Brit. J. Pharmacol. (1951), **6**, 263.

THE MODE OF ACTION OF MORPHINE UPON THE INTESTINE

BY

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

From the Department of Pharmacology, University of Oxford

(Received February 23, 1951)

For more than sixty years differing views have been held about the action of morphine upon the intestine. The evidence was reviewed in detail in a recent paper (Vaughan Williams and Streeten, 1950), in which a new method of measuring intestinal propulsion was employed to demonstrate the relative potencies of analgesics on the activity of the bowel. Pethidine and amidone were found to be less active than morphine in retarding intestinal transport, in the ratio 75: 2.5: 1, the figures representing the number of molecules of *active base* of pethidine and amidone required to produce the same effect as one molecule of morphine base. In the same paper an explanation of the mode of action of morphine was offered, which resolved the apparent conflicts between the conclusions drawn by different workers employing a variety of methods. Further evidence is presented here which supports this explanation.

Many people have shown that morphine causes an increase of intestinal " tone "; that is to say, it induces a sustained contraction of a segment of intestine which will force fluid or air out of a recording balloon placed within the lumen. An increase in amplitude and frequency has also been observed in the so-called " peristaltic waves." Such changes in recorded intraluminal pressure have often been taken to imply that morphine would accelerate the propulsion of intestinal contents. This view was supported by the observation of Templeton and Adler (1940) that the force tending to drive onward a balloon placed in a Thiry-Vella loop, and held back by a thread attached to a spring, was temporarily augmented after injections of morphine; and by the results of Quigley, Highstone, and Ivy (1934), who observed that the passage of a lubricated rubber bolus, inserted into a Thiry-Vella loop, was at first accelerated by morphine, though the main effect of the drug was a prolonged slowing of the rate of its propulsion.

On the other hand, numerous *x*-ray studies of the movement of radio-opaque meals, observations of the expulsion of intestinal contents from fistulae in human patients, and measurements of the rate of passage of faecal pellets in rabbits, and of carbon suspensions in rats, had all shown that morphine reduced intestinal propulsive activity. In spite of the latter evidence, however, the view is still held by many surgeons and others that morphine improves the efficiency of intestinal propulsion, a belief based upon evidence obtained from intraluminal balloons or

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

boluses, or derived from personal observations of intestinal activity during operations. Douglas (1949) noted that in dogs with Biebl loops morphine sulphate promoted " active contractions of the intestine," and Chesterman (1945) stated that " true peristalsis is increased for short periods " by morphine.

Measurements of the transport of fluid by cannulated Thiry-Vella loops (Vaughan Williams and Streeten, 1950) suggested an interpretation of the action of morphine which could reconcile these apparent contradictions. It was observed that the inhibition of propulsion caused by morphine occurred within a few minutes of injecting the drug, and that its onset was simultaneous with the expected increase in " tone," i.e., reduction in volume of the lumen of the loop. When the tone relaxed spontaneously for a brief interval, the transport of fluid was immediately resumed, only to cease again as soon as the lumen was occluded once more. The hypothesis was therefore put forward that the inhibition of intestinal transport produced by morphine was brought about by the very increase in tone which had been supposed by some previous workers to have improved it; and that the failure of propulsion was due, not to any paralysis or paresis of the intestinal muscle, but to a sustained contraction which closed off the lumen and impeded the development of co-ordinated propulsive movements. The results of Templeton and Adler (1940) and Quigley, Highstone, and Ivy (1934), already quoted, could thus be attributed to their employment of the unphysiological stimulus of inserting into the intestine solid boluses or balloons which forcibly dilated its walls. It is of interest that they noticed that after morphine more force was required to insert the boluses.

Methods

The preparation of the loops and the apparatus have already been described (Streeten and Vaughan Williams, 1951; Vaughan Williams, 1951). Briefly, a short segment of intestine, with a pedicle carrying nerves and blood vessels, was separated from the alimentary tract, the continuity of which was restored by a side-to-side anastomosis. Perspex cannulae were sewn into each end of the segment, and were fixed to the abdominal wall in such a way that, after the recovery of the dog from the operation, they gave permanent access to both ends of the loop, which itself lay within the abdominal cavity. To obtain records of intestinal motility, the cannulae were attached by water-tight joints to apparatus which enabled Tyrode solution to pass through the loop under controlled conditions of temperature and pressure, its rate of movement into and out of the loop being separately recorded. A comparison of the records enabled the volume, and thus the " tone," of the loop to be deduced.

Before it could be expelled from the loop, the fluid had to be raised by the contractions of the distal end to a height above the level of the reservoir from which it was running into the proximal end. Every drop of fluid transported having been lifted through a known and adjustable vertical distance, the rate of transport provided a quantitative estimate of the propulsive work done, measurable directly in gramme centimetres.

Results

In our previous paper (1950) it was suggested that an accelerated propulsion of solid boluses by the intestine and an increased pull exerted upon balloons after morphine was observed only because the intestinal wall was forcibly dilated by such objects. If this interpretation is correct, the complete inhibition of the transport of *fluid* induced by morphine should eventually be overcome if the dilating effect

of a bolus were imitated by increasing the pressure of the fluid at the entrance to the loop. The results of such a procedure are shown in Fig. 1, which depicts the activity of a loop (from the jejunum) about 12 cm. long. Tyrode solution was flowing in at a pressure of 10 cm., and had to be raised to a height of 11 cm. by

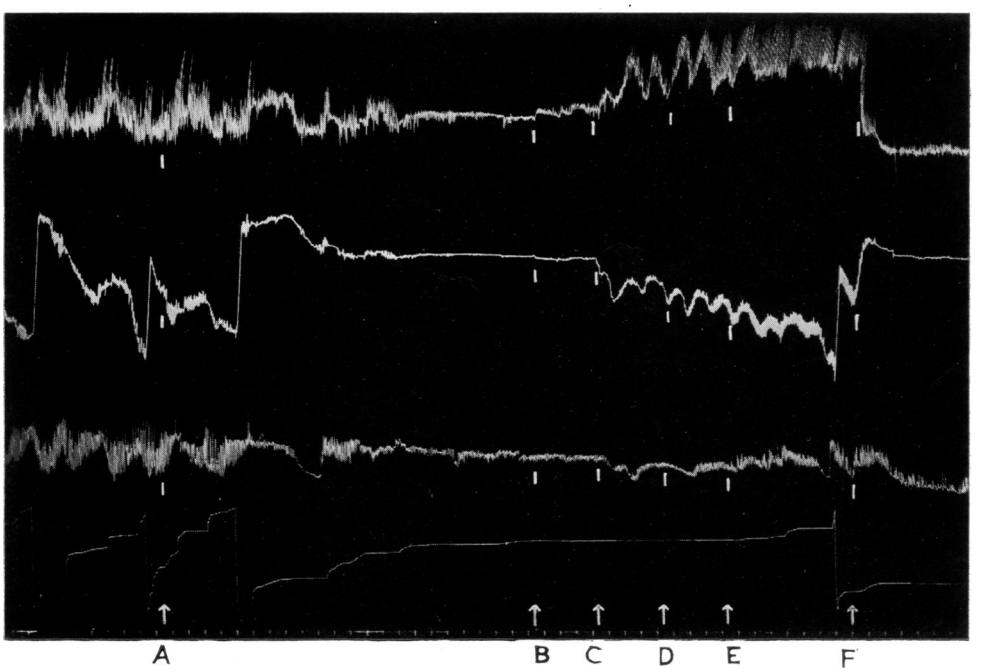

FIG. 1.—Activity of jejunal loop. Tyrode was flowing in at a pressure of 10 cm., and was pumped by the loop's contractions to a height of 11 cm. From above downwards: contractions of the proximal end of the loop; rate of flow into the proximal end; contractions of the distal end; rate of outflow from the distal end; time in minutes. At A, morphine sulphate (0.17 mg./kg.) was injected subcutaneously. At B, C, and D, the level of the inflow reservoir was raised to 13, 15, and 17 cm. Tyrode respectively. Not until the pressure was raised to 19 cm., at E, was the constricting effect of morphine overcome and the transport of fluid resumed. On the return of the pressure, at F, to 10 cm. once more, transport again ceased immediately.

the contractions of the loop before it could be expelled. The top tracing records the contractions of the proximal end, and every downward movement observed in the second tracing marks the admission of fluid into the loop. The third tracing depicts the contractions of the distal end of the loop, and each *upward* movement shown in the fourth tracing records the expulsion of fluid into an outflow recorder. The vertical straight lines in the second and fourth tracings mark the discharge, by a relay, of 10 ml. of fluid from the outflow recorder, and the simultaneous resetting of the inflow recorder by an equal volume of air. At A, 0.17 mg. morphine sulphate per kg. was injected subcutaneously. Five minutes later the rate of expulsion of fluid (fourth record) began to diminish, and shortly afterwards both inflow and outflow ceased altogether. Examination of the inflow and outflow records between the injection and the cessation of flow reveals that, whereas 11.8 ml. Tyrode had

been expelled from the loop, only 4.5 ml. had been admitted. The volume of the loop had thus diminished by 7.3 ml., indicating a closing down of its lumen.

At B, the pressure of the fluid in the proximal cannula was raised to 13 cm. In a normal loop under such circumstances (that is, with a pressure of 13 cm. at the proximal end and of only 11 cm. at the distal) fluid would have run passively through the loop. Under the influence of morphine, however, this did not occur, nor did it do so at C and D when the pressure was raised still further to 15 and 17 cm. respectively. As can be seen from the top record, the proximal end of the loop was stimulated to vigorous contractions by these high pressures; nevertheless, the lumen of the loop still remained closed, not a drop of fluid ran through the loop, and the contractions of the distal end of the loop (3rd tracing) were unaffected. When the pressure was raised to 19 cm. Tyrode, at E, the resistance of the contracted muscle was finally overcome, fluid ran both into and out of the loop, and the relay mechanism duly discharged 10 ml. from the outflow recorder. At F, the inflow pressure was returned to 10 cm., resulting immediately in the closure of the loop once more and a complete cessation of flow.

This result suggested that the belief that the inhibition of transport was due to simple closure of the loop in response to morphine might be confirmed equally well by the injection of drugs known to relax intestinal tone. In the experiment shown in Fig. 2, 0.13 mg. morphine sulphate per kg. was injected subcutaneously at A, with results similar to those in Fig. 1. At B, 0.042 mg. *l*-adrenaline per kg.

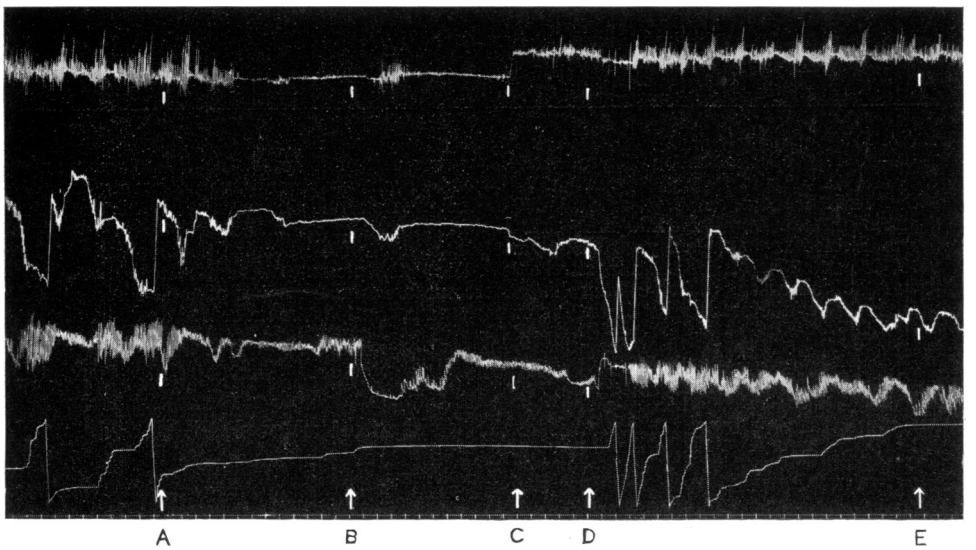

FIG. 2.—Activity of the same loop as in Fig. 1. Inflow pressure 10 cm. Tyrode, outflow sidearm 11 cm. above cannulae. At A, morphine sulphate (0.13 mg./kg.) was injected subcutaneously. At B, an intravenous injection of 0.042 mg. *l*-adrenaline per kg. was given, resulting in a dilatation of the loop, but not in the resumption of the transport of fluid. At C, the level of the inflow reservoir was raised to 12 cm., i.e., 1 cm. above the level of the outflow side-arm. At D, an intravenous injection of the same dose of adrenaline resulted in the flow of fluid through the loop. At E, the inflow pressure was returned to 10 cm. Tyrode.

was injected intravenously. Within a minute the tone of the intestine relaxed, and fluid ran into both the proximal end (2nd tracing) and back from the outflow tube into the distal end (3rd tracing). At the same time some contractions developed at the proximal end (top tracing). The effect was short-lived, however, and a few minutes later the situation was the same as before. At C the pressure at the proximal end was raised 2 cm. so that it was now 1 cm. above that at the distal end. At D the same dose of adrenaline was injected as at C. The fact that the inflow pressure was now higher than the outflow permitted fluid to run passively through the relaxed loop. At the same time, the presence of the fluid within the loop apparently stimulated the intestinal muscle, for the contractions were more vigorous and were maintained for a longer period than before. Eventually, however, as the effects of the adrenaline diminished, the lumen again closed down, and at E the passage of fluid once more ceased, when the pressure at the proximal end of the loop was reduced.

A similar effect, in an experiment on another dog, can be seen in Fig. 3. At A, 0.32 mg. morphine sulphate per kg. was injected subcutaneously, fluid transport

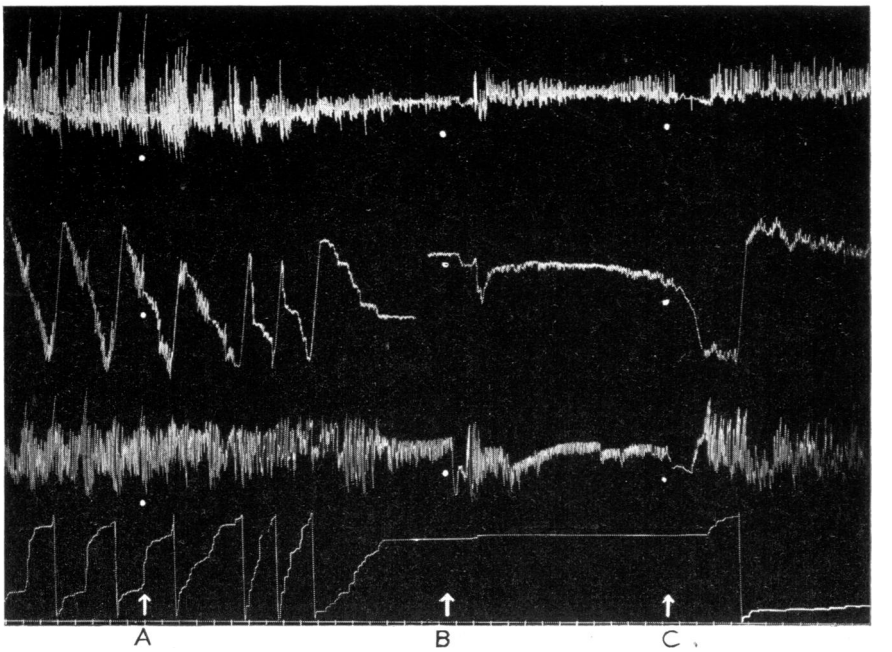

FIG. 3.—Activity of a different jejunal loop. Inflow pressure 9 cm. Tyrode, and outflow side-arm 10 cm. above cannulae throughout. At A, morphine sulphate (0.32 mg./kg.) injected subcutaneously. Intravenous injections were given of *l-nor*adrenaline: at B, 0.02 mg./kg. and, at C, 0.04 mg./kg. Fluid admitted to the loop during the relaxation caused by *nor*adrenaline was expelled again almost immediately.

ceasing completely within 15 min. The slight initial increase in the rate of transport was within the limits of variation normally encountered. The inflow pressure was 9 cm. Tyrode, and the outflow side-arm was 10 cm. above the loop throughout the experiment. (The break in the second record just before B represents a resetting

of the inflow recorder to avoid a subsequent overlap in the records.) At B, 0.02 mg. *l-nor*adrenaline per kg. was injected intravenously, causing a brief relaxation of the loop; not enough fluid entered to stimulate propulsion, however, and only two drops were expelled into the outflow recorder. At C, 0.04 mg. *l-nor*adrenaline per kg. was injected, resulting in the admission of 6.5 ml. from the inflow reservoir. This acted as a sufficient stimulus to promote the resumption of propulsive contractions, and some fluid was transported through the loop. Transport again ceased as the effects of the *nor*adrenaline diminished.

Atropine will also antagonize the effect of moderate doses of morphine, its effect being more prolonged than that of adrenaline or *nor*adrenaline. In Fig. 4, 0.32 mg.

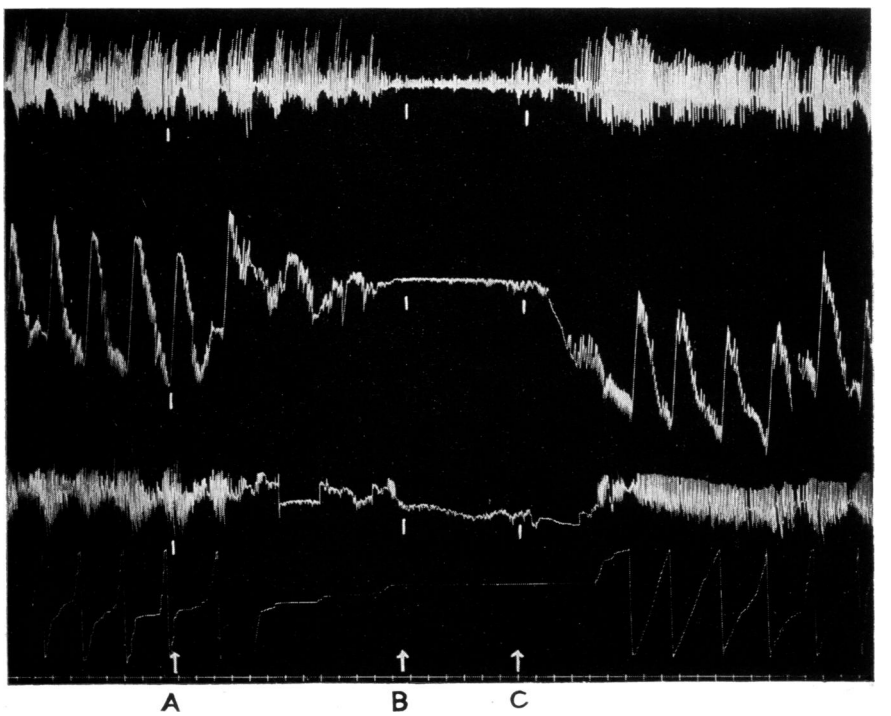

FIG. 4.—The antagonism to a moderate dose of morphine by atropine. At A, morphine sulphate (0.32 mg./kg.) injected subcutaneously. At B, the dog had a fit of retching. Under the influence of morphine, however, the big changes in intra-abdominal pressure resulting therefrom were not transmitted to the recording levers. At C, atropine sulphate (0.11 mg./kg.) was injected intravenously, and resulted in a resumption of fluid transport. Inflow pressure 9 cm., outflow side-arm 10 cm. above cannulae throughout.

morphine sulphate per kg. was given at A, and resulted in a fit of retching (B). In an untreated dog, although ordinary respiratory movements are not recorded on the tracings, such violent movements as these would have caused large excursions of all levers. Under the influence of morphine, however, the loop was contracted down, and presumably had either expelled all the fluid from its lumen, or had such a high tone in its walls that its contents were insulated from the big changes in

abdominal pressure associated with vomiting, for these were not transmitted to the recorders. At C, 0.11 mg. atropine per kg. was injected intravenously, and resulted in a resumption of intestinal transport, with a different rhythm but at approximately the same rate as before the morphine. If a larger dose of morphine was given, however, its effect was more powerful than that of the atropine, for it could not be antagonized by increasing the dose of atropine. This finding is illustrated in Fig. 5. The beginning of the tracing shows the activity of the same loop as that

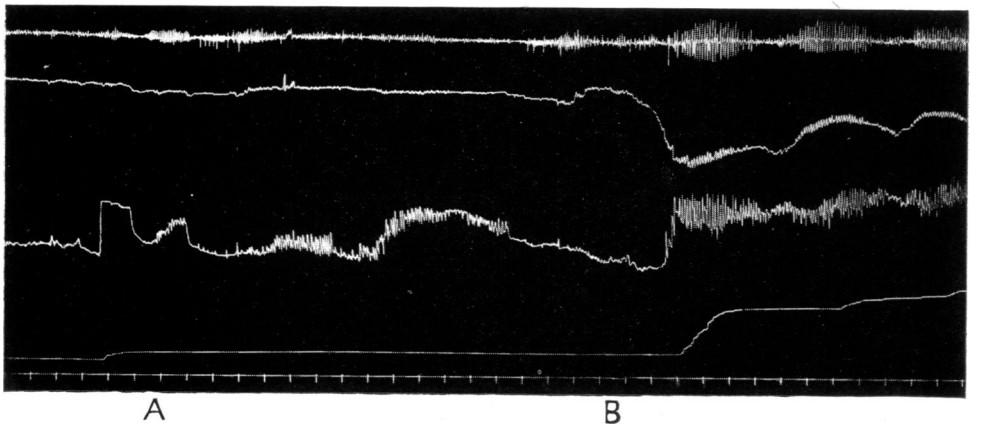

FIG. 5.—Twenty minutes before the commencement of the tracing, morphine sulphate (0.33 mg./kg.) had been injected subcutaneously and proved, in this dog (the same as that of Figs. 1 and 2), sufficiently large to produce an *in vivo* concentration such that adrenaline (0.04 mg./kg.) at A, and atropine (0.16 mg./kg.) at B, injected intravenously were now no longer able to antagonize appreciably the inhibition of fluid transport.

of Figs. 1 and 2 (which was more sensitive to morphine than that of Figs. 3 and 4), 20 minutes after an injection of 0.33 mg. morphine sulphate per kg. An intravenous injection of 0.016 mg. adrenaline per kg. had already been ineffective. At A, 0.04 mg. adrenaline per kg. was injected intravenously, and at B, 0.16 mg. atropine per kg. (the equivalent of approximately ten times the usual human dose), with little effect. It is clear that an antagonism to morphine by atropine could be expected to be demonstrated only if large doses of morphine were avoided, and this fact may explain the failure of some authors (Plant and Miller, 1926) to demonstrate such an antagonism, which was subsequently reported by many others (Gruber, Greene, Drayer, and Crawford, 1930; Oettel, 1935; Kanan, 1937; Myers, 1939; Adler and Ivy, 1940; Adler, Atkinson, and Ivy, 1942).

DISCUSSION

The results support the hypothesis that the inhibitory action of morphine upon intestinal propulsion is brought about by a prolonged contraction, which closes the intestinal lumen and prevents the development of co-ordinated propulsive contractions. This hypothesis reconciles the apparent conflict between the evidence, obtained from balloons and similar devices, that morphine increases intestinal activity, and the results from *x* rays of opaque meals and from other methods of measuring

intestinal *propulsion*, which have demonstrated that morphine retards the passage of contents along the bowel.

In a study of the influence of intraluminal pressure upon the transport of fluid by Thiry-Vella loops (Streeten and Vaughan Williams, 1951) it was shown that propulsive efficiency decreased when the jejunum was distended by pressures greater than 10 cm. Tyrode. Oettel (1934) stated that the intestinal contractions of the dog became " fatigued " when a balloon within the bowel was distended to 20–30 cm. H_2O for any length of time; and Krueger, Howes, and Gay (1935), employing pressures of 30–32 cm. H_2O in a similar preparation, found that the number of peristaltic waves during control experiments was " small in all dogs and equal to zero in many." A pressure at the inflow cannula of 10 cm. Tyrode was therefore regarded as the upper limit of " normal," and was used in the experiments presented here. Under such conditions morphine completely abolished the transport of fluid through the loops. This abolition was not due to any paralysis of the intestinal wall, for if fluid could be induced to enter the loop by raising the pressure at the inflow cannula, or by injections of relaxant drugs such as adrenaline or *nor*adrenaline, propulsive contractions were immediately resumed and the fluid expelled once more.

It is suggested, therefore, that the temporary acceleration of the passage of inserted boluses after morphine, and the increase in intestinal activity demonstrated by intraluminal balloons, has been demonstrated only as a consequence of the forcible distension of the intestinal wall by these unphysiological objects. Information about the distending pressures used in experiments with balloons has not always been published (exceptions being Plant and Miller (1926), 25–35 cm. water; Krueger (1934), 30–32 cm. water; Krueger, Howes, and Gay (1935), 30–32 cm. water), but it is noteworthy that, in the few balloon experiments in which a *reduction* of contractions after morphine was reported, lower pressures were employed, e.g., 15 cm. in the studies of Gruber, Brundage, DeNote, and Heiligman (1935).

In the experiments described in this paper moderate doses of morphine were used, ranging from 0.13 mg./kg. to 0.33 mg./kg., which for a human being of 60 kg. correspond to doses of 8 and 20 mg., or roughly $\frac{1}{8}$ and $\frac{1}{3}$ grain. That the effect of a moderate dose of morphine is mediated *in vivo* by some mechanism not present *in vitro* was suggested by the finding that the threshold concentration required to produce an effect *in vitro* was of the order of one hundred times the concentration calculated to be effective *in vivo* (Vaughan Williams and Streeten, 1950). The antagonism of moderate doses of morphine by atropine suggested that a cholinergic transmission was involved somewhere in the pathway mediating the effect. Large doses would, of course, raise the concentration of the drug in the extracellular fluid *in vivo* to levels which have been shown to be effective *in vitro*, and which could, therefore, exert a direct action upon the intestinal wall.

The mechanism of the action of moderate doses of morphine *in vivo* is far from clear and has already been discussed (Vaughan Williams and Streeten, 1950). It is of interest that the action upon the intestine of the drug amidone, which has been shown to have effects very similar to those of morphine, has been proved to be exerted through the vagi. In cross-circulation experiments, in which the head of a recipient dog was supplied with blood from a donor, Scott, Chen, Kohlsteadt, Robbins, and Israel (1947) showed that an injection of amidone into the donor circulation resulted in changes in intestinal activity (recorded by balloons) in the

recipient similar to those observed in a whole dog, although the recipient's trunk was connected to its perfused head by the vagus nerves alone. It is possible that morphine exerts its effect in a similar way. Against this must be set the evidence of Magnus (1906), Plant and Miller (1926), and Dreyer (1929), who found that denervation of the intestine did not abolish the effects of morphine. Magnus used doses of 30–40 mg. and Dreyer of 4 mg./kg., both of which would produce a concentration *in vivo* comparable to that effective *in vitro*, and which could, therefore, have produced a direct effect upon the intestinal wall. Plant and Miller, who used smaller doses of morphine (0.5 mg./kg.), admitted that their denervations were only partial. Parasympathetic denervation is known to result in the supersensitivity of the denervated effectors (Shen and Cannon, 1936), and the possibility cannot be ignored that the denervated receptors reacted to transmitter released by the fibres still left intact. None of these denervation experiments, therefore, can be taken as disproving the participation of the vagi in the effect of moderate doses of morphine on the intestine.

Appreciation of the mechanism of action of morphine has some clinical importance; in estimating, for example, the likelihood of its being beneficial in cases of intestinal distension or paralytic ileus. The evidence from experimental work is that, unless the intraluminal pressure is high, morphine has no stimulant action upon intestinal propulsion, but, on the contrary, abolishes it. If there is intestinal distension, and if the causes of such distension can be regarded as analogous to dilatation of the intestinal walls by boluses or balloons, then there is experimental support for the belief that morphine could temporarily facilitate intestinal propulsion. But, even under such circumstances, the phase of stimulation lasts for a period of minutes only, and is followed by a depression measurable in hours.

Such considerations apply, of course, to the effects of morphine upon the intestine only, and its depressant action there might well be thought to be outweighed by its beneficial effects in relieving anxiety and discomfort. A rational conclusion from the available evidence, therefore, would be that a single injection of morphine at the commencement of treating a case of paralytic ileus might be of value, but that continued administration of the drug could only result in an increasingly profound inhibition of intestinal propulsion, the return of which to normal would actually be prevented. It would seem preferable in such cases to use the other drugs now available, which, in doses of comparable analgesic potency, have been shown to have relatively less effect than morphine upon intestinal propulsion. Doses of both pethidine and amidone normally used for analgesia are below the threshold required to produce any observable inhibition of intestinal propulsion. Pethidine is the least active on the intestine, but its analgesic effect is qualitatively less good; i.e., increasing the dose does not compensate for its inability to relieve severe pain. Amidone, on the other hand, combines the advantages of great potency as an analgesic with relatively minor activity as an intestinal inhibitor.

SUMMARY

1. Observations have been made of the tone and amplitude of contractions of cannulated Thiry-Vella loops in conscious dogs, and simultaneously of the rate at which the loops transport Tyrode solution under controlled conditions of temperature and pressure.

2. Morphine inhibits intestinal propulsion. The inhibition is caused by a closure of the intestinal lumen, not by any paralysis or paresis of the intestinal wall.

3. While under the influence of moderate doses of morphine, the loops will again transport fluid if they are distended by high pressures, or relaxed by adrenaline or *nor*adrenaline.

4. Atropine antagonizes moderate, but not large, doses of morphine.

5. The explanation offered of the mode of action of morphine is shown to reconcile apparent contradictions in previous evidence.

References

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.
Chesterman, J. T. (1945). *Brit. med. J.*, **2**, 740.
Douglas, D. M. (1949). *J. Physiol.*, **110**, 66.
Dreyer, N. B. (1929). *J. Pharmacol.*, **36**, 477.
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.
Kanan, M. A. (1937). *Proc. Soc. exp. Biol., N.Y.*, **36**, 506.
Krueger, H. (1934). *J. Pharmacol.*, **50**, 254.
Krueger, H., Howes, H., and Gay, H. (1935). *J. Pharmacol.*, **55**, 288.
Magnus, R. (1906). *Pflüg. Arch. ges. Physiol.*, **115**, 316.
Myers, G. N. (1939). *J. Hyg., Camb.*, **39**, 391.
Oettel, H. (1934). *Arch. exp. Path. Pharmak.*, **175**, 588.
Oettel, H. (1935). *Arch. exp. Path. Pharmak.*, **177**, 317.
Plant, O. H., and Miller, G. H. (1926). *J. Pharmacol.*, **27**, 361.
Quigley, J. P., Highstone, W. H., and Ivy, A. C. (1934). *J. Pharmacol.*, **51**, 308.
Scott, C. C., Chen, K. K., Kohlsteadt, K. G., Robbins, E. B., and Israel, F. W. (1947). *J. Pharmacol* **91**, 147.
Shen, S. C., and Cannon, W. B. (1936). *Chinese J. Physiol.*, **10**, 359.
Streeten, D. H. P., and Vaughan Williams, E. M. (1951). *J. Physiol.*, **112**, 1.
Templeton, R. D., and Adler, H. F. (1940). *Amer. J. Physiol.*, **131**, 428.
Vaughan Williams, E. M. (1951). *J. Physiol.*, **112**, 32*P*.
Vaughan Williams, E. M., and Streeten, D. H. P. (1950). *Brit. J. Pharmacol.*, **5**, 584.