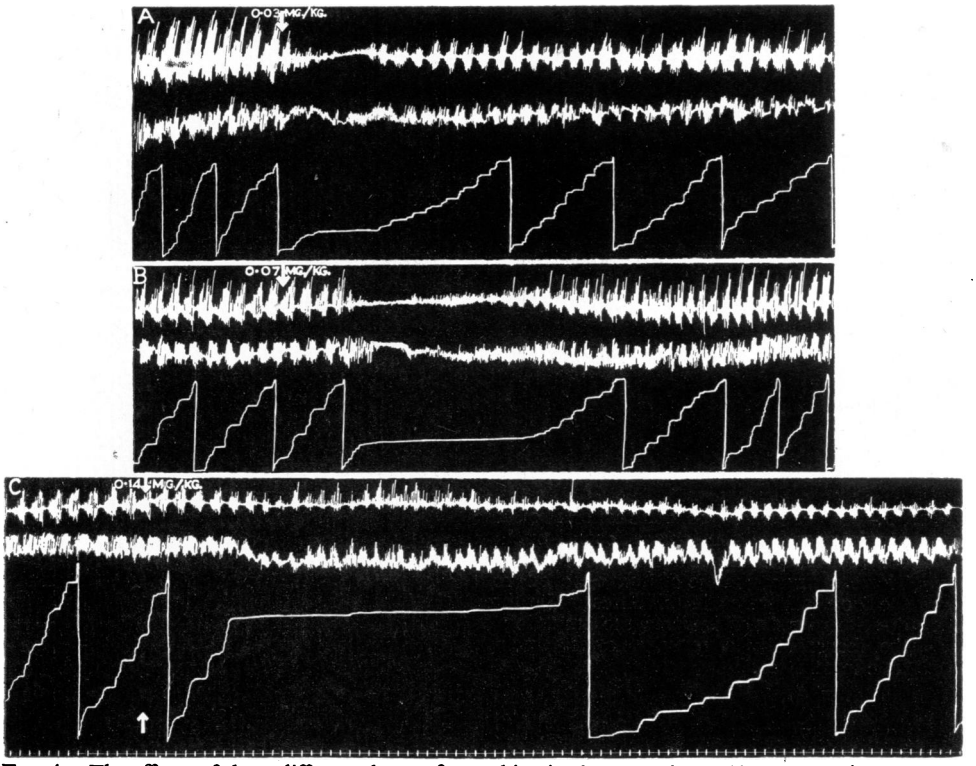

FIG. 4.—The effects of three different doses of morphine in the same dog. Upper record: response to 30 μg./kg. morphine s.c. Middle record: response to 70 μg./kg. morphine s.c. Lower record: response to 140 μg./kg. morphine s.c.

established, and to calculate the mean work done per five minutes. To take an example, such a mean might be 10 g. cm. The actual amounts of work done each five minutes were then plotted as differences from this mean on an integrating curve. If, in the example taken, the work done in each of six five-minute periods was 10, 8, 8, 15, 10, and 9 g. cm., the figures plotted would be 0, −2, −4, +1 (the sum of −4 and +5), +1, 0. Thus, although there were fluctuations in the rate of work done by the loop above and below the mean, there was no maintained alteration in the mean rate of working. Such a change did occur, however, after the injection of an inhibitory drug, and the method of plotting shows, cumulatively, the diminution in the work done. When, after the effects of the drug have worn off, a rate of work equal to the original rate is re-established, there is no further cumulative change, and the curve plotted then becomes parallel to the base line representing the control period. The distance between the two parallels gives the total work " lost " as a result of the action of the drug. Fig. 6 shows the effects of 0.118 mg./kg. of morphine plotted in this way, and the effects of three doses in one dog are plotted in Fig. 7. (The blank portion of the first curve in Fig. 7 indicates that, since the original rate of work was already re-established after 50 minutes, the experiment was not continued for 110 minutes as in the other two experiments.)

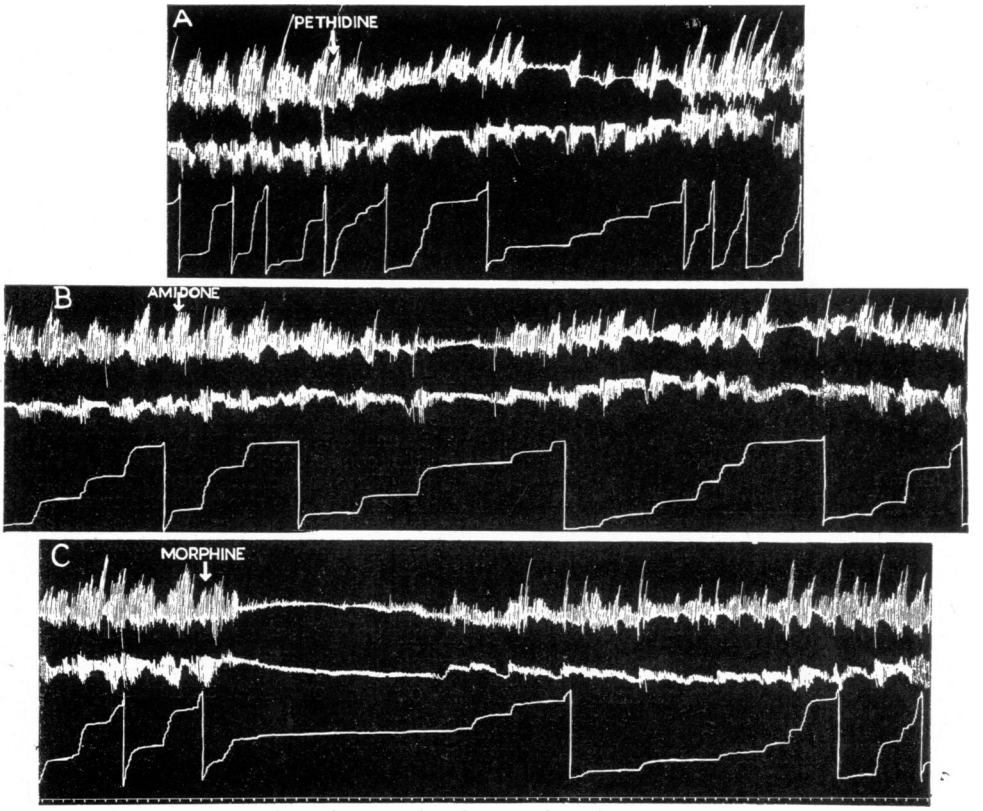

FIG. 5.—The effects, from above downwards, of doses of pethidine, 60 μg./kg., amidone, 80 μg./kg., and morphine, 3.3 mg./kg., in the same dog. (This was not the same animal as that from which the records of Fig. 4 were obtained.)

This method of assessing the effects of the drugs made it possible to plot dose-response curves for all three drugs, and these are shown in Fig. 8. Not all the experiments done are depicted in this graph, since several much larger doses were given, causing inhibitions lasting many hours, and their inclusion would have involved the use of a much smaller scale. Statistical calculations of the significance of the differences between these curves is omitted, for it can be seen with the naked eye that there is no overlap between the points representing the actions of different drugs.

Calculations of the ratios of the relative potencies of the three drugs by both methods—determination of the threshold dose, and the dose necessary to diminish the total work done by an arbitrary figure of 100 g.cm.—are in surprisingly good agreement. The threshold doses were found to be 29 μg./kg. for morphine (sulphate), 77 μg./kg. for amidone (hydrochloride), and 1.7 mg./kg. for pethidine (hydrochloride). The ratios of the relative potencies are recorded in Table I. These ratios are expressed as the number of molecules of active base of amidone and pethidine necessary to produce the same effect as one molecule of morphine base.

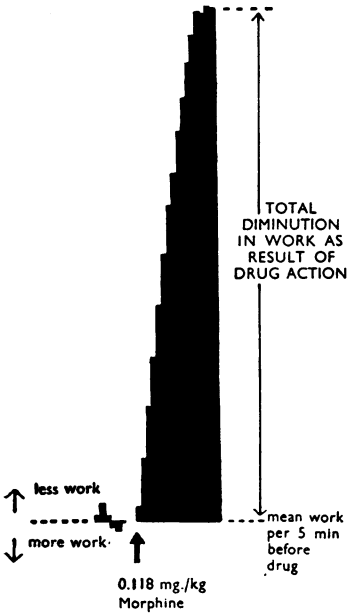

FIG. 6.—Total diminution in propulsive work caused by a dose of morphine. At the left of the tracing, variation of work done every five minutes about the mean (dotted line). At arrow, subcutaneous injection of 0.118 mg./kg. of morphine. Ordinates: Work in g.cm. Abscissae: Time: each step represents five minutes. The difference between the actual propulsive work done in each five-minute period and the mean propulsive work per five minutes in the control period is plotted integrally against time. When the curve becomes once more parallel to the base line, the rate of work has returned to the same level as before the injection. The difference between the two parallels represents the total propulsive work "lost" as a result of the action of the drug.

From these results the equivalent doses for a human subject of 70 kg. can be calculated. Whereas morphine gr. $\frac{1}{4}$ (15 mg.) would abolish intestinal propulsion for an hour or more, the same dose of amidone would be only just sufficient to cause a detectable inhibition, and pethidine in doses as high as 200 mg. would be well below the threshold for inhibition of propulsive activity.

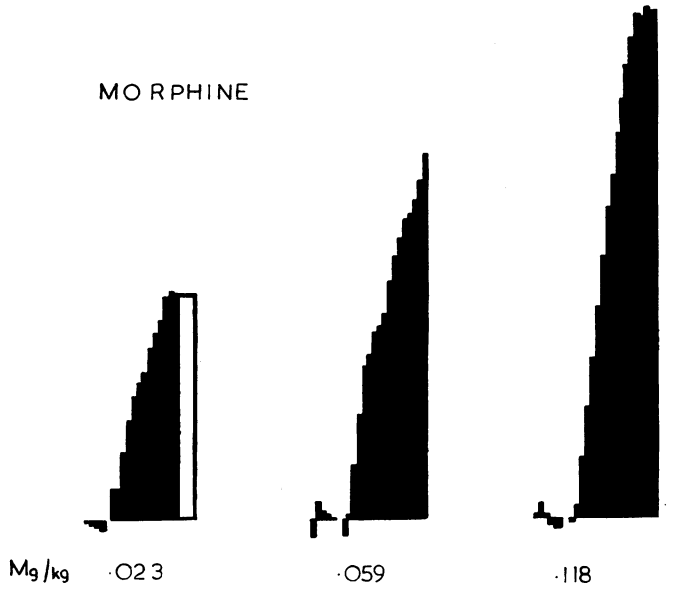

FIG. 7.—The effect of three doses of morphine plotted in the same manner as was described in Fig. 6. Ordinates: work in g.cm. Abscissae: time. The blank portion of the first curve indicates that the experiment was discontinued, since the rate of work had already returned to normal.

TABLE I

Method	Ratios of equipotent doses of		
	Morphine	Amidone	Pethidine
Threshold dose	1	2.86	784
Dose required to reduce work done by 100 g.cm.	1	2.54	750

Mode of action

It seemed of interest to discover how the reduction in propulsive work was brought about, and further experiments were undertaken, first to reveal the physical changes taking place in the loop, secondly to determine whether a central mechanism was involved.

In order to discover what changes occurred in the volume of the loop contents under the influence of morphine, an inflow recorder was added to the apparatus. This involved a number of alterations to the equipment, to ensure that there were no temperature differences in any part of the recording system, and these have been described elsewhere (Vaughan Williams, 1950). Briefly the principle was to record, by means of a second float recorder, every drop of fluid running into the loop, just as the existing outflow recorder registered each drop which was expelled. In order that the inflow recorder might be reset at intervals after a given volume of fluid had flowed into the loop, it was arranged that, when the relay emptied the outflow recorder, the fluid running out of it displaced an equal volume of air into the inflow

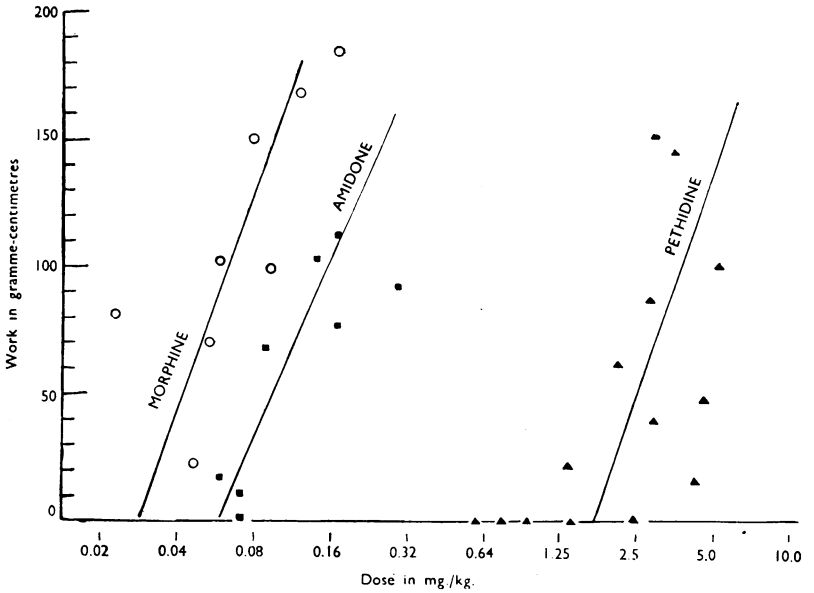

FIG. 8.—Dose-response curves for morphine, amidone, and pethidine. Ordinates: total diminution in propulsive work caused by the action of the drug. Abscissae: dose, in mg./kg., on a logarithmic scale. Circles, morphine. Squares, amidone. Triangles, pethidine.

system, and reset the inflow recorder. The operation of this apparatus is demonstrated in Fig. 9. A rubber tube had been fitted in place of the Thiry-Vella loop,

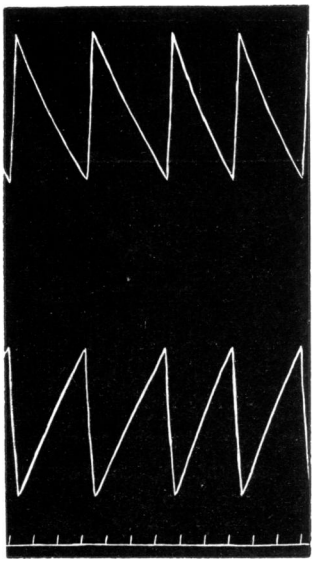

FIG. 9.—Simultaneous tracing from inflow and outflow recorders. Fluid is running from the inflow to the outflow side of the apparatus, through a rubber tube in place of the loop. As the upper recorder descends, indicating inflow, the lower rises, indicating outflow. When the discharge of the relay empties the outflow recorder, the fluid running out displaces air into the inflow system, thus simultaneously resetting the inflow recorder.

and fluid was made to flow through it from the inflow reservoir into the outflow recorder. In the figure only the tracings from the inflow and outflow recorders are shown. It can be seen that, as fluid runs into the tube, the inflow recorder descends, and, since fluid is running out at the same rate, the outflow recorder rises at the same rate as the inflow recorder falls. When the relay discharges, both recorders are reset to their original positions. It will be appreciated that *in vivo*, when an intestinal loop was interposed between inflow and outflow recorders, if fluid was removed from the system by absorption, or added to it by secretion, the records would not be parallel as they are here.

In Fig. 10 the effect of a very small dose of morphine (80 μg./kg.) is shown. The inflow pressure was set at 7 cm. Tyrode, and the outflow sidearm was 8 cm. above the level of the cannulae. From above downwards the records were: contractions of the proximal end of the loop, inflow into the loop, contractions of the lower end of the loop, outflow from the loop, time in minutes. Three minutes after the injection of morphine, the contractions of the lower end of the loop became smaller; the third lever stayed near the top of its excursion, indicating that the lower end of the loop was contracted (A). These small contractions were, nevertheless, able to force fluid out of the loop at almost a normal rate for two further minutes. At B the inflow lever *rose*, indicating that fluid was forced back into the inflow reservoir. Since fluid had been forced out of both ends of the loop, the volume of the loop must have diminished. During the next seventeen minutes, calculation of the amounts of fluid going in and out of the loop (allowing for the mean rate of absorption as measured before the injection and after recovery) reveals that more had been expelled than had entered, indicating a further diminution in the loop volume. The loop must, therefore, have been contracted down, and its

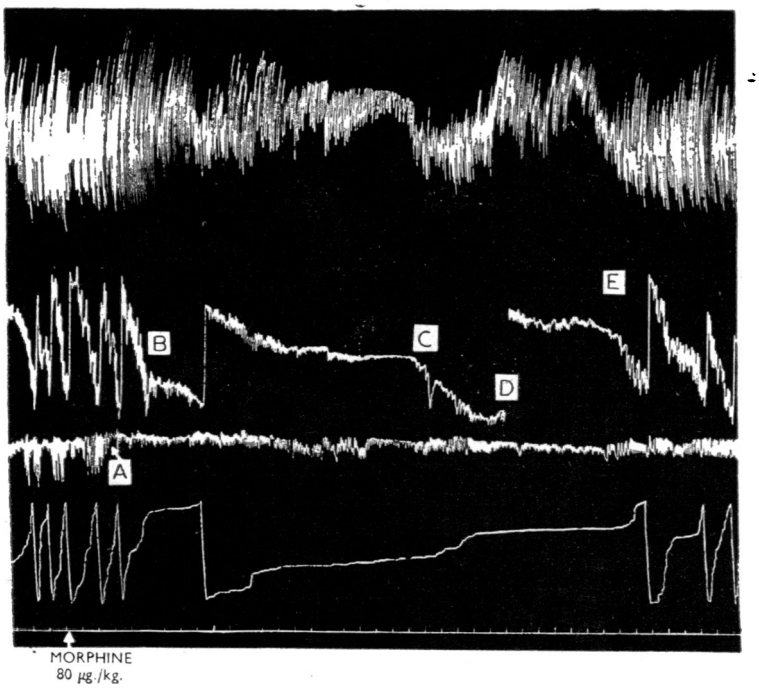

FIG. 10.—Effect of a subcutaneous injection of morphine. Top tracing: contractions of proximal end of loop. Second tracing: inflow record. Third tracing: contractions of distal end of loop. Fourth tracing: outflow record. Fifth tracing: time in minutes. At the first arrow 80 μg./kg. morphine injected subcutaneously. At A the contractions of the distal end diminish. The lever is at the top of its excursion, indicating that the muscle is contracted, i.e., is stopping in systole. At B, fluid is forced out of the proximal end of the loop back into the reservoir, simultaneously with the expulsion of fluid from the lower end. The mean level of the top lever also rises, showing a contracture of the proximal end. At C, relaxation of proximal end —fall of top lever; also, fluid flows into the loop. D, level of inflow recorder reset by addition of 10 ml. Tyrode to the system. E, proximal end of loop again relaxes, and transport by the loop is resumed.

inability to relax prevented the further passage of fluid. At C the proximal end suddenly relaxed (fall in top lever) and fluid ran into the loop (fall in second lever). This fluid was then expelled once more (rise in fourth lever) and transport was again prevented. At D, 10 ml. was added to the inflow system to prevent the tracings running into one another. At E the proximal end once more relaxed, fluid re-entered the loop, and transport rapidly recovered and returned to its former rate. The conclusion drawn from this and similar experiments was that, during the period of inhibited propulsive activity induced by morphine, the muscle of the loop was in a state of contracture.

Intervention of central mechanism

If no central mechanism was involved in the inhibitory effect of morphine, then the concentration of the drug necessary to cause inhibition *in vivo* should be of the same order as that required *in vitro*. Further, if such a central mechanism was

operative in the action of morphine but not, for example, in that of amidone, then the ratios of the potencies of the two drugs would be different *in vivo* and *in vitro*.

In vitro experiments on rabbit and dog intestine were carried out with the object of revealing such differences. Trendelenburg (1917) preparations of rabbit intestine were used with the addition of inlet and outlet valves and of the same outflow recorder as was used in the experiments already described, so that the contractions of the segment of gut pumped fluid into the recorder (Streeten, 1950). For the dog experiments, a segment of gut, adjacent to that used to make a Thiry-Vella loop, was excised at operation, and the arteries and veins of its pedicle were immediately cannulated. The blood was washed out of the vessels by perfusion with Tyrode, and large cannulae were tied into both ends of the segment. The latter were then attached to the recording apparatus in exactly the same way as the Thiry-Vella loops; the only difference being that, whereas the *in vivo* loops were supplied with blood and nerve impulses and lay in the abdominal cavity, the isolated segment was perfused with Tyrode and lay in a bath of oxygenated Tyrode at 38° C. It was found that under these conditions the loop would transport fluid for two hours or more against a pressure gradient, at up to half the rate achieved by a Thiry-Vella loop. Injections of drugs were made into the tube perfusing the vessels.

Both sets of experiments were in agreement, in that the concentrations of both amidone and morphine necessary to produce any effect were far higher than would be produced by doses effective *in vivo*. Assuming that a drug is diluted in 300 ml. for every kilogram of body weight (1/10 weight for blood volume + 1/5 weight for extracellular fluid) the threshold inhibitory concentrations of morphine and amidone *in vivo* would be in the neighbourhood of 10 μg. per 100 ml. and 25 μg. per 100 ml. respectively. In the most sensitive of the preparations of isolated dog intestine the introduction of as much as 50 μg. morphine into the arteries of a piece of gut weighing 12 g. was necessary to produce any observable inhibition—that is to say, the concentration of drug required was at least one hundred times as great as that which would have been produced by effective doses *in vivo*. Similarly, the ratio of *in vitro* to *in vivo* threshold doses of amidone was found to be high—namely, forty to one. The same is not true for pethidine, however, which inhibits propulsive activity *in vitro* at concentrations not very different from those effective *in vivo*.

The results obtained on rabbit intestine presented a similar picture. The mean effective threshold concentrations of amidone and pethidine were in the ratio 1 : 4. The effect of morphine on the propulsive activity of rabbit gut was very variable. In some experiments, although there was an alteration in the type of contraction, the propulsive activity was unaffected by concentrations as high as 4 mg. per 100 ml. A few segments responded with increased propulsive activity, though the majority were inhibited. But here again the concentration of morphine required to produce any effect on propulsion at all was at least one hundred times as great as that produced by effective doses *in vivo* in dogs.

The conclusion drawn from these experiments is that, since the concentrations of morphine and amidone effective in isolated rabbit and dog intestine are of quite a different order from those effective in the dog *in vivo*, some mechanism other than a direct effect upon the muscle or intrinsic nerves of the gut must be involved in the *in vivo* activity of the drugs. Since the difference between effective *in vivo* and *in*

vitro concentrations of pethidine is small, no such conclusion can be drawn for pethidine.

Frequency of contractions

None of the drugs caused any consistent change in the frequency of the contractions. Normally the frequency is remarkably constant, the variation seldom being more than one contraction per minute from the mean. During the action of these analgesics the variation was somewhat larger, the frequency sometimes having changed by as much as two contractions per minute. The change was not, however, consistent in its direction, the contractions being sometimes more, sometimes less frequent. The failure to find a constant effect of morphine on the frequency of contractions is in agreement with the results of Gruber, Brundage, DeNote, and Heiligman (1935) in dogs, and of Abbott and Pendergrass (1936) in man, but an increased frequency after morphine has been reported by Forster (1940), Devine (1946), and Plant and Miller (1926), and a decrease in frequency has been said to occur after morphine by Krueger, Howes, and Gay (1935) and by Oettel (1935).

The rate of work re-established after recovery from the effects of the drugs was usually the same as before the drug was given. After pethidine on three occasions, and on one occasion after morphine, the loop settled down to work at a steady but faster rate after recovery from the phase of inhibition. Also on two occasions with pethidine, when the dose given was just below the threshold for inhibition, the loop worked at a more rapid rate for about fifteen minutes. These more rapid rates did not occur consistently, but they are mentioned because they were occasionally met with, though only in the circumstances mentioned; namely, during the phase of recovery, or when the dose was just sub-threshold.

Discussion

The above results indicate that morphine, amidone, and pethidine all inhibit the propulsive power of cannulated Thiry-Vella loops. It has been shown that this inhibition occurred simultaneously with a contracture of the loop, whose contents were expelled. This cessation of activity in systole, as it were, has been held to account for the diminution in the amplitude of the individual contractions. If, as is shown in Fig. 10, the muscle momentarily relaxed, so that fluid was once more enabled to enter the lumen, propulsive activity was immediately resumed and the fluid expelled. When balloons are inserted into the lumen to measure intestinal tone, precautions are taken to prevent their expulsion. That is to say, the intestinal muscle is kept forcibly dilated, and responds with a continued " increase of tone." Thus the inhibition of intestinal transport observed here is quite consistent with the increase of tone found by so many workers, for it appears to be the contracture of the loop which obstructs the transport.

Methods requiring the insertion of solid boluses also necessitate forcible dilatation of the intestine. Abbott and Pendergrass (1936), using Miller-Abbott tubes with terminal balloons, found that the rise in tone following injections of morphine in man was greatest in the duodenum, but became progressively less the further the balloon was placed down the small intestine. Assuming the same graded response in dogs, it is not surprising that the increase of tone caused by morphine accelerates

the expulsion of a solid object already within the intestinal lumen, or forcibly introduced therein. If hard faeces are likened to a bolus, a similar explanation would account for the defaecation which often occurs in dogs immediately after a large dose of morphine. Thus, again, the acceleration of the passage of a solid bolus, which is inserted by force into the lumen, by a contracture of intestinal muscle, is not inconsistent with the obstruction presented by a similar contracture to the transport of *fluid* under the conditions of pressure employed in these Thiry-Vella loops, which previous work has shown to be optimal for transport under normal conditions when no drug has been given.

It is emphasized that the method described here is designed to demonstrate the propulsive work done by the loop, and not the total work, though this could, in fact, be calculated approximately from the amplitude of the contractions and the prevailing pressure. Krueger, Howes, and Gay (1935) have shown that, when a segment of intestine is dilated by a balloon connected to a water column, the total work done by the intestine after morphine (0.1–10 mg./kg.) in holding up the column is actually increased. This result is not inconsistent with a diminution in *propulsive* work which can only be effected by co-ordinated contractions. If a loop of intestine develops a prolonged contracture, it is impossible for such co-ordinated propulsive movements to occur, even though the capacity for work by the muscle itself might be greater in response to stretching by artificial procedures.

The large difference between threshold concentrations of morphine effective *in vivo* and *in vitro* has been taken to imply that a central mechanism is involved in the action of small doses *in vivo*. It is not necessarily supposed that the drug initiates an outflow of impulses from a central source; its action, for example, could equally well be the potentiation of impulses already arriving under normal conditions (but absent, of course, *in vitro*). Sato (1935) observed that the constipating effects of morphine in rabbits could be abolished by removal of the coeliac ganglion or by section of the spinal cord between segments C7 and T1, but not by vagotomy and destruction of the sacral part of the cord. His own conclusion from this evidence was that the inhibitory action of the drug was mediated by stimulation of the centre for sympathetic nerves. Magnus (1906) failed to abolish the drug's constipating effect (on cats with milk diarrhoea) by dividing the mesentery at its attachment to the posterior abdominal wall, the mesenteric vessels being left intact. Dreyer (1929) also failed, by cutting the splanchnic nerves and the vagus, to abolish the increase of intestinal tone caused by morphine in cats; and Plant and Miller (1923, 1926) found that recent denervation actually increased the response to the drug of Thiry-Vella loops in dogs. Morphine has long been known (Elliott, 1912) to cause depletion of the suprarenals' reservoir of adrenaline. This fact is, however, probably unrelated to morphine's inhibitory effect on intestinal propulsion, for Vámossy (1897) and Dreyer (1929) found that adrenalectomy did not alter the response of the bowel, and Plant and Miller (1926) observed that adrenaline relaxed the increase of tone induced by morphine. Thus the part played by the sympathetic system in the action of morphine is far from clear.

Evidence of the involvement of a cholinergic mechanism has also been sought by many workers. Atropine has been claimed to reverse the increase of intestinal tone after morphine in cats by Myers (1939), in man by Adler, Atkinson, and Ivy (1942), and in dogs by Gruber, Greene, Drayer, and Crawford (1930), Oettel (1935),

Kanan (1937), and Adler and Ivy (1940). The observation, however, that morphine amidone, and pethidine are all inhibitors of cholinesterase (Bernheim and Bernheim, 1936; Eadie, 1941; Brindley, 1944; Eadie, Bernheim, and Fitzgerald, 1948) is probably not related to the action of these substances on the intestine, for the concentrations which have been shown to inhibit the enzyme are far greater than would be produced in a living animal. Moreover, Eichler (1943) has shown that acetylcholine will abolish the inhibitory effect of morphine on peristalsis in isolated preparations of guinea-pig intestine, studied by Baur's (1923) method.

Thus, although there is support for the belief that the action of morphine *in vivo* involves the intervention of a mechanism not present *in vitro*, no conclusive evidence of the nature of the mechanism is yet available.

The ratios of equipotent doses of morphine, amidone, and pethidine for analgesia in man have been given by Christensen and Gross (1948) as 1.0: 0.3: 10. Thorp (1949) found that in rats *dl*-amidone hydrochloride was a slightly more powerful analgesic than morphine sulphate, and Trioxil (1948) observed in human subjects that 10 mg. amidone was equivalent in analgesic properties to 15 mg. morphine.

As already noted in a preliminary communication (Streeten and Vaughan Williams, 1950b), the clinical significance of our results, therefore, is that, since the ratio of equipotent doses of morphine, amidone, and pethidine in inhibiting intestinal propulsion is 1.0: 2.5: 750, amidone has an advantage of approximately 5: 1 and pethidine of 75: 1 over morphine when an analgesic is required which does not interfere with the propulsive motility of the intestine.

SUMMARY

1. Measurements have been made, in conscious dogs, of the rate at which physiological fluid was transported by cannulated Thiry-Vella loops of intestine, under controlled conditions of temperature and pressure. The method used permitted an accurate assessment in g.cm. of the propulsive work done.

2. Morphine, amidone, and pethidine were all found to depress intestinal propulsion. The inhibitory potencies of the three drugs were compared by determining the threshold doses for inhibition of propulsion and the doses of each drug which would reduce the loop's performance of work by an arbitrary amount, 100 g.cm. The ratio of doses found to produce the same inhibition of intestinal propulsion was morphine 1, amidone 2.5, pethidine 750. Since the ratio of doses having the same analgesic effect is approximately 1: 0.5: 10, amidone has an advantage of 5 to 1 and pethidine of 75 to 1 over morphine, when an analgesic is required which does not interfere with intestinal motility.

3. Relatively much smaller doses of morphine and amidone inhibited motility *in vivo* than were found to be necessary for the inhibition of fluid propulsion in *isolated* preparations of dog small intestine. This implies the intervention of some central mechanism *in vivo*. The evidence is against the involvement of such a mechanism in the action of pethidine.

4. Simultaneous records of the rate at which fluid was admitted and expelled from the loops have shown that the inhibition of propulsive activity by morphine is associated with the expulsion of the intraluminal contents by a prolonged

contracture; on relaxation (after a small dose) transport is resumed. An interpretation of the mode of action of morphine is suggested which resolves the apparent conflicts in previous evidence.

References

Abbott, W. O., and Pendergrass, E. P. (1936). *Amer. J. Roentgenol.*, **35**, 289.
Adler, H. F., Atkinson, A. J., and Ivy, A. C. (1942). *Arch. intern. Med.*, **69**, 974.
Adler, H. F., and Ivy, A. C. (1940). *J. Pharmacol.*, **70**, 454.
Batterman, R. C. (1943). *Arch. intern. Med.*, **71**, 345.
Baur, M. (1923). *Arch. exp. Path. Pharmak.*, **100**, 95.
Bernheim, F., and Bernheim, M. L. C. (1936). *J. Pharmacol.*, **57**, 427.
Brindley, I. (1944). *Fed. Proc.*, **3**, 5.
Christensen, E. M., and Gross, E. G. (1948). *J. Amer. med. Ass.*, **137**, 594.
Climenko, D. R. (1942). *Proc. Soc. exp. Biol., N.Y.*, **1**, 15.
Curry, J. J. (1947). *J. Amer. med. Ass.*, **133**, 243.
Devine, J. (1946). *Brit. J. Surg.*, **34**, 158.
Dreyer, N. B. (1929). *J. Pharmacol.*, **36**, 477.
Dvorak, H. J., Carlson, H. A., Erickson, T. C., Smith, V. D., and Wangensteen, O. H. (1931). *Proc. Soc. exp. Biol., N.Y.*, **28**, 434.
Eadie, G. S. (1941). *J. biol. Chem.*, **138**, 597.
Eadie, G. S., Bernheim, F., and Fitzgerald, D. B. (1948). *J. Pharmacol.*, **94**, 19.
Eichler, O. (1943). *Arch. exp. Path. Pharmak.*, **202**, 420.
Elliott, T. R. (1912). *J. Physiol.*, **44**, 374.
Forster, A. C. (1938). *Proc. Soc. exp. Biol., N.Y.*, **38**, 332.
Forster, A. C. (1940). *Ann. Surg.*, **112**, 370.
Gottlieb, R. (1910). *Dtsch. med. Wschr.*, **36**, 1549.
Gregory, R. A. (1950). *J. Physiol.*, **111**, 119.
Gruber, C. M., Brundage, J. T., DeNote, A., and Heiligman, R. (1935). *J. Pharmacol.*, **53**, 120.
Gruber, C. M., Greene, W. W., Drayer, C. S., and Crawford, W. M. (1930). *J. Pharmacol.*, **38**, 389.
Gruber, C. M., Hart, E. R., and Gruber, C. M., jun. (1941). *J. Pharmacol.*, **73**, 319.
Gruber, C. M., and Robinson, P. I. (1929). *J. Pharmacol.*, **37**, 101.
Kanan, M. A. (1937). *Proc. Soc. exp., Biol., N.Y.*, **36**, 506.
Karr, N. W. (1947). *Fed. Proc.*, **6**, 343.
Krueger, H., Eddy, N. B., and Sumwalt, M. (1941). *The Pharmacology of the Opium Alkaloids*, Part I. U.S. Public Health Reports, Suppl. 165.
Krueger, H., Howes, H., and Gay, H. (1935). *J. Pharmacol.*, **55**, 288.
Magnus, R. (1906). *Pflüg. Arch. ges. Physiol.*, **115**, 316.
Magnus, R. (1908). *Pflüg. Arch. ges. Physiol.*, **122**, 210.
Mahlo, A. (1913). *Dtsch. Arch. klin. Med.*, **110**, 562.
Myers, G. N. (1939). *J. Hyg., Camb.*, **39**, 391.
Myers, G. N., and Davidson, S. W. (1938). *J. Hyg., Camb.*, **38**, 432.
Nasse, O. (1865). *Zbl. med. Wiss.*, **3**, 785.
Nothnagel, H. (1882). *Virchow's Arch.*, **89**, 1, cited by Trendelenburg.
Ochsner, A., and Gage, I. M. (1933). *Amer. J. Surg.*, **20**, 378.
Oettel, H. (1935). *Arch. exp. Path. Pharmak.*, **177**, 317.
Orr, T. G., and Carlson, H. E. (1926). *Arch. Surg., Chicago*, **27**, 296.
Pancoast, H. K., and Hopkins, A. H. (1915). *J. Amer. med. Ass.*, **65**, 2220.
Plant, O. H., and Miller, G. H. (1923). *J. Pharmacol.*, **21**, 202 P.
Plant, O. H., and Miller, G. H. (1926). *J. Pharmacol.*, **27**, 361.
Quigley, J. P., Highstone, W. H., and Ivy, A. C. (1934a). *Amer. J. Physiol.*, **108**, 151.
Quigley, J. P., Highstone, W. H., and Ivy, A. C. (1934b). *J. Pharmacol.*, **51**, 308.
Reid, P. E. (1931). *Proc. Soc. exp. Biol., N.Y.*, **29**, 220.
Rowlands, E. N., Chapman, W. P., Taylor, A., and Jones, C. M. (1950). *Surg. Gynec. Obstet.*, **91**, 129.
Sato, M. (1935). *Tohoku J. exp. Med.*, **26**, 83.
Schapiro, N. (1913). *Pflüg. Arch. ges. Physiol.*, **151**, 65.
Schaumann, O. (1940). *Arch. exp. Path. Pharmak.*, **196**, 109.
Schwenter, J. (1912–13). *Fortschr. Röntgenstr.*, **19**, 1.
Scott, C. C., and Chen, K. K. (1946). *J. Pharmacol.*, **87**, 63.
Scott, C. C., Chen, K. K., Kohlsteadt, K. G., Robbins, E. B., and Israel, F. W. (1947). *J. Pharmacol.*, **91**, 147.
Slaughter, D., and Gross, E. G. (1940). *J. Pharmacol.*, **68**, 96.
Stierlin, E., and Schapiro, N. (1912). *Münch. med. Wschr.*, **59**, 2, 2714.

Streeten, D. H. P. (1950). *Surg. Gynec. Obstet.*, **91**, 421.
Streeten, D. H. P., and Vaughan Williams, E. M. (1950a). *J. Physiol.* (in press).
Streeten, D. H. P., and Vaughan Williams, E. M. (1950b). *Lancet*, **2**, 213.
Templeton, R. D., and Adler, H. F. (1940). *Amer. J. Physiol.*, **131**, 428.
Thorp, R. H. (1949). *Brit. J. Pharmacol.*, **4**, 98.
Trendelenburg, P. (1917). *Arch. exp. Path. Pharmak.*, **81**, 55.
Trioxil, E. B. (1948). *J. Amer. med. Ass.*, **137**, 920.
Uchiyama, J., Kirchhof, A. C., and David, N. A. (1947). *Proc. Soc. exp. Biol., N.Y.*, **66**, 417.
Vámossy, Z. (1897). *Dtsch. med. Wschr.*, **23**, 457.
von den Velden, R. (1909). *Münch. med. Wschr.*, **56**, 2, 1667.
Vaughan Williams, E. M. (1950). *J. Physiol.* Proceedings of July Meeting.
Weissel, W., Youmans, W. B., and Cassels, W. H. (1938). *J. Pharmacol.*, **63**, 391.
Yonkman, F. F. (1944). *Anesth. Analges.*, **23**, 207.
Yonkman, F. F., Noth, P. H., and Hecht, H. H. (1944). *Ann. intern. Med.*, **21**, 7.
Zehbe, M. (1913). *Therap. Monatsh.*, **27**, 406.