THE EFFECTS OF MORPHINE, DIACETYLMORPHINE AND SOME RELATED ALKALOIDS UPON THE ALIMENTARY TRACT

PART II. SMALL INTESTINE AND ILEO-COLIC SPHINCTER

By G. NORMAN MYERS, M.D., Ph.D., M.R.C.P.

From the Pharmacological Laboratory, Cambridge

(With 6 Figures in the Text)

CONTENTS

I. Introduction

During the second half of the nineteenth century, investigators directed their attentions to the effects of opium and its alkaloids upon the various systems of the living body. Since then a great deal of literature has accumulated, and the wide divergence both in the observations and conclusions is remarkable.

The present investigation is mainly directed towards comparing the actions and effects of some synthetic alkaloids which are related to morphine and codeine. For this reason it was necessary to include morphine, heroin, and codeine within the scope of the present investigation.

Nothnagel (1882) exposed the small intestine of rabbits under influence of ether, and recorded the movements produced after stimulating the gut with a crystal of sodium chloride. The response was diminished after the subcutaneous injection of 20–40 mg. of morphine, but increased by doses of 100 mg. He records the occurrence of increased contractions when no sodium chloride had been applied. After the injection of a moderate dose of morphine, active peristalsis was also produced by applying a crystal of sodium chloride to an isolated segment of the intestine, which had its mesenteric attachments divided. He concludes that a moderate dose of morphine stimulates, while larger doses cause paralysis of the splanchnic nerves. He attributed the constipating action of morphine to the effects of splanchnic stimulation. Spitzer (1891) repeated these experiments using non-etherized rabbits, and confirmed Nothnagel's results. He obtained similar results using frogs, as

https://doi.org/10.1017/S0022172400012055 Published online by Cambridge University Press

well as evidence indicating a peripheral decrease in the irritability of the intestine. Pal (1900), using curarized dogs, introduced a rubber balloon into an exposed loop of small intestine and made records of intestinal movements before and after the intravenous injection of varying doses of morphine and heroin. Both large and small doses of these drugs produced an increase in intestinal tone and movements. He records that section of the nerve fibres to a loop of intestine did not modify the results, and believes that the effects of morphine are due to stimulation of ganglion cells in the wall of the intestine. In 1906 Magnus repeated the work of Nothnagel and failed to show any decrease in intestinal movements with moderate doses of morphine. Using larger doses, however, he observed increased irritability and spontaneous contractions of the small intestine. He applied a solution of morphine directly to the superior cervical ganglion of the rabbit and cat, and found no evidence of depression as shown by the responses obtained in the iris after stimulation of the preganglionic fibres. He demonstrated that 40–50 mg. of morphine arrested milk diarrhoea in cats, even after section and subsequent degeneration of the nerves passing from the coeliac, superior and inferior mesenteric ganglion cells. In a later investigation (1908) he used X-ray methods, observed the progress of the bismuth meals in dogs and cats, and noted that constipating doses of opium and morphine produced only negligible effects upon the small intestine. About one-half of his animals showed a slight delay in the passage of the bismuth meal along the small intestine. Rodari (1909) states that the principal action of opium on the intestine is to decrease the peristaltic waves. He used anaesthetized dogs and cats, and observed that intravenous "Pantopon" produced an immediate increase in peristaltic waves. Some time later, however, the waves diminished, and finally ceased as the intestinal tone increased. The results were not altered after section of the nerves passing to the small intestine. Schwenter (1912), using X-ray methods on cats, obtained evidence of relaxation and decreased activity of both small and large intestine. Schapiro (1913) investigated, by means of X-rays, the passage of a bismuth meal, introduced into an artificial opening in the ileum of a dog. The animal was fed by mouth at the same time as the bismuth meal was introduced into the fistula. He records that small doses of morphine produce an increase in the amplitude of peristalsis of the ileum and an acceleration of the passage of the alimentary contents through this portion of the alimentary tract. The colon showed a loss of tone. In a second experiment, upon the same animal, no food was given by mouth; otherwise the conditions were the same as in the previous experiment. In this case morphine lengthened the time for the bismuth meal to pass through the ileum, although the peristaltic contractions were increased. No changes were observed in the colon. Mahlo (1913) made screen observations and skiagrams, using young adults who had been given tincture of opium by mouth. He observed delayed passage of food from the stomach and through the small intestine. The food made a prolonged delay in the caecum. Uhlmann & Abelin (1920), using anaesthetized rabbits and

guinea-pigs, found that small doses of opium decreased the tone and peristaltic movements, while larger doses caused a marked increase in both tone and movements. Zunz (1909), using animals, and Zehbe (1913), using human subjects, were able to demonstrate, by means of X-ray technique, a closure of the pyloric sphincter. This delayed the passage of food from the stomach to the intestines. Plant & Miller (1926) studied the contraction of an isolated loop of ileum (Thiry-Vella fistula) in twelve dogs after operation. The main advantages claimed for their method are absence of anaesthesia, and that the effects of the drug on muscular activity are not modified by the presence of food, products of digestion, or digestive juices. A balloon filled with water was inserted into the isolated intestine and graphic records of movements made over a large number of hours. They found that small doses of morphine stimulated all the phases of muscular activity. The tone was increased and the amplitude and frequency of peristaltic movements augmented. After a time the frequency was diminished, although the tone remained above normal. Similar results were observed in their experiments on the human subject, when observations were carried out in a case of ileostomy, and two cases of hernia containing coils of small intestine. The peristaltic waves could be seen and counted. In their animal experiments degeneration of the extrinsic nerves of the intestine exaggerated the usual morphine effects. Heroin, codeine, papaverine, and narcotine produced similar reactions. In 1933, Krueger adopted the methods of Plant & Miller, and his results with morphine agreed with those of Plant & Miller as well as those of Gruber & Robinson (1929).

The present investigation is primarily concerned with the effects produced by dilaudid, dicodid, and eukadol upon the alimentary tract, with a view to comparing their actions with those of morphine and diacetylmorphine (heroin) and methylmorphine (codeine). Dilaudid is the hydrochloride of dihydromorphinone. It is a derivative of morphine, and is manufactured from this source. It is a white amorphous substance which is soluble in water and alcohol, but insoluble in ether. The aqueous solution has a neutral reaction. Dicodid is dihydrocodeinone hydrochloride, and its chemical structure shows it to be a derivative of thebaine. It can, however, be prepared from codeine, and so must be regarded as a derivative of codeine, and so of morphine. Eukadol is the hydrochloride of dihydroxycodeinone; but is manufactured from thebaine. As opium contains but a small quantity of thebaine the production must be very limited.

II. METHODS

The contractions of the small intestine were studied in the duodenum, jejunum, and ileum of decerebrate cats. A laparotomy was performed and a rubber balloon inserted through an artificial opening made in the wall of the gut. The balloon was connected to a water manometer, which was in turn connected to a tambour recorder. The pressure of water in the manometer was never sufficiently great to cause distention of the intestine. The movements

of the ileo-colic sphincter were recorded by means of a method involving the use of a special piece of apparatus devised for this purpose (Myers, 1934). Varying doses of the drugs were used, ranging from very small amounts (0·001 mg./kg.) to large doses (10 mg./kg.) and over fifty animals were used in the investigation.

The drugs were usually injected intravenously into the femoral vein, although in a few cases they were injected subcutaneously into the flank or intravenously into the external jugular vein. Whichever route was employed the results were always the same, except for a short delay in the onset of the effects when the subcutaneous route was employed. The cats were fed on a meat and milk diet until 24 hr. before the experiment when the meat was withdrawn and a small amount of meat extract, mixed with the milk, substituted. The graphic records were continuous and usually of 5–8 hr. duration and only rarely exceeded this period.

III. Experiments

(1) *The effects of morphine hydrochloride*

(*a*) *On the small intestine.*

The effects of morphine hydrochloride upon the small intestine were very definite, and usually appeared in about 3–15 min. after the administration of the drug. The time required for the onset of the effects was roughly proportional to the dose given; with small doses the time required was much greater than with larger amounts of the drug, when the effects were produced almost immediately. Small doses (0·05 mg./kg.) produced a gradual but well-marked increase in tone, reaching a maximum in about half an hour, and lasting from 3 to 8 hr. before any signs of a decrease to normal tone was evident. This relaxation to normal was a gradual process and generally required from 15 to 30 min. As the tone increased under the influence of the drug, the peristaltic movements slowly increased in amplitude until the increase amounted to as much as 300–600 % of the normal amplitude. In some cases where the normal movements were almost negligible the percentage increase was even greater than these figures. With small doses the increase in amplitude lasted from 1 to 2 hr.; with larger doses (Fig. 1) 3–5 hr. The frequency of the movements was generally slightly increased soon after the administration of the morphine, but later, when the movements were large, there was always a decrease in frequency, which became more marked as the experiment progressed and the tone returned to its normal level. Rhythmical contractions showed little alteration in rate; but their amplitude was increased in nearly all cases. The injection of adrenalin hydrochloride (0·2 c.c. 1/40,000) always modified the effects produced by morphine. Inhibition of movements and loss of tone followed. The tone generally returned to normal level after 15 min., but the movements often remained subnormal for twice this time. The injection of hypophysin (0·1 unit or more per kg.) caused an immediate

loss of tone, and abolition of movements, which was followed by recovery within 10 min. About 5–10 min. later, the records showed an increase in movements much greater than those produced by morphine alone (Fig. 2). In two experiments hypophysin produced no action even when very large doses were employed. The effects of atropine were interesting. The injection of atropine sulphate, sufficient completely to "paralyse" vagal nerve endings (1 mg./kg.) at a point when the morphine effects were marked, always caused a complete abolition of intestinal movements and a loss of tone to a subnormal level. The subsequent injection of a further dose of morphine during this phase, however, always produced an increase in tone and movements often greater than before.

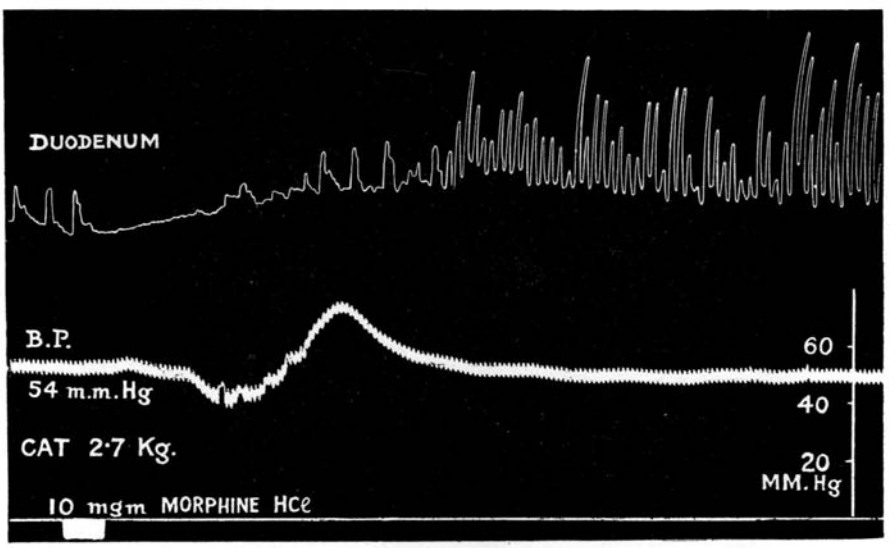

Fig. 1. Cat, 2·7 kg. Decerebrate. Duodenal movements and blood pressure. Showing the effect of 10 mg. morphine HCl. Time ½ in. per min.

(*b*) *On the ileo-colic sphincter.*

The most constant effect of morphine hydrochloride upon this structure was an immediate well-marked increase in tone, indicating a closure of the sphincter. At the same time the normal movements of the sphincter became regular in rhythm and were increased in amplitude, or movements were initiated if the sphincter was quiescent before the drug was given. The tonal effects were dependent upon the dosage employed and were much greater with larger than smaller doses, although in all cases the effects were prolonged over long periods. The maximum increase in tone was generally obtained in about 2 min. when doses of 1 mg./kg. were employed, whereas small doses of 0·05 mg./kg. required 15–30 min. When the maximum tone had been obtained, a slow progressive relaxation to normal level took place and required from 30 min. to 2 hr. or more. In a few experiments the sphincter movements were

https://doi.org/10.1017/S0022172400012055 Published online by Cambridge University Press

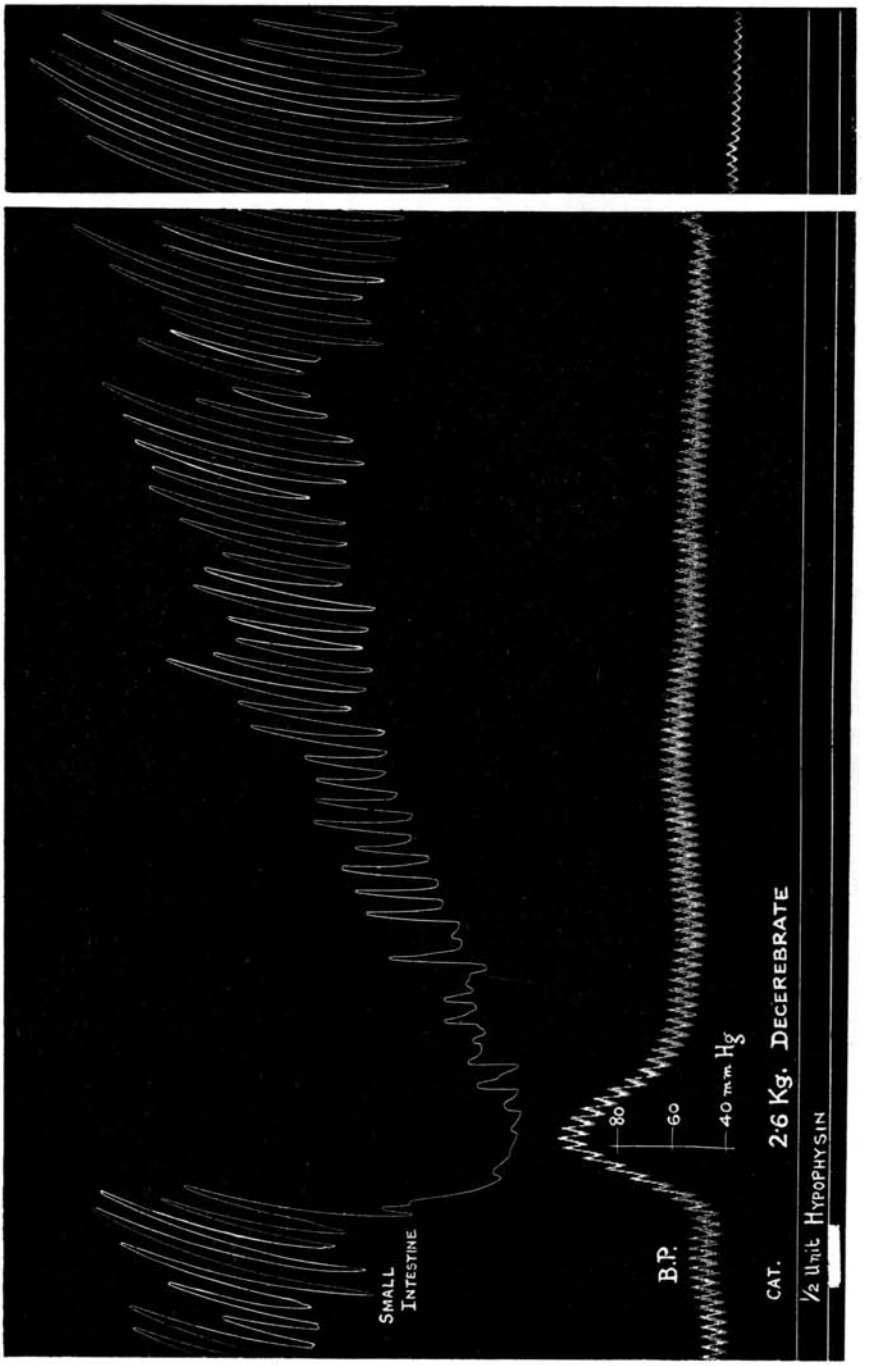

Fig. 2. Cat, 2·6 kg. Decerebrate. Movements of jejunum and blood pressure. Illustrating the effects produced by an injection of 0·5 unit of hyophysin. 0·2 mg. morphine HCl was injected 45 min. earlier. There is an interval of 10 min. between *A* and *B*. Time 1¼ in. per min.

https://doi.org/10.1017/S0022172400012055 Published online by Cambridge University Press

initiated by the drug after a normal period of quiescence but did not last longer than a few minutes. In all cases, however, an increase in sphincter tone was recorded.

(2) *The effects of diacetylmorphine hydrochloride (heroin)*

(*a*) *On the small intestine.*

These were substantially the same as those of morphine, and differed only in one or two details. The effects of heroin were generally immediate except when very small doses were employed, when a lapse of 2 or 3 min. often took place before the earliest effects were seen. The most typical effects were shown in an increase of the amplitude of movements, as well as an increase in tone. These effects (Fig. 3), especially the increase in movements, were more marked after heroin than morphine. Slightly smaller doses of heroin were required to produce these effects than morphine, and the results obtained indicated that heroin was about 40% more active than morphine. Although heroin produced such an increase in activity of the intestine, the condition of increased tone which it produced did not last as long as that produced by morphine. In many experiments the tone had relaxed to a subnormal level after 10–15 min., only to increase and relax again alternately in periods lasting approximately 2 min. each. This condition of alternating tone usually lasted for 2–3 hr., once it had been established. Like morphine, heroin increased the amplitude of the rhythmical contractions while the rate remained practically unaltered. As in the case of morphine, the injection of atropine caused a complete abolition of movements and a loss of tone to a subnormal level (Fig. 4).

(*b*) *On the ileo-colic sphincter.*

Heroin produced an increase in tone and movements of this sphincter. The increase in tone was profound when large doses (1 mg./kg.) were injected, and was least when very small doses (0·005 mg./kg.) were employed. In the latter case, however, the movements were generally increased to a very much greater degree than in the former. In all cases the increase in tone rarely exceeded a period of 30–60 min., after which the tone level became either normal or very slightly subnormal, whereas the increased movements continued for a further 1–4 hr. These effects were produced by doses as large as 5 mg./kg.

The injection of 0·5 c.c. of 1/40,000 adrenalin was able to abolish the effects of heroin by producing a temporary inhibition of movements and loss of tone lasting a few minutes; recovery to its previous condition took place after 15 min. Similar results were recorded following the injection of 0·25 unit of hypophysin, but the loss of tone and movements lasted only a few minutes, after which both were exaggerated to a degree far in excess of that produced by the previously injected heroin. The injection of nicotine, in doses sufficient to "paralyse" ganglion cells, did not modify the effect produced upon the sphincter by heroin.

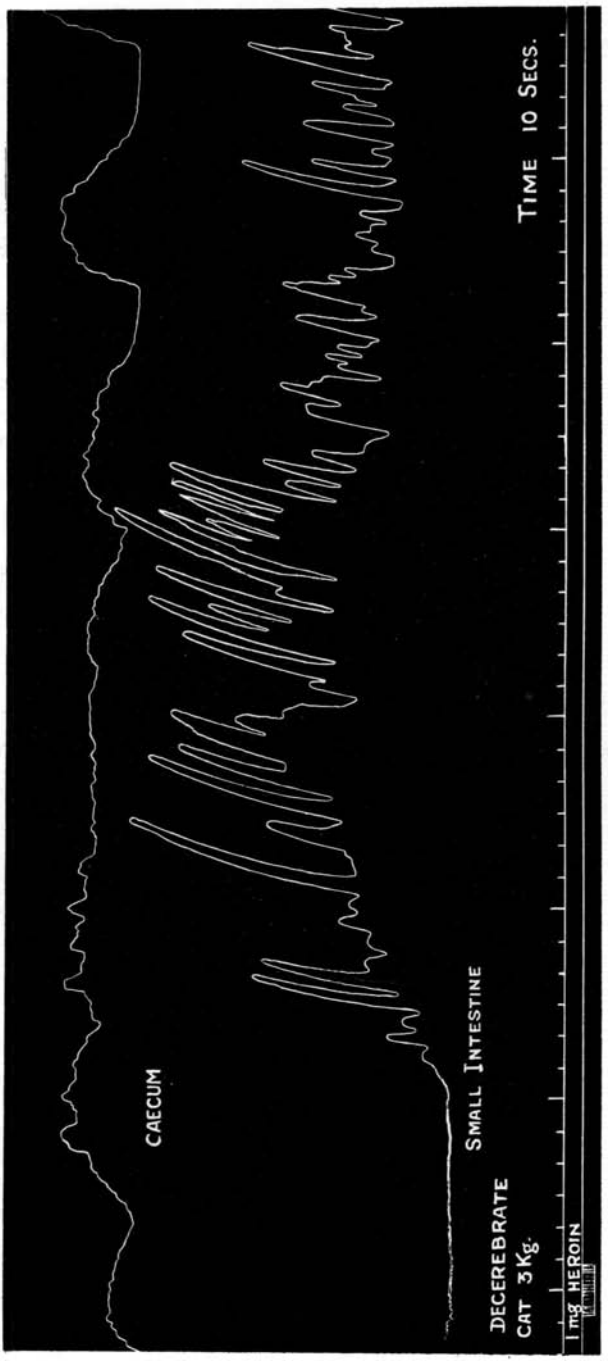

Fig. 3. Cat, 3 kg. Movements of caecum and jejunum. Showing the immediate increase in tone and amplitude of movements of the jejunum, in response to an injection of 1 mg. heroin.

https://doi.org/10.1017/S0022172400012055 Published online by Cambridge University Press

(3) *The effects of codeine phosphate*

(*a*) *On the small intestine.*

This drug produced effects which were similar to, although very much less marked than those of morphine. The amounts of codeine phosphate required to produce these effects were greatly in excess of those of morphine. This was well shown with doses of 0·05 mg./kg. This dose of codeine did not produce any effects upon the small intestine in five different animals, whereas

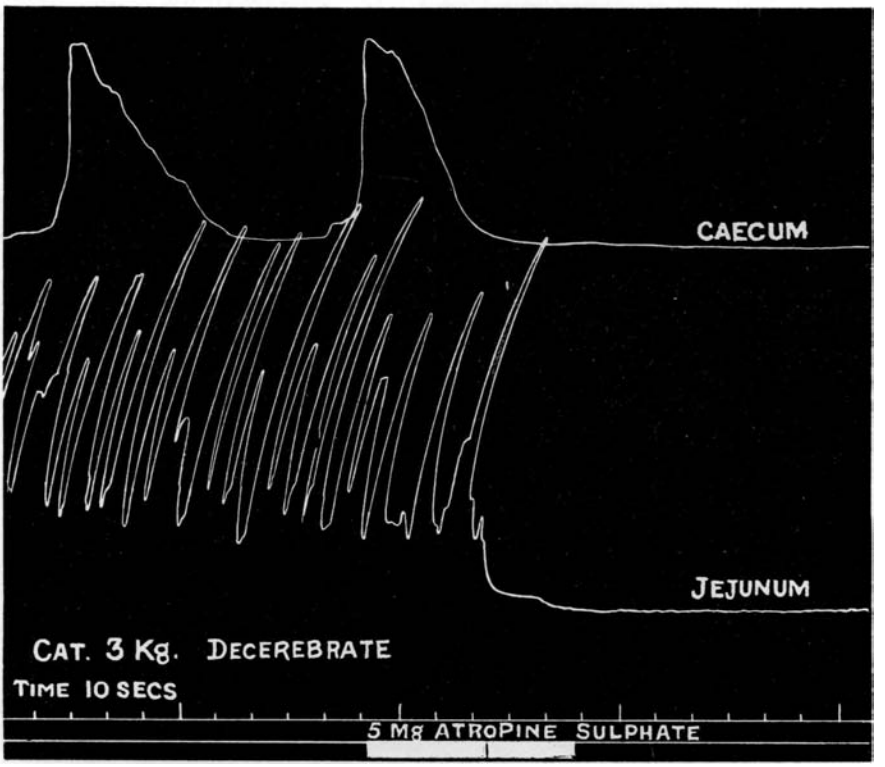

Fig. 4. Showing the effects of atropine after heroin. 2 mg. of heroin had been injected 5 min. prior to the administration of 5 mg. of atropine sulphate.

much smaller quantities of morphine always produced, in a well-marked manner, the effects which have been described earlier in this communication. The injection of as much as 0·25 mg./kg. of codeine phosphate was necessary to produce even small effects upon the small intestine.

(*b*) *On the ileo-colic sphincter.*

0·25 mg./kg. of codeine produced a slow progressive increase in tone of the sphincter which reached a maximum after 10–15 min. This interval was shortened when larger doses (3 mg./kg.) were employed, and the duration of

the period of increased tone was greatest after the larger doses. The rhythmical movements showed no change in most of the experiments; but in three instances slow rhythmical movements appeared approximately 30–45 min. after the injection of the drug.

(4) *The effects of dihydromorphinone hydrochloride (dilaudid)*

(*a*) *On the small intestine.*

Dilaudid produced effects which are almost identical with those of morphine (Fig. 5). The chief difference between the two drugs was a quantitative one,

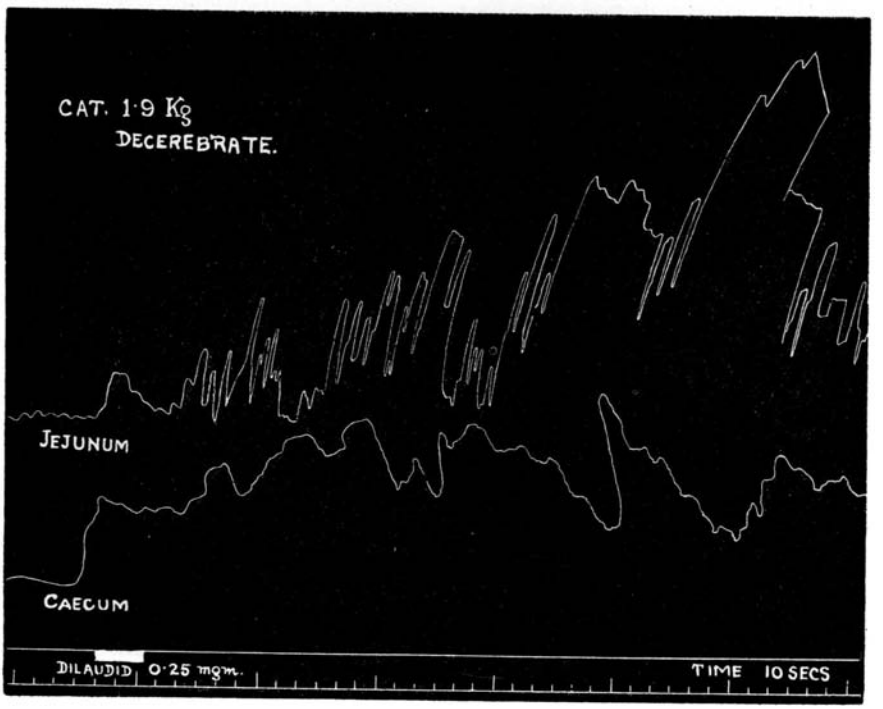

Fig. 5. The effects of 0·25 mg. dilaudid on the jejunum and caecum.

that is, the amounts required to produce these effects. The minimum amount of dilaudid required to produce the effects in a cat was found to be approximately 0·005 mg./kg., while the corresponding dose of morphine was about 0·05 mg. From these figures it would appear that dilaudid is approximately ten times more active upon the small intestine than morphine.

(*b*) *On the ileo-colic sphincter.*

The effects upon this structure were well demonstrated after an injection of 0·05 mg./kg. of dilaudid. The drug produced an immediate increase in tone and movements of the sphincter, reaching a maximum tone level in 2–6 min.

https://doi.org/10.1017/S0022172400012055 Published online by Cambridge University Press

The increased movements had almost disappeared 12 min. later, while the general tone of the sphincter remained well above normal, although not so great as the maximum level reached shortly after the drug had been administered. At the same time as these sphincter effects were recorded a sudden increase in activity of the small intestine took place, resulting in an enormous increase in the movements of the intestine, which was accompanied by a further small increase in intestinal tone. These effects lasted from 1 to $2\frac{1}{2}$ hr., during which time there were periods of slightly less activity, which appeared to alternate every 10–20 min.

(5) *The effects of dihydrocodeinone hydrochloride (dicodid)*

(*a*) *On the small intestine.*

The injection of 0·4 mg./kg. produced a very small increase in tone which was progressive, reaching a maximum about 50 min. later; 5 min. afterwards the tone relaxed to normal, and about seven well-marked contractions took place during the next 2 min. The intestines remained quiescent during the next 7 min. and then suddenly became active again for 3 or 4 min. During this time both tone and movements were increased. A sudden decrease in tone to a slightly subnormal level then occurred, while the movements became almost negligible. The intestine remained in this inactive state for 15 min., at the end of which a further period of renewed activity in movements at normal tone level commenced and lasted 6 min. These alternate periods of inhibition and excessive activity took place over a period of $1\frac{1}{2}$–$2\frac{1}{4}$ hr. Similar results were obtained with doses of 1 and 2 mg./kg. The increased tone effects were at once abolished after the injection of sufficient atropine to "atropinize" the animal completely. Movements were not considerably reduced although not completely suppressed. The injection of further doses of 0·1 mg./kg. of dicodid did not produce any response, while stimulation of the peripheral end of the cut vagus failed to produce any effects. Very large doses of dicodid (5–10 mg./kg.) produced an immediate inhibition of movements and loss of tone, an effect which resembles the inhibition produced by adrenalin. Complete recovery of both tone and movements followed in about 10 min.

(*b*) *On the ileo-colic sphincter.*

The sphincter showed a decided increase in tone and movements about 2 min. after the injection of 0·03 mg./kg. of dicodid. The tone reached a maximum after 20–40 min., when it slowly began to relax to normal, and movements showed a decided increase in amplitude. The movements now became less frequent. Normal tone was established during the ensuing 5–10 min., but was maintained for only about 5 min. when it began to increase again, and relaxed to normal once more after a further 20–30 min. The movements during this period increased progressively. About 60 min. after the drug had been injected the tone became slightly subnormal and remained

so throughout the remainder of the experiment (6 hr.). The movements reached a maximum at 3 hr., and were maintained for a further 3 hr., when they began to diminish slowly in amplitude.

(6) *The effects of dihydro-oxycodeinone hydrochloride (eukadol)*

(*a*) *On the small intestine.*

Small doses of this drug (0·01 mg./kg.) produced a constant effect, namely, an increase in the amplitude of the intestinal movements, without any great change in muscular tone. With this dosage only three animals out of six showed any changes in tone, which were always in the nature of a negligible increase, followed by a very slight decrease below the normal level. Similar results were recorded using doses as large as 0·5 mg./kg. (Fig. 6). Amounts

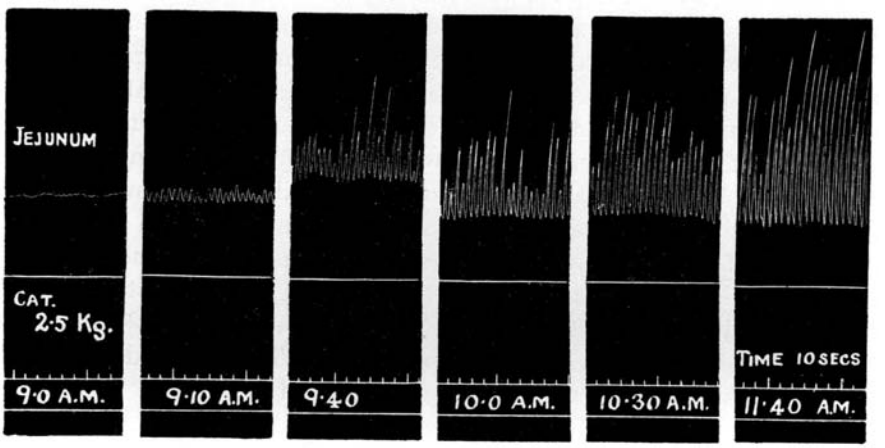

Fig. 6. Cat, 2·5 kg. Movements of the jejunum. 0·5 mg. eukadol was injected at 9.04 a.m. The maximum effects were recorded at 11.40 a.m., after which they progressively declined until normal conditions were reached at 5.40 p.m. The animal was still in good condition and the blood pressure was only 20 mm. Hg below that recorded at 9 a.m.

in excess of this, however, generally produced a slight increase in tone as well as movements. The tone effects usually lasted 30 min. or more before normal tone level was re-established, whereas the increased movements often persisted for many hours afterwards (3–4 hr.).

(*b*) *On the ileo-colic sphincter.*

Eukadol increased the general activity of this structure. Doses as small as 0·05 mg./kg. produced a slow progressive increase in tone, lasting approximately 30 min. before returning to normal level. This increase in tone was never very marked, and was quantitatively much less than that produced in response to an injection of similar amounts of morphine, heroin, or dilaudid. Once the tone had returned to normal it generally remained at this level

during the remainder of the experiment. In a few animals, however, a marked degree of relaxation of the sphincter slowly followed the period of increased tone, and remained, in a greater or lesser degree, for 2 or 3 hr. The movements of the sphincter were always increased in amplitude, and became more regular. The increase was gradual and continued for 3–4½ hr. before showing any signs of a decrease. The decrease in movements to normal was slow, and required ½–1½ hr.

IV. DISCUSSION

The results of this investigation show that all the drugs studied produce effects upon the small intestine and ileo-colic sphincter which are to some extent similar. The effects produced by morphine, diacetylmorphine, and dihydromorphinone are almost identical. They all produce an increase in the activity of these two structures, resulting in an increase in tone and movements. The intestine shows an increase in the amplitude of its movements in addition to the increase in tone. These effects usually persist for several hours. At first the frequency of peristaltic waves is slightly increased, but later is decreased to a rate slightly below that of normal. The rhythmical contractions are not altered in rate, but their amplitude is increased.

The main difference between these three drugs is a quantitative one. A careful study of the amount of each drug required to produce the effects clearly indicates that dihydromorphinone is the most powerful of the three drugs, with diacetylmorphine a poor second, and morphine a close third. The dosage figures indicate that dihydromorphinone is about 10 times more active, and diacetylmorphine 1½ times more active than morphine. These figures, while not claiming to be precisely accurate, are based on a long series of animal experiments and give a sufficient indication of the relative activities of these three drugs.

That these drugs act upon some peripheral structure in the gut wall is clearly shown by the effects of atropine and other drugs upon the intestine under their influence.

Plant & Miller (1926) have shown that fairly complete section and degeneration of the intrinsic nerve supply to the small intestine produces an exaggeration of the effects produced by morphine upon the small intestine. In 1933, Myers demonstrated that small amounts of dihydromorphinone increased the sensitivity of the vagus nerve to electrical stimulation. These experiments, therefore, produce strong evidence that the point of action of these drugs is probably the motor cells of Auerbach's plexus, or the terminations of the vagus nerve in the intestinal wall.

Of the remaining drugs, dihydrocodeinone is the most active upon the small intestine and ileo-colic sphincter. Its effects are much less marked than morphine, but greater than those produced by codeine, and so its position must be regarded as lying between morphine and codeine.

The effects produced by dihydro-oxycodeinone are much less than those of the other drugs investigated, and so its position comes after codeine. The

most constant effect of this drug is an increase in the movements of both the small intestine and the sphincter. An increase in tone of both these structures can only be obtained by the use of very large doses (1–5 mg./kg.). The increase in tone, however, is much less than that due to the other drugs. In so far as the experimental figures obtained in this investigation permit the making of an estimate of the relative activity of this drug, they indicate that dihydro-oxycodeinone is approximately 7–10 times less active on these structures than morphine.

V. Summary

1. The effects of morphine upon the small intestine are an increase in the tone and peristaltic movements. The frequency of peristaltic movements is slightly increased at first, but later decreased. The frequency of the rhythmical contractions remains more or less constant while their amplitude is increased. The tone and movements of the ileo-colic sphincter are increased.

2. Atropine modifies the effects of morphine by producing a decrease in tone and movements of the intestine, for varying periods of time. The subsequent injection of morphine during the period of inhibition produces, however, a further increase in tone and movements. Adrenalin causes a temporary inhibition of tone and movements after morphine.

3. Diacetylmorphine and dihydromorphinone produce similar effects; but are more active than morphine. Dihydromorphinone is approximately 10 times more active, and diacetylmorphine $1\frac{1}{2}$ times more active than morphine.

4. Dihydrocodeinone, codeine and dihydro-oxycodeinone produce similar effects to morphine but are much weaker, especially in so far as the production of increased tone is concerned. Regarding relative activities dihydrocodeinone lies between morphine and codeine, while dihydro-oxycodeinone is placed after codeinone.

REFERENCES

Gruber, C. M. & Robinson, P. I. (1929). *J. Pharmacol.* **37**, 101.
Krueger, H. (1933). *J. Pharmacol.* **50**, 254.
Magnus, R. (1906). *Pflüg. Arch. ges. Physiol.* **115**, 316.
— (1908). *Pflüg. Arch. ges. Physiol.* **122**, 210.
Mahlo (1913). *Dtsch. Arch. klin. Med.* **110**, 562.
Myers, G. N. (1934). *J. Physiol.* **81**, 35*P*.
— (1933). *Brit. med. J.* **2**, 372.
Nothnagel (1882). *Virchows Arch.* **79**, 1.
Pal (1900). *Wien. med. Pr.* **41**, 2040.
Plant, O. H. & Miller, G. H. (1926). *J. Pharmacol.* **27**, 361.
Rodari (1909). *Ther. Mh.* (*Halbmh.*), **23**, 540.
Schapiro, N. (1913). *Pflüg. Arch. ges. Physiol.* **151**, 65.
Schwenter, R. (1912). *Fortschr. Geb. Rontgenstr.* **19**, 1.
Spitzer (1891). *Virchows Arch.* **123**, 593.
Uhlmann & Abelin (1920). *Z. exp. Path. Ther.* **21**, 58, 75.
Zehbe, M. (1913). *Ther. Mh.* (*Halbmh.*), **27**, 406.
Zunz, E. (1909). *Biochem. Zbl.* **9**, 208.

(*MS. received for publication* 4. v. 39.—Ed.)