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

PART I. STOMACH AND PYLORUS

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(With 7 Figures in the Text)

In 1886 Schutz killed a dog with morphine, excised the stomach and observed its movements when placed in a moist chamber. He describes a few contractions at the cardiac end of the stomach while the antrum remained motionless. Contractions were only produced by the application of powerful electrical stimuli. Distension of the organ with air produced feeble contractions of the cardiac end. In 1901 Glaessner introduced 10 mg. morphine HCl into the isolated stomach of a frog and noted a subsequent relaxation and cessation of movements. Fujitani (1910), using frogs, records that very dilute solutions of morphine HCl decreased the force and frequency of stomach movements. Large amounts abolished the contractions. Hirsch (1901) produced permanent duodenal fistulae in dogs and measured the escape of fluid from the pyloric end of the stomach. Water introduced into the stomach readily escaped from the fistula. After morphine was administered the water was retained in the stomach for many hours. He also observed an increase in the muscular activity of the stomach and concluded that the drug caused a contraction of the pyloric sphincter. In 1908 Magnus, using X-ray methods on dogs and cats, demonstrated a marked delay in the passage of an opaque meal from the stomach to the duodenum after the administration of morphine salts. He explained the delay as being caused by a tonic contraction of the pyloric sphincter, antrum and pyloric end of the stomach, which he observed a few minutes after the drug had been given. The cardiac sphincter was also contracted causing an accumulation of gas within the stomach and a subsequent dilation of the fundus from this cause. He observed a marked delay in the emptying of the stomach and found food there 6 hr. after the administration of the drug. Morphine did not alter the peristalsis of the antrum, and he concluded that opium constipation is due to a closure of the pyloric sphincter. Van den Velden (1909) also used X-ray technique and observed the effects of morphine upon the stomach of the human subject. His observations agree with those of Magnus, but he also records the appearance of hour-glass contractions in the antrum as well as strong peristalsis and antiperistalsis in the same area. In 1909 Rodari introduced coloured water into the stomach of a dog and observed its escape from an artificial duodenal fistula. Opium delayed its

https://doi.org/10.1017/S0022172400012043 Published online by Cambridge University Press

appearance 30 min. and when ultimately passed was found to be increased in bulk. He attributes the delay to pylorospasm and the increased bulk to increased gastric secretion caused by the opium. In another series of experiments he exposed the alimentary tract in anaesthetized dogs and rabbits and observed increased movements following the injection of intestinal extracts; when opium was also given, gastric peristalsis was abolished and later the organ became contracted and ischaemic. Schwenter (1912) adopted X-ray methods on cats and made observations lasting 24 hr. after the administration of opium. His results were not constant. Delayed passage of food from the stomach was seen in a number of his animals. Others, however, showed the meal entering the duodenum within the normal time limits. Only one experiment showed a pronounced contraction of the pyloric end of the stomach. This lasted 1 hr. and was followed by a relaxation. In this case the passage of food from the stomach was only slightly delayed. Mahlo (1913), using young adults, administered tincture of opium after a barium meal had been given. In one subject, X-rays revealed a contraction of the pyloric antrum without any delay. Nearly all the others showed a lowering of the level of the greater curvature, indicating a relaxation of the stomach, and a delayed emptying of the stomach. Schapiro (1913), using healthy human subjects, studied the effects of morphine and tincturated opium upon the stomach. X-rays showed a delayed emptying in about 50% of his subjects. The remainder, however, showed either no change or a shortening of the normal emptying time. He apparently made no record of gastric peristalsis. Plant & Miller (1928) carried out a lengthy research into this problem, using unanaesthetized dogs with permanent gastric fistulae. A bottle-neck fistula was made in the upper portion of the fundus. These animals were used over periods of 3–18 months, and movements of the stomach were recorded by a balloon method. The most constant effect recorded after morphine is a decrease in the tone of the stomach. Ten out of eleven dogs which were given 0·25–16 mg. of morphine per kg. weight showed a resultant decrease in tone which was accompanied by a decrease in the frequency and amplitude of peristaltic waves. Doses greater than 0·5 mg. per kg. abolished gastric peristalsis for several hours, while small doses of 0·25 mg. per kg. or less increased the amplitude of peristalsis but diminished its frequency. One animal showed an increase in the amplitude of the peristaltic waves with any size of dose, but relaxation of the stomach was always evident. Similar effects were produced with diacetyl-morphine, codeine, papaverine and narcotine. They also found that the amount of morphine to produce emesis varied in different dogs. Some vomited after doses of 0·05 mg. per kg. but did not do so after a larger dose, while others showed a reversal in these amounts. Tetzner & Turold (1921), using human subjects, report that morphine produces increased force of contraction of the stomach. Abbott & Pendergrass (1934) introduced balloons into the alimentary canal of human subjects via the oesophagus. A barium meal was then given and the behaviour of various parts of the tract observed by means of

X-ray methods. 10–30 mg. of morphine sulphate produced a marked contraction of the duodenum within 2 min. of its administration and lasted 20 min. At the end of this period peristaltic movements increased for a time, being followed by a phase of inactivity lasting as long as 24 hr. Further observations indicated that the duodenum responded more actively to morphine than the jejunum while the ileum was least responsive.

The object of the present investigation was to make a study of the effects produced upon the stomach and pyloric sphincter by dihydromorphinone HCl (dilaudid), dihydrocodeinone HCl (dicodid), and dihydro-oxycodeinone HCl (eukodol). Owing to the disagreements in the literature and in order to make the study a comparative one, it was found necessary to include morphine, diacetylmorphine (heroin) and codeine in the investigation.

METHODS

The administration of the drugs was by the intravenous route, when either the femoral vein or the external jugular vein was used. In a few cases they were injected subcutaneously, when the effects produced were identical with those recorded when the intravenous route was employed, except that they were slightly slower in onset. The movements of the stomach were recorded by two different methods. In each case a laparotomy was performed and an artificial opening made in the wall of the second part of the duodenum. A thin-walled rubber balloon tied on a catheter was passed through the opening into the stomach. The balloon was filled with water and the catheter connected to a small water manometer which was in turn connected to a recording tambour. The second method was devised with the object of recording stomach and pyloric movements simultaneously and necessitates the use of a special piece of apparatus designed for the purpose (Myers, 1934). Over fifty decerebrate cats were used in the investigation, and at the close of each experiment a post-mortem examination was conducted to ascertain that the balloon, or the special apparatus, was lying in the correct position.

THE EFFECT OF MORPHINE HCl

(*a*) *On the stomach*

In spite of the large number of animals used in this investigation, the effects produced by morphine were far from constant. In a series of eight cats, two showed no alteration whatever in stomach tone or movements, no matter whether the dose of morphine was small or large. The doses employed ranged between 0·005 and 20 mg. per kg. Two animals showed an increase in tone in varying degrees, but in only one was it well marked. In this case the increase in tone was accompanied by three to five slowly moving contractions of great amplitude, each one lasting approximately 15 sec. Later the movements quickly diminished in amplitude until of negligible dimensions, although the increase in gastric tone was prolonged for 30 min. or more (Fig. 1). In

each instance the increased gastric activity was produced in response to the injection of doses of 5 mg. per kg. or more. Four animals showed a slight loss of gastric tone and a decrease in the frequency and amplitude of peristaltic waves following the injection of the drug. The lowest tone levels were usually recorded 10–30 min. after the drug had been injected (0·25–5 mg. per kg.). During the first hour the movements of the stomach sometimes increased in amplitude while the tone was subnormal, but the period of increased move-

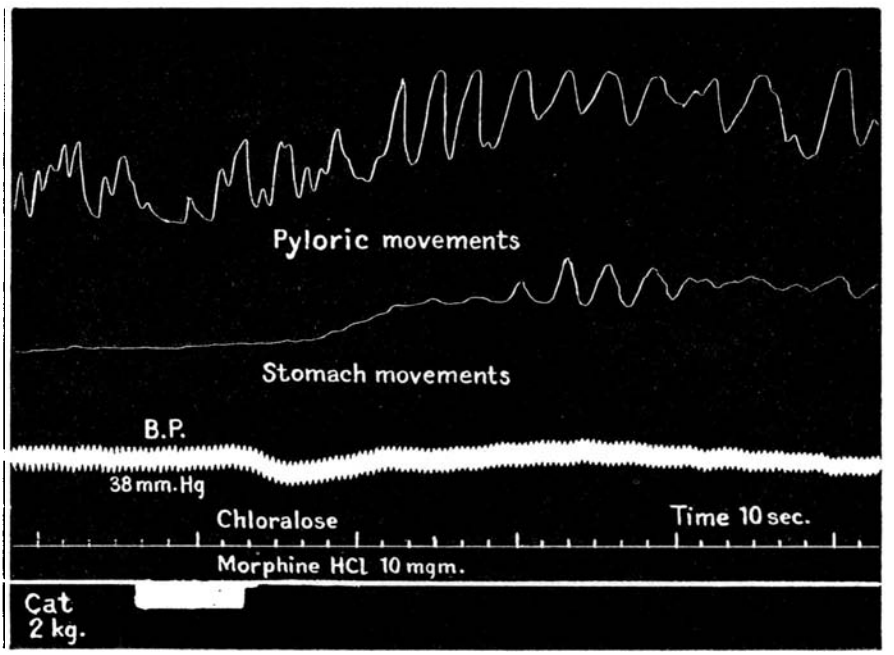

Fig. 1. Showing the increase in tone and movements of the stomach and pyloric sphincter produced in response to morphine HCl (5 mg. per kg.).

ments rarely lasted more than 2–6 min. (Fig. 2). From these results it is apparent that the effects of morphine upon the stomach are very variable, although the major number of experiments indicate a decrease in tone accompanied by some decrease in the frequency and amplitude of the movements. It is therefore impossible to predict with certainty what effects might be expected to follow the injection of any particular dose of the drug. One constant feature, however, was seen in most of the animals. No matter whether the stomach tone increased or decreased in response to morphine, the duration of the effects upon the organ were more or less proportional to the dose administered. The larger the dose employed the longer the duration of the effects. The movements always returned to normal before the tone. With small doses (0·01–0·5 mg. per kg.) the movements began to approach normal limits again in from 1 to 3 hr., while the tone effects generally lasted $1\frac{1}{2}$–4 hr. These times were usually increased with larger doses.

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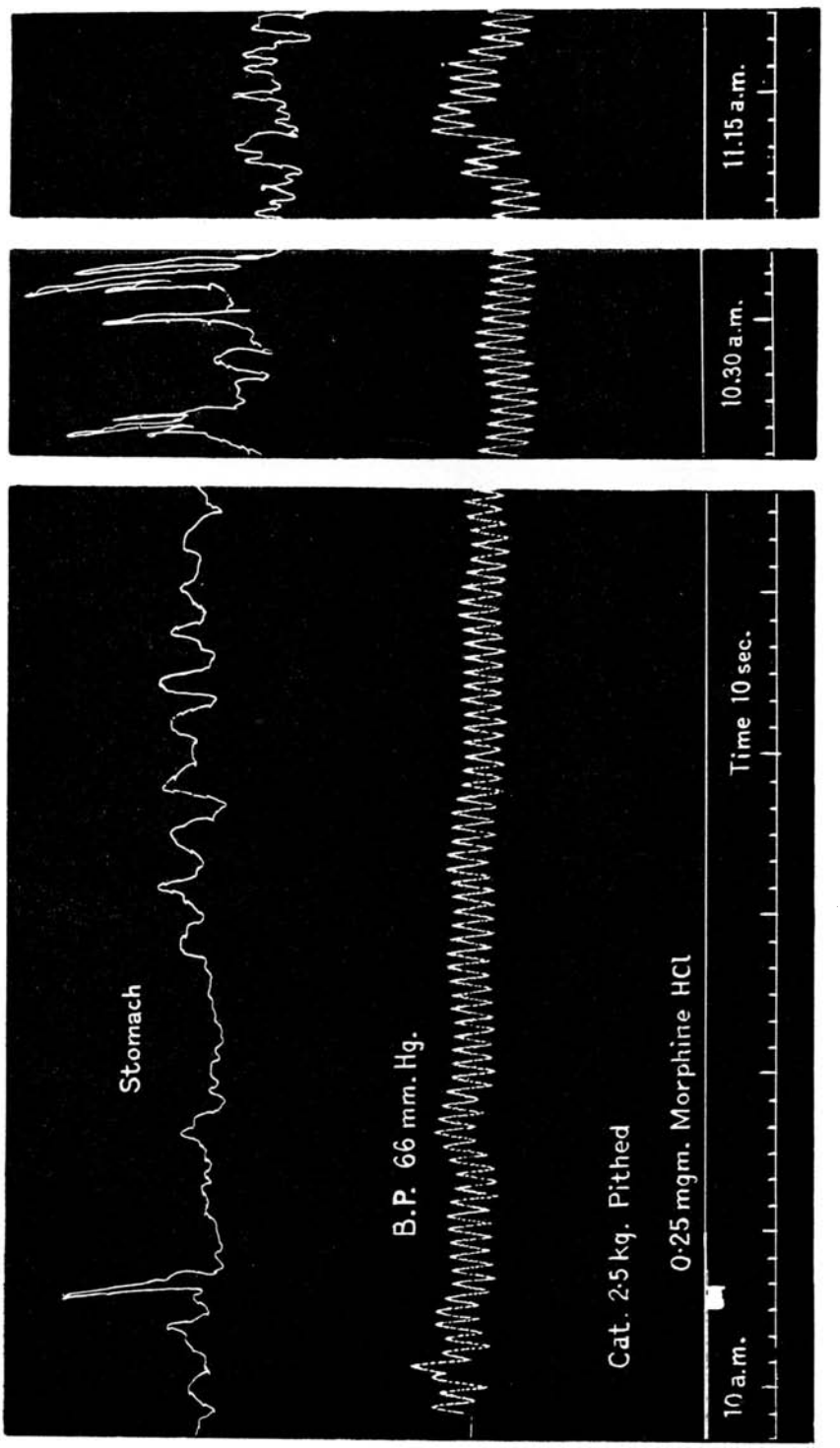

Fig. 2. Cat, 2·5 kg. Stomach movements and blood-pressure. Showing the effects of 0·25 mg. morphine HCl upon the tone and movements of the stomach. Note the relaxation recorded at 11.15 a.m.

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(*b*) *On the pyloric sphincter*

The effects of morphine upon this structure are very constant with all effective doses, and the most striking feature is the increase in tone produced within a few minutes of injecting the drug. The contractions increase in amplitude and frequency and take on a regular rhythm (Fig. 3). These effects can be produced over a wide range of doses (0·01–20 mg. per kg.). The magnitude and duration of the effects is approximately proportional to the dose employed. Large doses produce their effects almost immediately and may persist for many hours (2–7), whereas small doses (0·01–0·25 mg. per kg.) produce their effects more slowly and require from 2 to 30 min. for the maximum tone effects to take place. These effects are of shorter duration with small doses and may last only 45 min. or as long as 4 hr.

THE EFFECTS OF DIACETYLMORPHINE HYDROCHLORIDE (HEROIN)

The effects of this drug upon the stomach and pyloric sphincter are very similar to those produced by morphine. One or two minor points of difference, however, were revealed during the course of the investigation. Smaller doses of heroin than morphine were generally required to produce effects upon these structures. The difference in dosage was not great, and on calculation heroin was found to be approximately 30–50% more active than morphine.

(*a*) *On the stomach*

Small doses of heroin (0·20 mg. per kg.) were usually without effect upon the stomach, whereas larger doses (0·5–2 mg. per kg.) sometimes produced a slight increase in tone with little or no increase in the amplitude and frequency of movements. 15–30 min. later the tone was subnormal and remained so for 2–3 hr. The injection of 1 mg. of atropine per kg., when the tone was increased by heroin, produced a marked relaxation of the stomach, while the movements were diminished in amplitude without any change in their frequency. In one-half of the experiments, 1 mg. of heroin per kg. caused a slight loss of tone of the stomach with a diminution of both the amplitude and the frequency of contractions.

(*b*) *On the pyloric sphincter*

Heroin (0·20 mg. per kg.) produces an immediate increase in tone of the sphincter which is similar to that produced by morphine. Within a few minutes the amplitude and frequency of the movements gradually increased to a maximum which is attained in 5–10 min. While the increase in tone is generally greater than that produced by morphine, the increase in the amplitude of the movements is usually not so great as with morphine. The increase in sphincter tone is not influenced by the injection of sufficient nicotine to stimulate ganglion cells. The injection of 0·25 c.c. of adrenalin (1/20,000), however, generally causes a marked loss of tone, often to a subnormal level, accompanied by

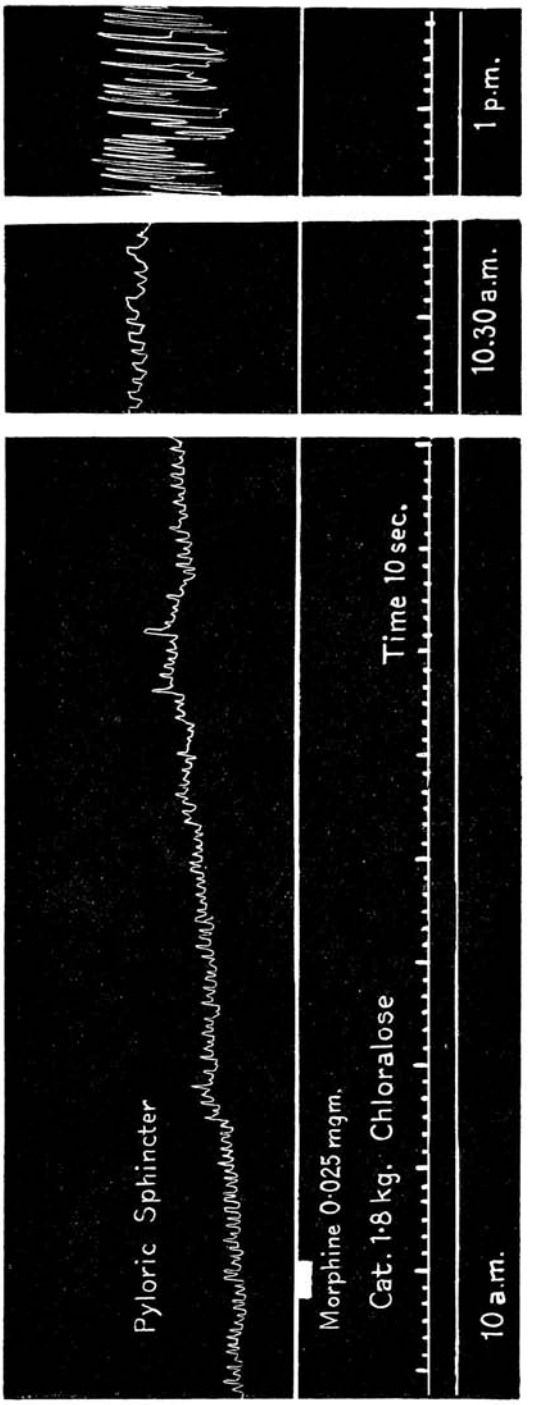

Fig. 3. Cat, 1·8 kg. Movements of the pyloric sphincter. Showing the increase in tone and movements following the injection of a small dose of morphine HCl. The condition seen at 1 p.m. was maintained for a further 4 hours.

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inhibition of movements. This effect is only temporary and rarely lasts more than 5 min., when both tone and movements regain their former activity. This is a particularly interesting observation because the same dose of adrenalin often caused contraction of the sphincter when given to the same animal before heroin had been injected. It might be pointed out, however, that the response of the sphincter of the normal cat to adrenalin was found to be variable. Sometimes contraction with diminished movements was recorded; at other times relaxation with a decrease in the amplitude of rhythmical contractions was seen. This effect lasted 3–5 min. and was followed by a moderate increase in tone above the normal level and accompanied by some increase in the amplitude of the rhythmical contractions. Whether heroin causes a true reversal of the adrenalin effect upon the pyloric sphincter by depression of the motor components is difficult to say in view of the variable response to adrenalin seen in the normal cat. It has been suggested by Earl Thomas (1929) that the response produced by adrenalin in the normal cat is dependent upon the initial tone of the structure; that is, if the initial tone be low, then contraction takes place. If this is so, then the reversal of the adrenalin effect after the administration of heroin, which increases the sphincter tone, is very simply explained.

The effects of methyl morphine (codeine)

(*a*) *On the stomach*

The action of codeine is considerably weaker than either morphine or heroin. No effects were produced with doses less than 1 mg. per kg., and doses in excess of this figure were needed to produce even small effects upon the stomach. 2 mg. per kg. or more produced a slight increase in the amplitude with diminished frequency of the movements lasting approximately 15–20 min., the tone was then reduced very slightly to a subnormal level. Normal tone was re-established 30–45 min. later. These effects were observed in three animals. A further three animals showed a very slight increase in tone and amplitude of movements reaching a maximum in 35 min. when the tone and movements became normal during the next 5 min. No further changes in tone or movements were recorded during the next 2½ hr. Although the effects produced in these two groups of animals differ, it should be emphasized that in every case the effects were very small and almost negligible when compared with those of morphine.

(*b*) *On the pyloric sphincter*

The effects of codeine phosphate upon this structure are constant and, although not so marked as in the case of morphine or heroin, bear a great similarity to these drugs. The injection of a small dose of codeine (0·05 mg. per kg.) produced a small but gradual increase in the tone of the sphincter lasting from 5 to 10 min., after which it decreased slightly to a subnormal

level. This decrease never lasted longer than 30 min. when normal tone was once more regained. The amplitude and rate of movements were unaltered. With larger doses (0·25 mg. per kg.) or more the initial rise in tone is slightly greater than with smaller doses, the maximum increase being recorded within 30–40 min. of the injection being given. The duration of this phase of increased tone is dependent upon the amount of the drug injected and may last from 30 to 90 min. before returning to normal. The longer periods were recorded after large doses. The secondary period of relaxation which follows the use of small amounts was never seen when large doses were employed. No change in the rate or amplitude of the sphincter movements was recorded.

THE EFFECT OF DIHYDROMORPHINONE HCl (DILAUDID)

(*a*) *On the stomach*

Like morphine, the effects of dilaudid upon the stomach are very variable. With small doses (0·02 mg. per kg.) most animals showed an immediate relaxation of the stomach with a decrease in the amplitude of the movements. 20–40 min. later, the tone had recovered to normal while the movements were more regular and increased in amplitude in excess of the normal. A second decrease in tone with increased movements followed in 10–20 min., and was sustained for a further 2–4 hr. (Fig. 4). With a slightly greater dose (0·13 mg. per kg.) some animals showed a progressive decrease in stomach tone reaching a maximum in about 20 min. and continuing at this level for 2 or more hours. During the whole of this period no changes in amplitude or rate of movements were observed (Fig. 5). In a series of nine experiments, six showed relaxation of the stomach, two contraction, and in one no changes were recorded. Amounts in excess of 1·5 mg. per kg. sometimes caused a slight increase in stomach tone, gradual in onset, and lasting from 30 to 70 min. This increase in tone was accompanied by a slight increase in the amplitude of the movements while in others there was no alteration. These increased movements closely resembled those already described following the use of morphine, and took the form of three to six slow-moving contractions, each one of greatly increased amplitude, and lasting approximately 15 sec. The contractions followed one another at intervals of 15–20 sec., and when the last one had passed away the subsequent movements became so small as to be negligible, although the general tone of the organ was slightly greater than normal.

(*b*) *On the pyloric sphincter*

Dilaudid produces more marked effects upon the pyloric sphincter than either morphine, heroin or codeine. The tone and amplitude of the movements are both increased, while the frequency of the movements is reduced. This action upon the sphincter follows immediately the drug is injected. Very small amounts of the drug are extremely active as is shown in Fig. 6, where 0·025 mg. was injected into a cat weighing 1·8 kg. The first effect is a profound

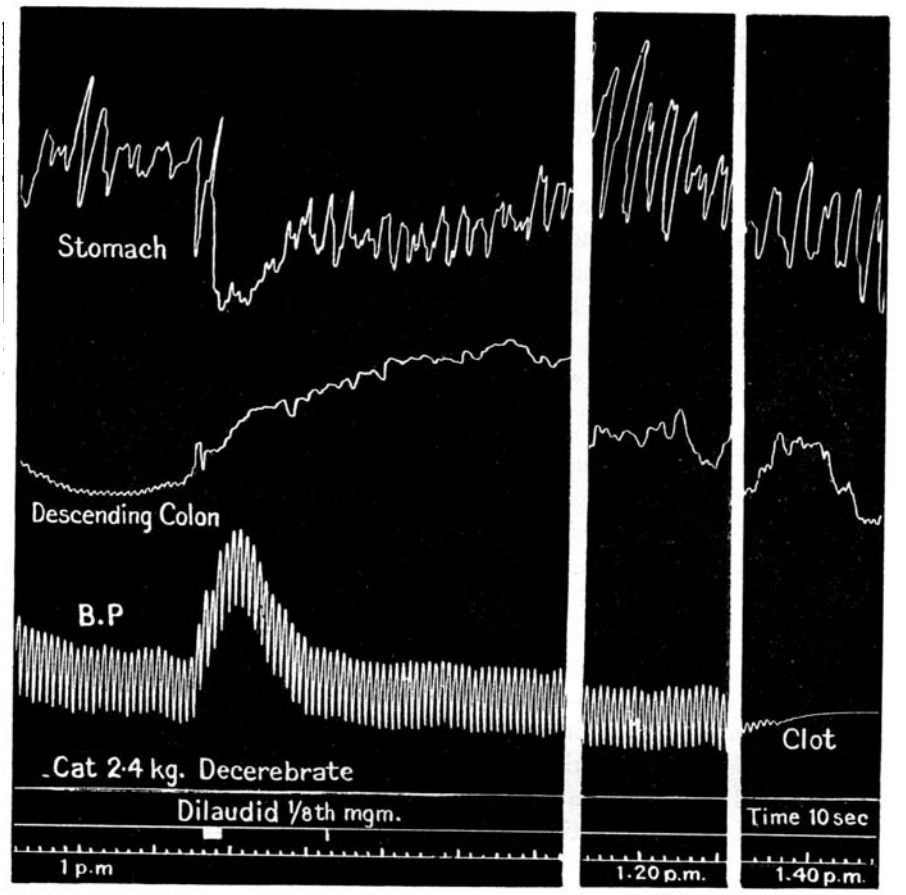

Fig. 4. Showing relaxation of the stomach and increased tone of descending colon produced by 1/8th mg. dilaudid. Time 10 seconds.

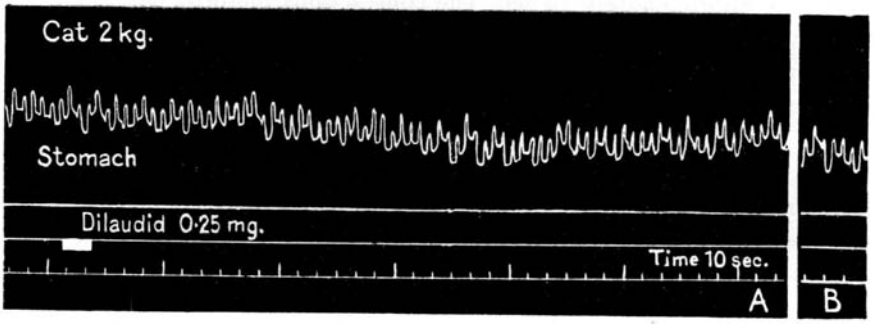

Fig. 5. Showing the relaxation of the stomach produced by the injection of 0·125 mg. dilaudid per kg. B is 16 min. after A.

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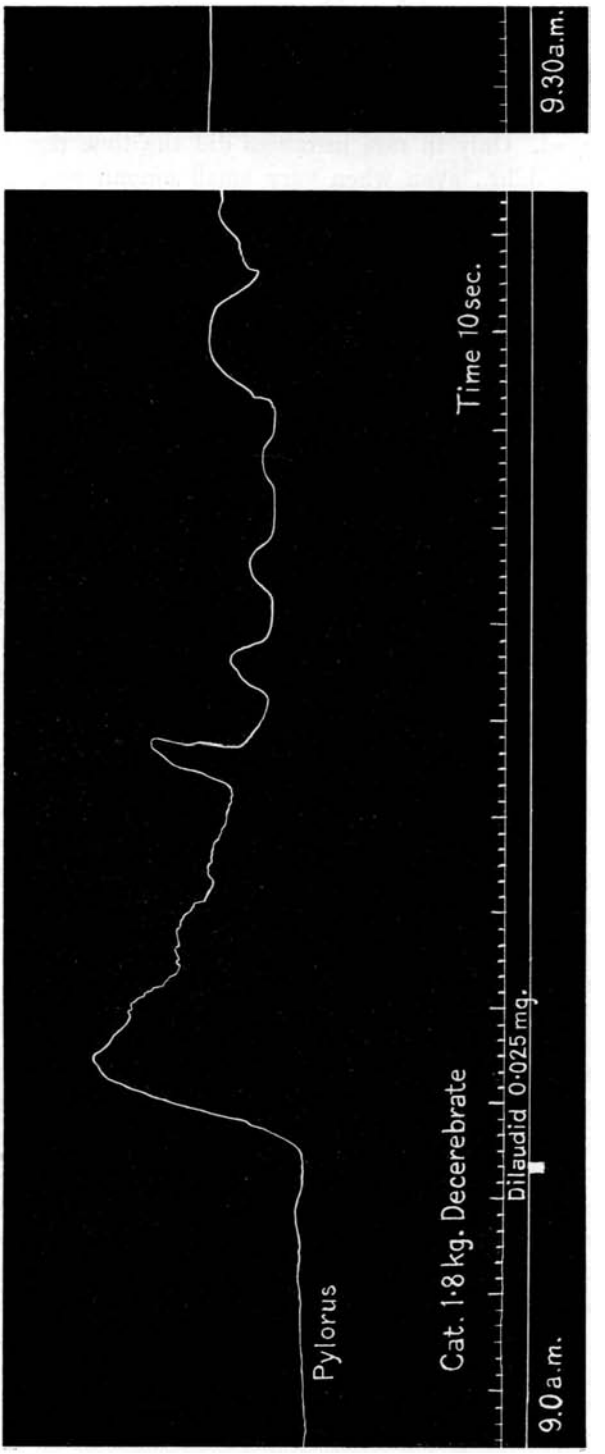

Fig. 6. Showing the increase in tone of the pyloric sphincter following a small dose of dilaudid. The condition was maintained for 4½ hours.

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increase in the general tone of the sphincter, reaching a maximum level in 1 or 2 min. This was followed by a decline in the excessive tone with the appearance of slow well-marked movements of the sphincter. The decline in tone is slow and does not regain a normal level for many hours, according to the dosage of the drug employed. Only in rare instances did the tone regain its normal level in less than 3 hr., even when very small amounts of dilaudid were administered. In some experiments the increased sphincter movements produced by dilaudid did not last beyond 30 min. when they disappeared and the sphincter showed only a condition of increased tone well above normal level. This is seen in Fig. 6. From time to time during the next 4 hr. the movements returned for a few minutes every 30–40 min. In other experiments, however, the increased movements were seen over a long period of 30–120 min. before they disappeared. 0·25 mg. per kg. produced a progressive increase in both tone and movements, reaching a maximum in 10–20 min., after which they slowly declined to normal level. The movements were reduced in frequency while the amplitude was increased. The increase in amplitude was sometimes enormous, and increases of four to eight times the normal movements were sometimes recorded. Larger doses did not usually produce greater effects, but rather prolonged the period of increased activity. In three experiments the injection of large doses (3 mg. per kg.) produced a slight relaxation of the sphincter below normal tone, while the movements were increased in amplitude and diminished in frequency. A comparison of the effective doses of dilaudid and morphine upon the pyloric sphincter revealed the greater potency of dilaudid over morphine. Doses of dilaudid as small as 0·01 mg. per kg. produced well-marked effects upon the activity of the sphincter which were more or less equivalent to those produced by 0·1 mg. of morphine. A calculation made over the whole series of experiments yielded a ratio of relative activity morphine : dilaudid :: 1 : 8.

The effects of dihydrocodeinone HCl (dicodid)

(*a*) *On the stomach*

In many ways these resemble those produced by codeine. 0·5 mg. per kg. produced a small gradual increase in tone reaching a maximum in about 25 min., when it slowly returned to normal during the next 6–12 min. Periods of increased tone followed by a gradual return to normal were frequently seen at this stage. Each wave lasted approximately 20 min. Three or four such waves in succession were generally recorded, after which they ceased and the tone diminished to a subnormal level. This relaxation of the stomach lasted a further 2 hr. Larger doses caused a more prolonged period of relaxation.

In so far as stomach movements are concerned 0·5 mg. per kg. produced a small but progressive increase in their amplitude, reaching a maximum at 180 min. after which they were maintained for a further 3·5–4 hr. before they began to return to normal again.

(*b*) *On the pyloric sphincter*

Small doses of dicodid (0·25–1 mg. per kg.) produced an immediate increase in tone and, later, amplitude of movements (Fig. 7). The tone reached a maximum about 15 min. after the injection when it progressively declined to a subnormal level during the next 30 min. This relaxation became increasingly more marked during the next few hours, while the movements continued to increase in amplitude in a most marked degree. As the amplitude increased, the frequency of the movements was correspondingly diminished. The maximum decrease in sphincter tone was always coincident with the maximum increase in the amplitude of movements and was generally recorded about 4–4·5 hr. after the administration of the drug. Large doses of dicodid (5 mg. per kg.) produced similar effects on tone and movements which were never so marked or so prolonged as when smaller doses were employed.

It is apparent that the effects of dicodid upon the sphincter show a close relationship to morphine in so far as the initial increase in tone is concerned, but several points on which the two drugs differ are seen in their later effects. The secondary relaxation produced by dicodid was generally seen to begin within 1½ hr. of giving the drug and became progressively more marked for some hours afterwards. This was rarely seen after morphine, and when present was extremely small and never appeared until many hours had elapsed from the injection being given. The subsequent increase in the amplitude of sphincter movements was usually greater in the case of dicodid than morphine.

THE EFFECTS OF DIHYDRO-OXYCODEINONE HCl (EUKODOL)

(*a*) *On the stomach*

The effects of eukodol are very similar to those of dicodid, but eukodol appears to be a little more active than dicodid when equal doses are employed.

(*b*) *On the pyloric sphincter*

Here again eukodol bears a strong resemblance to dicodid and codeine. 0·1 mg. per kg. produced an immediate but gradual increase in tone. At the same time movements increased in amplitude and became more regular. The increase in tone, however, rarely lasted longer than 10–20 min., after which it progressively declined to normal. This level was attained within 20–40 min. after the injection had been made. A slight decrease in tone rapidly followed, which continued for 4–5 hr. During the whole of this period the sphincter movements showed increased amplitude of movements with a slightly diminished frequency.

DISCUSSION

The results of this investigation have clearly shown that the effects produced by these drugs upon the stomach are extremely variable. The greatest differences in behaviour were seen with morphine, heroin, and dilaudid which

are undoubtedly the most active drugs of the series studied. The reason for these differences in behaviour in different animals of the same species is

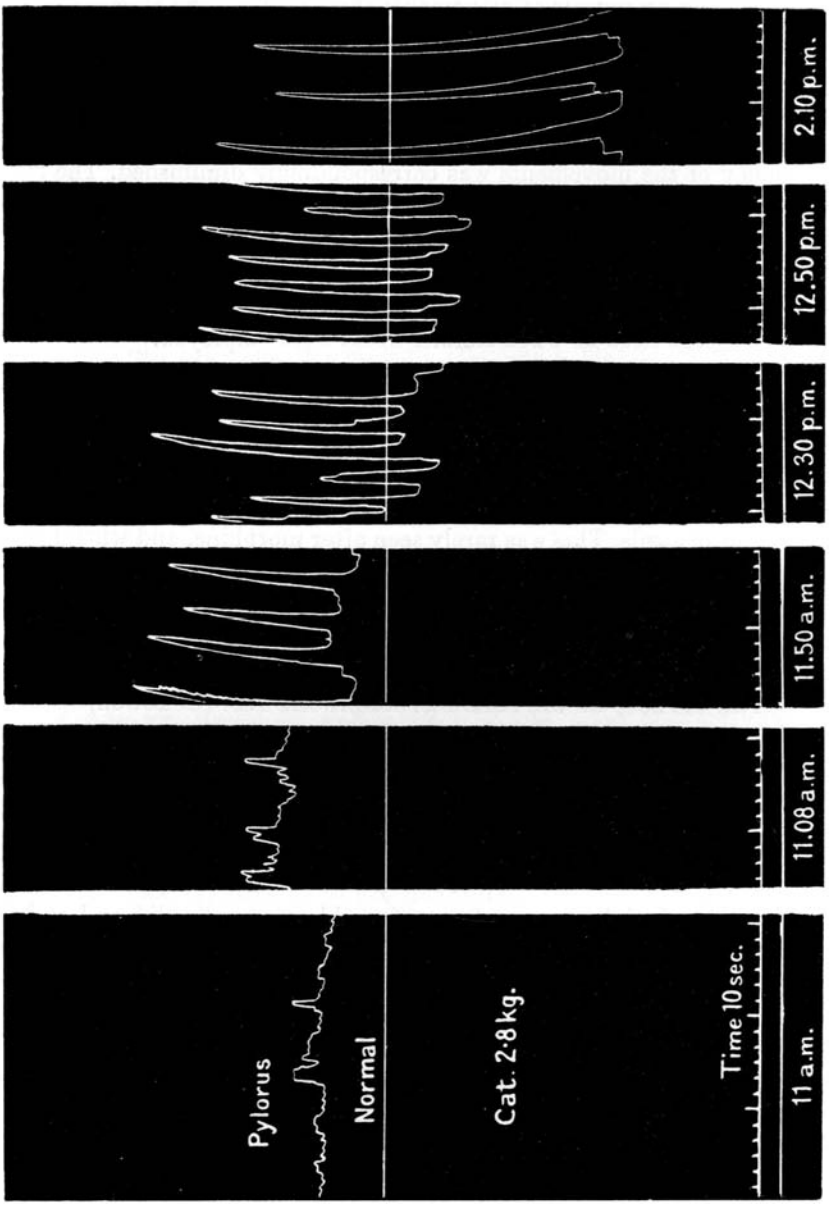

Fig. 7. Cat, 2·8 kg. Pyloric movements. 0·1 mg. dicodid was injected at 11·03 a.m.

difficult to explain, but it is not to be found in the drugs themselves or in the dosages employed. There seems little doubt that the explanation is to be found in the individual animals employed and may be due to the initial tone of the stomach itself. In so far as relative activity is concerned, dilaudid takes first

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place and closely resembles morphine in its effects, not only upon the stomach but upon the pyloric sphincter. It has been shown, from a study of the dosages employed, that dilaudid is approximately eight times more active than morphine. Little difference appears to exist between heroin and morphine except in so far as the dosage required to produce effects is concerned. Here it was calculated that heroin is about 40% more active than morphine.

The effects of codeine, dicodid and eukodol upon the stomach when compared with those of morphine, heroin and dilaudid are so small as to be negligible.

All the drugs studied in this investigation produce constant effects upon the pyloric sphincter. Dilaudid, heroin and morphine cause a profound closure of the sphincter which is accompanied by some increase in the amplitude of the rhythmical movements. These effects usually last several hours and are very pronounced, even after the administration of quite small doses. The nature of these effects is such as would account for a delayed passage of food from the stomach to the duodenum lasting five or more hours. The closure of the sphincter is of an intermittent character and the increased amplitude of the rhythmical movements may account for the slow passage of small amounts of food from time to time which has been observed by X-ray technique (van den Velden, 1909). The closure of the sphincter in response to morphine is generally slow and progressive and often requires 5–15 min. before it attains a maximum. During the earlier part of this period food in the stomach would be quite free to pass into the duodenum, but it would become increasingly difficult as the closure, or tone, became more pronounced. In the case of heroin and dilaudid the effects upon the sphincter are immediate and so the sphincter closes more promptly in response to these two drugs. The effects of codeine, dicodid and eukodol upon the sphincter are generally slow and progressive. They cause an increase in the tone and amplitude of the movements of the pyloric sphincter which is never very great and always of short duration, rarely exceeding 30 min. From these observations it is apparent that the passage of food from the stomach to the duodenum might be slightly impeded by codeine, dicodid, or eukodol, for a short time, but in any case it would never be much greater than ½ hr.

A close similarity is seen to exist between codeine, dicodid and eukodol, both in their effects upon the sphincters and the dosages required to produce these effects. The effects of these three drugs and their duration of action upon the stomach and pyloric sphincter are much less marked than those of dilaudid, heroin and morphine.

SUMMARY

1. The effects of morphine and diacetylmorphine upon the stomach of the cat are variable. The greater number of experiments showed a decrease in tone which was accompanied by a decrease in the frequency and amplitude of movements. Some animals showed an increase in stomach tone accompanied

by three to five slowly moving contractions of great amplitude while no changes were recorded in two cats.

2. Codeine sometimes produced a slight increase in the amplitude of stomach movements with a diminished frequency, while at first the general tone is unaltered. Tone is later reduced slightly to a subnormal level. In other cases it causes a very slight increase in tone and amplitude of movements. These effects are short lived and very small when compared with those produced by morphine or heroin.

3. The effects of dihydromorphinone (dilaudid) upon the stomach are far from constant. Most animals show an immediate relaxation of the stomach with a decrease in the amplitude of the movements. In a series of nine experiments, six showed relaxation of the stomach, two contraction, and in one no changes were recorded.

4. The effects of dihydrocodeinone (dicodid) on the stomach resemble those of codeine. They consist of a small gradual increase in tone followed by a relaxation to a subnormal level.

5. Dihydro-oxycodeinone (eukodol) produces effects which resemble those of dihydrocodeinone (dicodid).

6. All these drugs produce constant effects upon the pyloric sphincter. They all produce an increase in the tone of the sphincter accompanied by an increase in the amplitude of the rhythmical movements. Dilaudid is approximately eight times more active than morphine, while diacetylmorphine is about one and a half times more potent than morphine. The effects of these three drugs last several hours.

The effects of codeine, dicodid and eukodol show a great similarity. They are of short duration and very small when compared with morphine, heroin and dilaudid.

REFERENCES

Abbott & Pendergrass (1934). *Proc. physiol. Soc. Philad.* **10**, 15.
Fujitani (1910). *Arch. Exp. Path. Pharmak.* **62**, 118.
Glaessner (1901). *Arch. ges. Physiol.* **86**, 291.
Hirsch (1901). *Zbl. inn. Med.* **22**, 33.
Magnus (1908). *Pflüg. Arch. ges. Physiol.* **122**, 210.
Mahlo (1913). *Dtsch. Arch. Klin. Med.* **110**, 562.
Myers (1934). *Proc. Physiol. Soc.* **81**.
—— (1938). *J. Hyg., Camb.*, **38**, 432.
Plant & Miller (1928). *J. Pharmacol.* **32**, 413.
Rodari (1909). *Ther. Mh. (Halbmh.)*, **23**, 540.
Schapiro (1913). *Pflüg. Arch. ges. Physiol.* **151**, 65.
Schutz (1886). *Arch. exp. Path. Pharmak.* **21**, 342.
Schwenter (1912). *Fortschr. Röntgenstr.* **19**, 1.
Tetzner & Turold (1921). *Z. ges. exp. Med.* **12**, 275.
Thomas (1929). *Amer. J. Physiol.* **88**, 498.
van den Velden (1909). *Münch. med. Wschr.* **56**, 1667.

(*MS. received for publication* 19. I. 39.—Ed.)