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

PART IV. RECTUM

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(With 9 Figures in the Text)

CONTENTS

I. Introduction

In the earlier publications of this investigation the effects of morphine hydrochloride, codeine phosphate, dihydromorphinone hydrochloride, dihydrocodeinone hydrochloride, and dihydroxycodeinone hydrochloride upon the different parts of the alimentary tract, from the stomach to the descending colon, have been described (Myers, 1939 *a*, *b*, *c*).

A search of the literature dealing with the effects of morphine, diacetylmorphine and codeine upon the alimentary tract shows that little or no work has been done upon their effects on the rectum. Most workers do not seem to have carried their researches beyond the ascending or descending colon. In order to make this investigation complete the effects of this group of drugs, including the more recently produced allied drugs of this series, upon the rectum were studied, and the results are given in this communication.

II. Methods

Cats were the only animals used. In some experiments decerebrate preparations were used, while in others, chloralose was given as a general anaesthetic. A laparotomy was performed and a sausage-shaped balloon, slightly larger in diameter than the rectum, ligatured to a catheter was introduced into the rectum through an artificial opening made in the wall of the

lower end of the descending colon. The balloon was slightly distended and the catheter connected to a small water manometer, which was in turn connected to a recording tambour working on a kymograph. Continuous records of rectal movements were made over many hours. The pressure exerted by the water manometer was never sufficiently great to cause distention of the rectum. In order to test the response of the rectum to these drugs most experiments lasted 6 hr., but some were continued for 8 or 9 hr.

Usually the drugs were administered intravenously through the external femoral or jugular veins, but in a few experiments they were administered subcutaneously. The results obtained were comparable in every way, except that with subcutaneous injection, the onset was slower. The doses employed covered a wide range and varied between very small amounts (0·005 mg./kg.) and very large amounts (10 mg./kg.) which would have produced lethal effects in most cats.

III. EXPERIMENTS

(*a*) *Morphine hydrochloride*

The most constant effect of morphine as a well-marked increase in rectal tone, which quickly followed the administration of the drug, and lasted from 20 to 45 min., when the tone level usually became normal or was slightly raised. Later there were periods of increased tone and movements alternating with periods of relaxation and inhibition of movements. These effects are well illustrated in Fig. 1. In this experiment 0·17 mg./kg. was injected into the left femoral vein of a decerebrate cat. The drug produced an immediate and well-marked increase in tone which reached a maximum level within 3 min., after which it began to decline slowly to normal accompanied by a small increase in the amplitude of the peristaltic movements. Normal tone was re-established after an interval of 30 min., when the amplitude of the movements were still greater than normal. This condition lasted for 3 or 4 min. only, at the end of which a sudden and very marked secondary increase in tone and peristaltic movements began. This secondary period of rectal activity lasted 21 min., when both the tone and the movements quickly declined to normal within a space of 10 min. and declined further to a subnormal level during the next 10 min. The rectum remained in this condition for more than an hour. Another sudden increase in tone and movements occurred 125 min. after the morphine had been injected. The maximum tone effect was recorded within 2 min., and was soon followed by a rapid decline to normal level during the next 3 min., after which it continued to decrease to a subnormal level during the next 25 min. At this time a further period of renewed activity took place. This active phase consisted of a series of enormous contractions and relaxations, each one lasting about 2 or 3 min., excepting the first one which was of 5 min. duration. These very large movements continued for a period of 85 min. and then became less frequent. They continued at a rate of one every 30 min. during the next 3 hr., after which they ceased and the

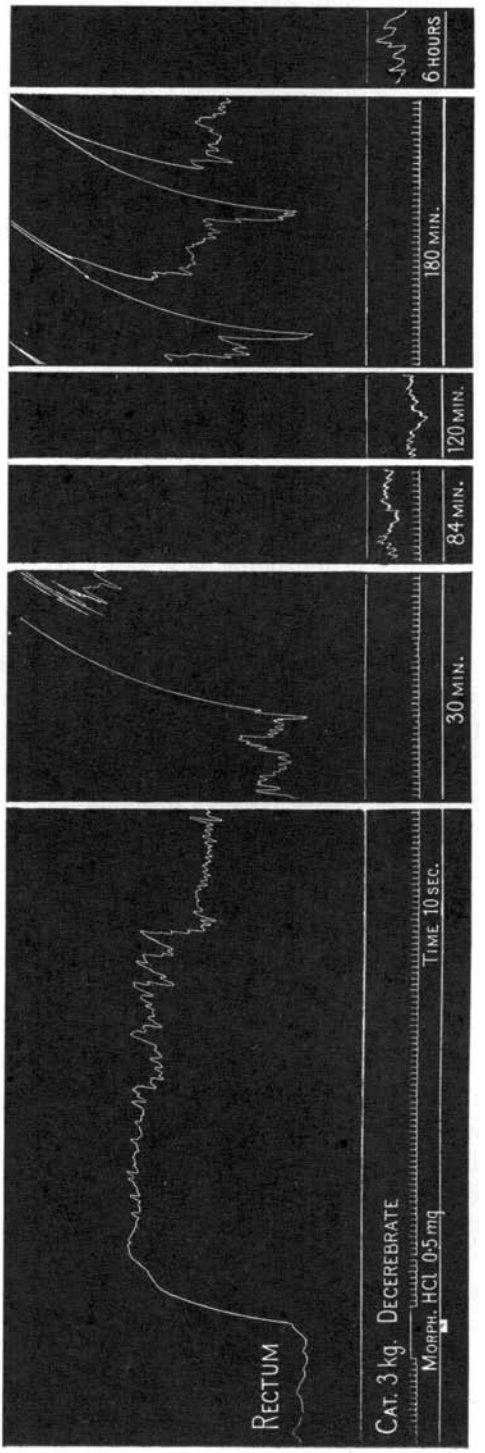

Fig. 1. Showing the effect of morphine HCl upon the rectum.

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rectum remained relaxed at a markedly subnormal level with very small movements for a further 3 hr., when the experiment was terminated. Similar results were recorded in other animals using doses ranging from 0·05 mg. to 1 mg./kg. The injection of sufficient atropine sulphate to completely "atropinize" the animal always abolished the increased tone and amplitude of movements produced by morphine and left the rectum in a relaxed condition, while the movements were almost, but not entirely, abolished (Fig. 2). Subsequent injections of morphine hydrochloride (0·05–0·5 mg./kg.) failed to reproduce the effects of morphine, which have been described, even after an interval of 2 hr.

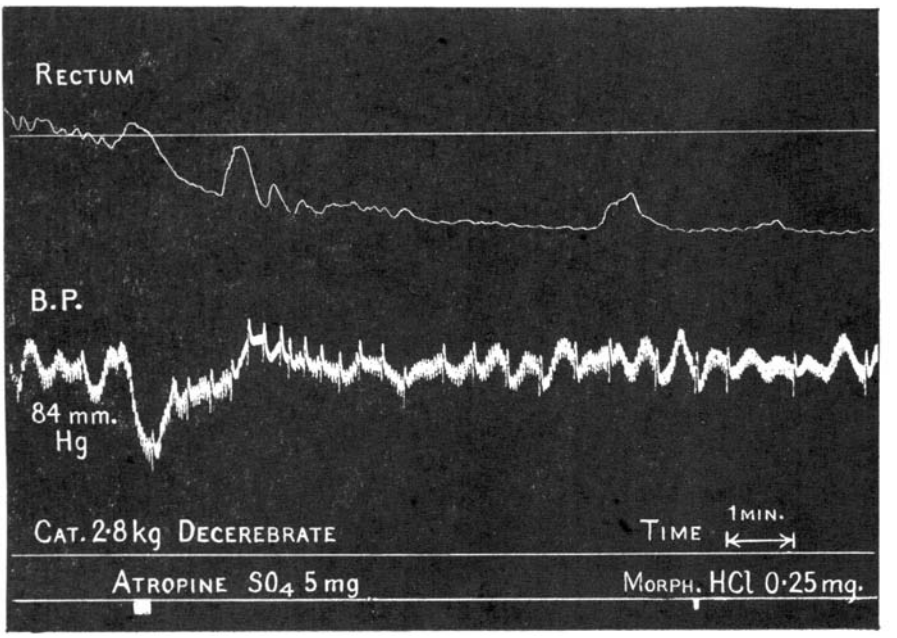

Fig. 2. Illustrating the effect of atropine sulphate upon the rectum 100 mins. after the previous injection of 0·25 mg. morphine HCl. The same amount of morphine is ineffective after atropine.

(*b*) *Diacetylmorphine hydrochloride* (*heroin*)

The effects of this drug upon the rectum were essentially the same as those of morphine hydrochloride. Certain minor differences between the effects of these two drugs, however, were observed. The greatest difference was found in the degree of relaxation of the rectum, which usually occurred 1–2 hr. after the administration of the drugs. This relaxation was always most marked after morphine. The loss of rectal tone produced by heroin was always so small as to be negligible, and in a few experiments this condition was never observed, even after a space of 7 hr. when the tone level was still quite normal.

Both drugs, however, always produced an immediate well-marked increase in tone of the rectum shortly after their administration. The tone level usually

returned to normal within 30–45 min. The periods of secondary rectal activity, already described in response to morphine hydrochloride, were seen in similar experiments where heroin was employed. A calculation made from the effective doses of these two drugs showed little difference in their relative potency upon the rectum.

(*c*) *Methylmorphine phosphate* (*codeine*)

The injection of 0·25 mg./kg. into the femoral vein always produced a slow progressive increase in the tone of the rectum. This increase usually reached a maximum level about 8–12 min. after the injection had been made, but was always so slight as to be negligible (Fig. 3), and was always accompanied by a series of increased movements, each one lasting about 1 min. or less. The first movement was the greatest in amplitude and each succeeding movement diminished in size until they had almost disappeared 20 min. after the drug had been injected. Normal tone was re-established about 30 min. after the administration of the codeine, and no further changes were observed. Doses smaller than 0·25 mg./kg. were nearly always without effect, while the effects of larger doses (1–2 mg./kg.) were more rapid in onset and more marked, but never lasted longer than 30 min., and they were never as great as those produced by morphine or heroin (Fig. 4). It is, therefore, apparent that codeine resembles morphine and heroin in its ability to increase rectal tone, although its effects are very much less marked and of shorter duration. After the administration of codeine the rectal tone was never observed to fall below normal, and in this respect it more closely resembles heroin than morphine. Secondary phases of increased rectal activity were never observed at any time after codeine administration, and this is a further point of difference between this drug and morphine or heroin.

(*d*) *Dihydromorphinone hydrochloride* (*dilaudid*)

In many cats the smallest effective dose was found to be about 0·02 mg./kg. This amount, when given intravenously, produced only a negligible increase in both tone and the amplitude of the rectal movements, which lasted 15–20 min. No further effects were observed during the next 6 hr. Other cats of approximately the same weight and in a similar condition gave a well-marked reaction to doses as small as 0·005 mg./kg. Fig. 5 shows the effects of this dose when injected into the femoral vein of a decerebrate cat weighing 2·1 kg. The record shows a progressive increase in tone which reached a maximum level in 4–5 min., after which it slowly declined to normal tone level, which was re-established 12 min. later. There was no change in the rate or amplitude of the peristaltic movements during this period. The general tone of the rectum began to decline to a markedly subnormal level 40 min. after the drug had been injected and at 80 min. reached its lowest level, where it remained for the remainder of the experiment (6 hr.). The rate of the movements remained more or less constant until 40 min. after the drug had been administered, when it decreased from the normal rate of 6 to 2 per min. At 80 min. the rate was very slow and irregular; only an odd movement showed every

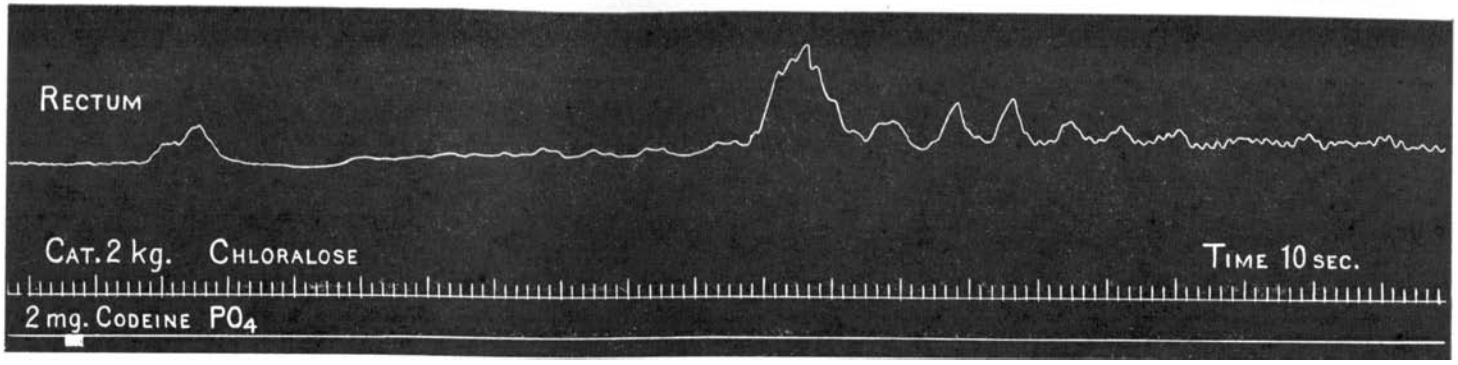

Fig. 3. Showing the effect of codeine phosphate upon the rectum.

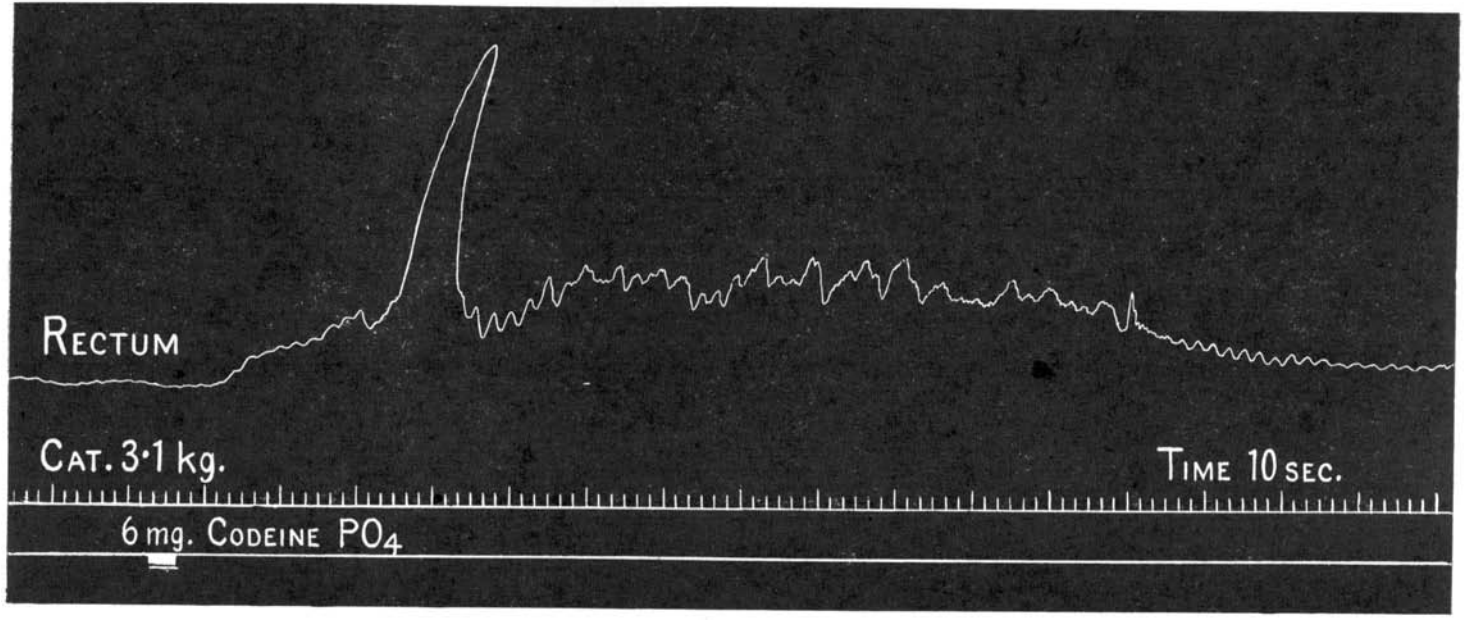

Fig. 4. Illustrating the effect of a large dose of codeine phosphate upon the rectal tone and movements.

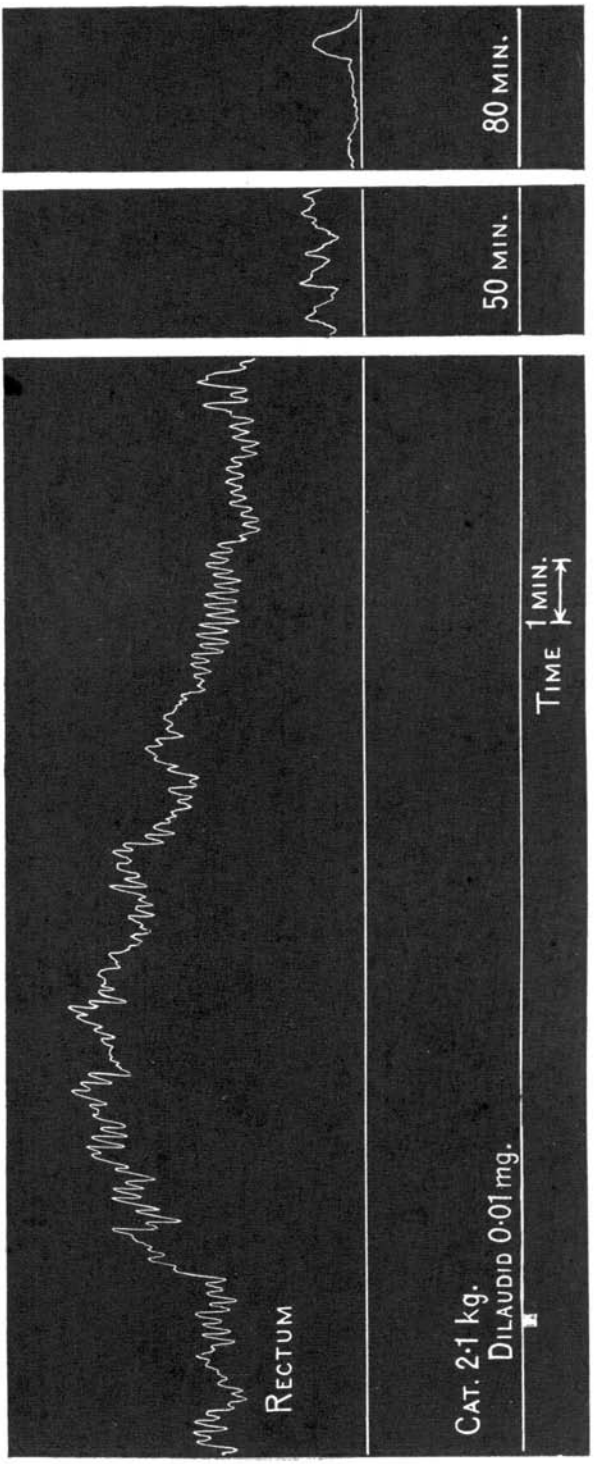

Fig. 5. Showing the effect of a small dose of dihydromorphinone HCl (dilaudid) upon the rectum.

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5–12 min., and this condition persisted until the experiment was terminated 4 hr. later. The amplitude of the movements remained more or less constant throughout, even when the rate of the movements was very erratic.

Larger doses of dilaudid (0·2–1 mg./kg.), given intravenously, always produced an immediate pronounced increase in rectal tone, which reached a maximum level at 2–5 min., when movements began to increase in amplitude. The maximum amplitude was attained within a few minutes, after which it slowly decreased to normal. Normal tone level and normal movements were usually re-established 30–45 min. after the injection had been given.

These effects were always abolished by the injection of enough atropine sulphate to completely "atropinize" the animal. Subsequent injections of dilaudid never reproduced the effects which have been described.

In these experiments the most constant effect of dilaudid upon the rectum was an increase in muscular tone, which never lasted longer than about 45 min. Later the tone became subnormal and remained in this relaxed condition for many hours. Small amounts of the drug did not influence the amplitude of the rectal movements; but a diminution in rate was usually evident some time later. Large doses always produced a moderate increase in amplitude, without any change in rate, for a period of about 30 min. after intravenous administration of the drug. Later the rate was often decreased and very irregular, while the amplitude sometimes remained slightly greater than normal. The increases in both tone and amplitude of movements were immediately abolished by atropine sulphate and subsequent injections of dilaudid were without effect.

From this evidence it will be seen that the effects of dilaudid upon the rectum are like those of morphine and heroin, although they bear a closer resemblance to those of morphine in so far as subnormal tone effects are concerned.

(*e*) *Dihydrocodeinone hydrochloride* (*dicodid*)

The principal action of dicodid appears to be a general stimulation of the rectum into greater activity. This increase in activity is much greater and more prolonged than with any of the drugs already described in this communication, and can be illustrated best by describing the results of a characteristic experiment (Fig. 6).

In this experiment a decerebrate cat weighing 3·2 kg. was used, and the rectum showed active movements before the intravenous injection of 0·25 mg. of dicodid. From the experience gained in earlier experiments this amount (0·08 mg./kg.) would represent a small dose of the drug. The injection was followed by an immediate pronounced increase in the tone of the rectum, while the amplitude of the movements was slightly diminished. The maximum tone level was reached in 3 min., when it began to decline during the next 6 min. to a level which was still above normal. Within 1 min. the tone level began to increase again quickly, but it did not reach the previously recorded maximum level. At this stage there was a small increase in the amplitude of

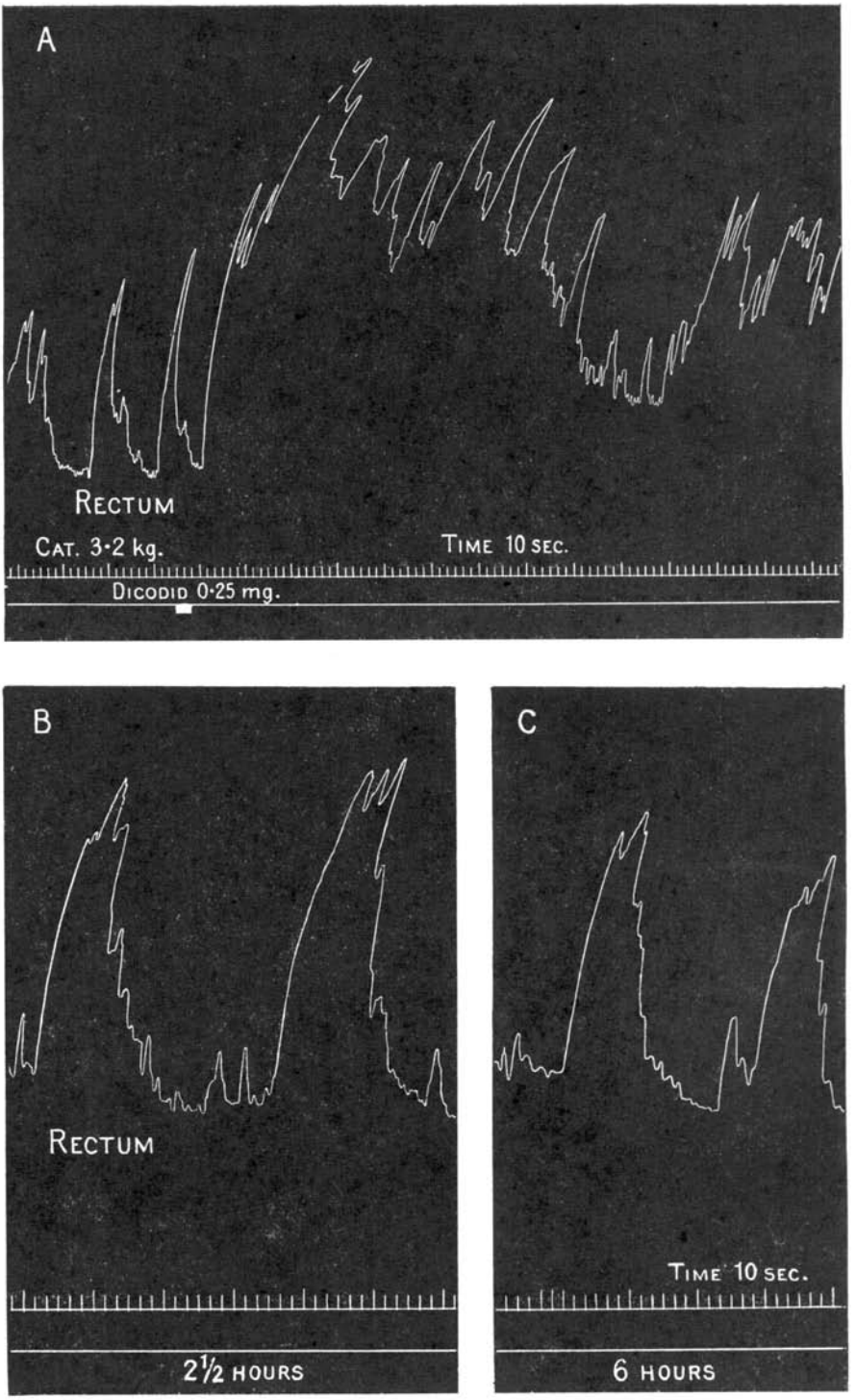

Fig. 6. A. Showing the effect upon the rectum produced by a first injection of dihydrocodeinone HCl (dicodid). B and C. 2½ and 6 hrs. later.

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the movements, and their rate increased from one in 90 sec. to one in 50 sec. This condition of increased tone and movements slowly declined during the next 15 min. until the movements became normal in amplitude and the general tone level was still slightly greater than normal. Another marked increase in tone took place 2 min. later, and reached the previously recorded maximum level, attained immediately after the drug had been injected. These periods of increased tone followed by relaxation recurred regularly at intervals of 15–25 min. during the next 4½ hr. At the end of the 8 hr. stage the tone of the rectum was still slightly greater than normal, while the movements were very active but their amplitude was a little less than normal. The rate of the movements varied at different times. The immediate effect of dicodid was a quickening of the rate from one in 90 sec. to one in 50 sec., but a well-marked slowing was seen 2½ hr. later, when the movements were one in 210 sec. This was the slowest period recorded, and later, at the 6 hr. stage, they became a little more frequent (one in 150 sec.) and remained more or less constant at this rate for the remainder of the experiment (8 hr.).

The injection of atropine sulphate in sufficient amounts to "atropinize" the animal always produced a complete inhibition of movements and a diminution of tone to a subnormal level. The injection of dicodid (0·8–0·25 mg./kg.) about 1 hr. later always produced an immediate well-marked increase in both tone and movements, which usually returned to normal 15–30 min. later. It is interesting to note that dicodid produces its effects after the administration of atropine, although the duration of the effects was much shorter than that observed in response to the same amount of the drug injected before the administration of atropine. In this respect the behaviour of dicodid differs from that of morphine or heroin. The general effects of dicodid upon the rectum resemble those of morphine except that dicodid was never observed to decrease the general tone of this portion of the alimentary tract to a subnormal level, even after 8 hr. This was a constant feature with morphine but not with heroin. On the other hand, dicodid produced a much greater increase in rectal activity, which was of longer duration than that produced by either morphine or heroin.

(*f*) *Dihydroxycodeinone hydrochloride (eukadol)*

The effects of this drug upon the rectum showed a resemblance to those produced by morphine on the one hand and those of dihydrocodeinone hydrochloride (dicodid) on the other. The smallest amount of eukadol to produce effects was found to be 0·05–0·1 mg./kg. The intravenous administration of 0·1 mg./kg. always produced an immediate and well-marked increase in the tone of the musculature of the rectum (Fig. 7). The maximum tone level was established within 3–5 min., when a pronounced increase in the amplitude of the movements of the rectum commenced. The maximum tone level was not maintained and declined to a slightly subnormal level during the next 15–30 min. At this stage the amplitude of the movements had declined to

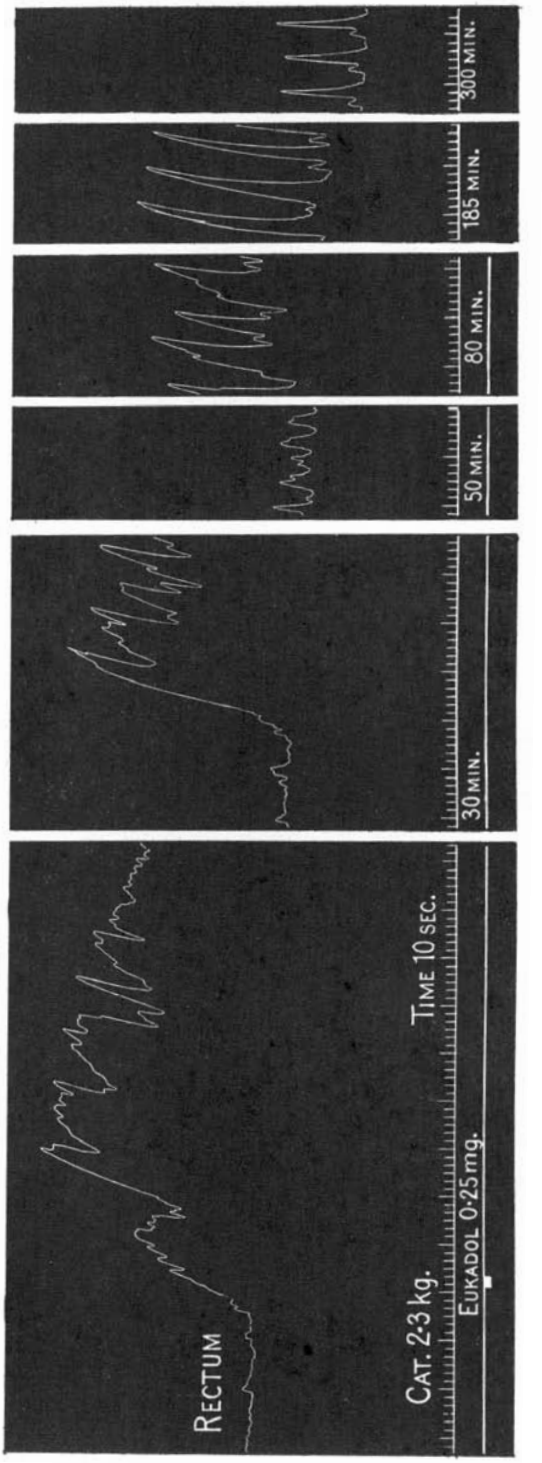

Fig. 7. Showing the effect of dihydroxycodeinone HCl (eukadol) upon the rectum.

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normal. Usually about 20–40 min. after the drug had been injected a secondary increase in both tone and amplitude of the movements occurred, which terminated 20–30 min. later, leaving the rectal tone at a slightly subnormal level and the amplitude of the movements much greater than normal. These phases of increased tone and increased amplitude of movements, each one of 18–25 min. duration, and separated by a short interval of 8–15 min., recurred regularly during the first 2–2½ hr. following the injection of the drug. The increase in tone became less marked with each succeeding phase of activity, while the movements became more pronounced in amplitude and slower in rate. The maximum amplitude was usually recorded at the 3–3½ hr. stage, when the tone was subnormal. From this stage the tone level began to decline still further, and the movements diminished in amplitude without much further change in their rate (one in 45 sec.). At the 6 and 8 hr. stages the rectum was still slowly relaxing in tone, and the movements becoming pro-

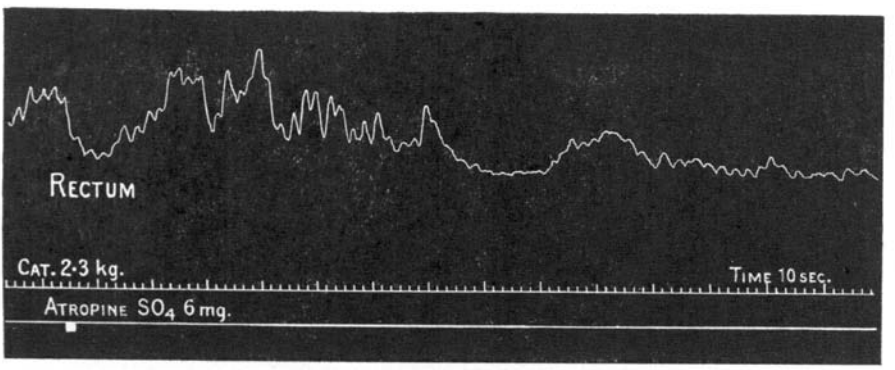

Fig. 8. Illustrating the effect of atropine sulphate injected intravenously 2 hrs. after the previous administration of 0·25 mg. eukadol.

gressively smaller in amplitude. The rate of the movements was not much altered after the drug was injected until about 1 hr. had elapsed, when it was increased. From this point onwards there was a decided decrease in rate, while the amplitude of the movements increased. In Fig. 7 the average normal rate of movements was one per 80 sec.; 35 min. after the drug had been injected the average rate was one per 35 sec.; at 50 min. one per 27 sec., which was the maximum rate recorded; at 80 min. it had fallen to one in 37 sec.; while at 185 min. the rate had decreased to one in 45 sec. No further slowing was recorded from this stage until the experiment terminated at 8 hr. Three out of eight cats exhibited bouts of vomiting at the 4–4½ hr. stage. The intervals between the bouts were approximately 5 min.

The injection of sufficient atropine to "atropinize" the animal always abolished any increase in rectal tone produced by the previous administration of eukadol. Movements were more markedly effected; being either abolished or reduced to negligible proportions (Fig. 8). The injection of 0·25 mg./kg. or

more of eukadol about 15 min. later invariably produced its effects upon the rectum, but always in a modified form. This is well illustrated by a comparison of Figs. 9A and 9B. The modified effects seen in Fig. 9B are entirely due to the previous administration of atropine because, in control animals, without atropine administration, the injection of a second dose of eukadol (0·25 mg./kg.), given 2¼ hr. after the first injection, produced effects upon the tone and amplitude of rectal movements of almost similar magnitude to those of the initial injection.

IV. Discussion

There is a close relationship in the effects produced by the various drugs used in this investigation. They all produce an increase in the general tone of the rectum in addition to an increase in the amplitude of the peristaltic movements. The degree of activity produced in the muscular elements varies according to the particular member of the series which is used, and the main points of similarity, and the differences between the various members will be outlined in this discussion.

The results of this investigation have shown quite clearly that morphine hydrochloride produced a well-marked increase in rectal tone lasting approximately 20–45 min. At the end of this time the general tone level was either normal or slightly above normal. During the next 3 or 4 hr. there were waves of increased tone followed by relaxation to normal, each wave lasting approximately 30 min. At the 5 or 6 hr. stage the rectal tone was always subnormal. Morphine increased the amplitude of the movements. At first the increase was small, but they reached a maximum at 3 hr., when they were very large and much slowed in rate. These increased movements, as well as the increased tone, were abolished by the administration of atropine sulphate, after which further doses of morphine were ineffective.

The effects produced by diacetylmorphine were similar to those of morphine except that it rarely left the rectum in a state of subnormal tone. In a few experiments there was some slight relaxation of the rectum at the 5 hr. stage, but it was always so small as to be negligible. This is a point of difference between these two drugs. As in the case of morphine, atropine abolished the effects of diacetylmorphine, and subsequent doses of the drug were without effect.

Codeine phosphate bears a close resemblance to morphine and diacetylmorphine in so far as the general effects upon tone and movements are concerned, but certain well-marked differences between the drugs were observed. The increase in tone produced in response to codeine was usually slow in onset, and progressively increased to a maximum at approximately 15 min. Even at this stage the increased tone was always small, and negligible in comparison with that produced by either morphine or diacetylmorphine, which was always well marked and reached its maximum effort in 3–6 min. No secondary phases of increased activity were ever observed after codeine administration, such as

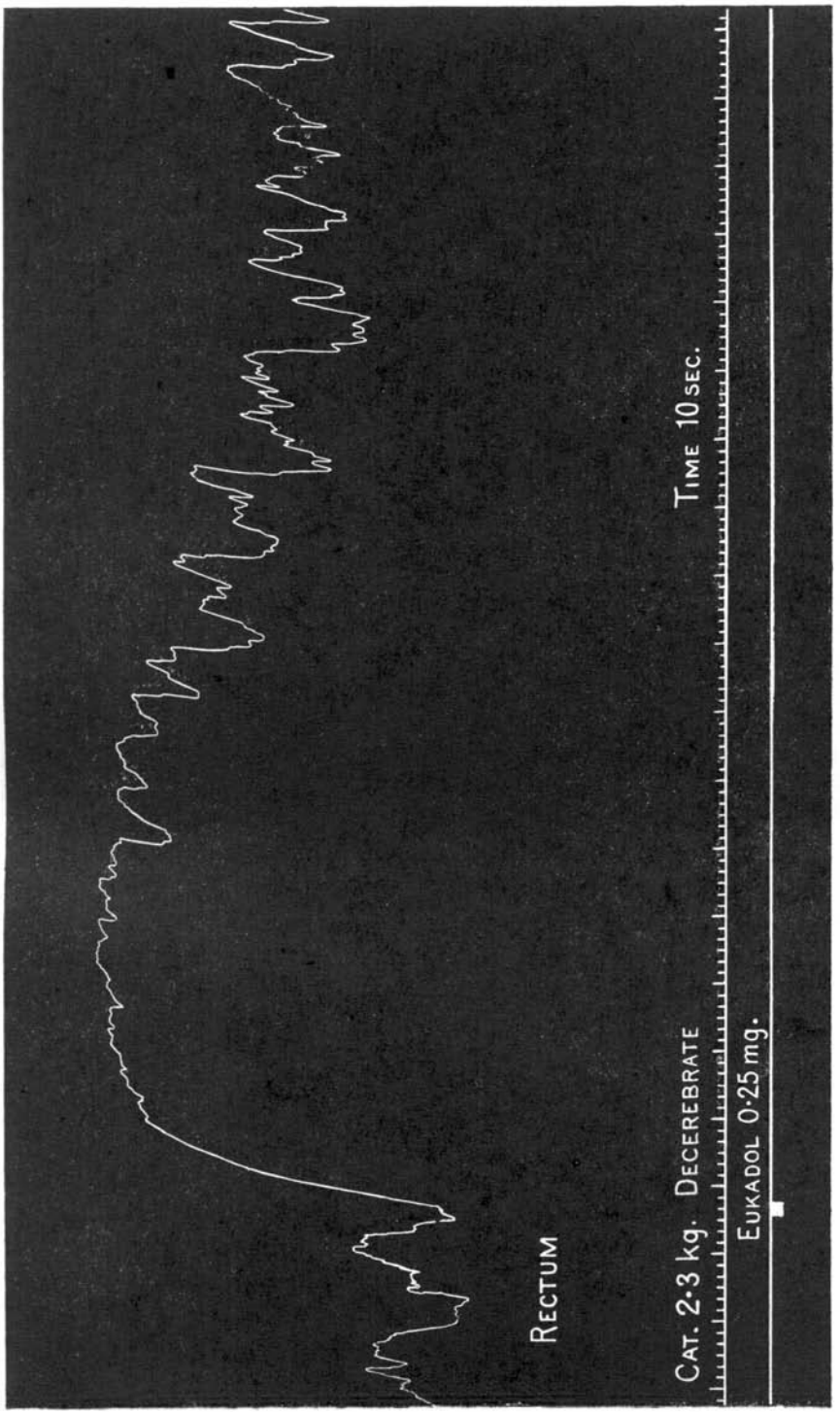

Fig. 9. A. Showing the effect of an intravenous injection of 0·25 mg. eukadol upon the rectum.

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were seen after morphine, heroin, dicodid or eukadol. When codeine was administered tone was rarely seen to pass below normal level, even at the end of 8 hr., and in this respect codeine resembles heroin rather than morphine. The duration of the effects of codeine were short lived and rarely extended beyond 30–45 min., which is another point of difference between codeine (methylmorphine) on the one hand, and morphine and diacetylmorphine on the other.

Dihydromorphinone hydrochloride (dilaudid) was found to be an active drug, even when very small doses were employed. The effects of small doses were mainly to increase tone rather than the amplitude of the movements. There was always an immediate increase in tone, resembling that produced by morphine, which usually declined to normal 30–40 min. later and then continued to a subnormal state within 70–90 min. Larger doses, comparable

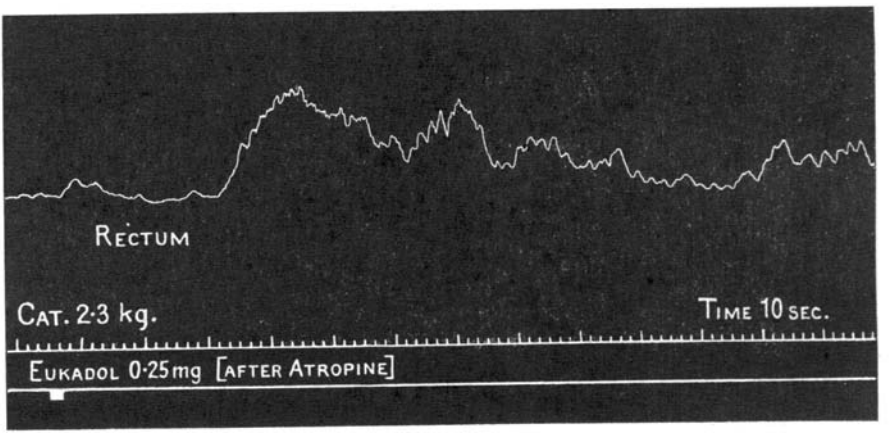

Fig. 9. B. Showing the effect of an intravenous injection of 0·25 mg. eukadol upon the rectum of the same animal 15 mins. after the injection of 6 mg. atropine sulphate.

with those employed when morphine and diacetylmorphine were used, produced an increase in the amplitude of movements as well as of tone. These effects rarely lasted longer than 30 min., when both tone and movements were normal once again. The tone level was usually subnormal 6–8 hr. later, and in this way the drug approximates more closely to morphine than heroin.

The effects of dihydromorphinone (dilaudid) were immediately abolished by atropine and further injections of dihydromorphinone were without effect. In this respect dihydromorphinone resembles both morphine and heroin.

The administration of dihydrocodeinone hydrochloride (dicodid) produced an increase in the activity of the rectum which was far in excess of any thing observed in response to either morphine, diacetylmorphine, methylmorphine, or dihydromorphinone. There was always an immediate increase in tone, reaching a maximum within 3–5 min., accompanied by some small diminution in the amplitude of the movements. After a short interval the amplitude increased above normal and the rate of the movements increased. Later there

were secondary increases in tone followed by relaxation to a level slightly greater than normal. These waves of increased tone kept recurring at intervals of 15–25 min. during the next 4½ hr. and were similar to those seen after morphine. At the 8 hr. stage the tone level was never observed below normal, and in this respect the drug resembles heroin.

Atropine caused an immediate inhibition of movements and a reduction of tone to a more or less normal level. The subsequent injection of dihydrocodeinone (dicodid) always produced its usual effects, which were, however, somewhat modified and of shorter duration; in this respect it differs from morphine, diacetylmorphine, codeine, and dihydromorphinone. The general effects of the drug, however, bear a strong resemblance to those of morphine, but are much more marked. It never caused a relaxation of tone level below normal, even after many hours, and in this respect it approximates more closely to diacetylmorphine (heroin) than morphine.

Dihydroxycodeinone hydrochloride (eukadol) produced very marked effects upon the activity of the rectum. It increased the tone to a marked extent, and later the movements. Secondary waves of increased tone, followed by relaxation to approximately normal level, were observed throughout the first 2½–3 hr. after the injection. Each wave was of 18–25 min. duration and separated from the next by an interval of 8–15 min. This drug always increased the amplitude of the movements in a most marked way. The maximum amplitude was usually recorded at the 3–3½ hr. stage, when the tone was subnormal. At the 8 hr. stage the tone was still subnormal, while the movements were still decreasing in both rate and amplitude. In so far as this drug increases both tone and movements it bears a resemblance to morphine. Its effects upon movements, however, are much greater than those produced by either morphine or heroin, and in this respect there is a close similarity between the effects produced by dihydroxycodeinone (eukadol) and dihydrocodeinone (dicodid). Atropine abolished the increased tone and amplitude of movements produced by dihydroxycodeinone. The subsequent injection of dihydroxycodeinone after atropine always produced a marked increase in tone without much change in the amplitude of movements; in this later observation there is a further point of similarity between dihydroxycodeinone and dihydrocodeinone. Among the many interesting points which this investigation has revealed, perhaps the most interesting is that codeine is undoubtedly the weakest drug in this series, and that while its general effects resemble those of morphine they are very much less marked and of short duration. On the other hand, dihydrocodeinone (dicodid) and dihydroxycodeinone (eukadol), both of which are more closely related to codeine from a chemical standpoint than any of the other drugs, are easily the most active drugs of the series in so far as their effects upon the lower bowel are concerned. They might reasonably have been expected to produce the mild, transient effects of codeine instead of being more active than either morphine or diacetylmorphine.

In the earlier stages of this investigation it was observed that the effects

of these narcotic drugs upon the caecum were generally much more marked than upon the small intestine. Now that the effects upon the rectum have been studied, a comparison of the relative sensitivity of the various parts of the entire alimentary tract can be made. This study shows that the rectum appears to be more active in response to these drugs than any other part of the alimentary tract, including the caecum. From this it would appear as if these drugs produce greater effects upon the lower than upon the upper portions of the tract. In fact, the lower the portion concerned the greater the activity.

V. Summary

1. The effects of morphine, diacetylmorphine (heroin), methylmorphine (codeine), dihydromorphinone (dilaudid), dihydrocodeinone (dicodid) and dihydroxycodeinone (eukadol) upon the rectum are described.

2. Morphine hydrochloride produces an immediate well-marked increase in rectal tone, which returns to normal about ½ hr. later. Waves of increased tone followed by relaxation are seen during the next 3–4 hr., each wave lasting approximately ½ hr. At the 5 or 6 hr. stage the tone is generally subnormal and remains so for many hours afterwards. The amplitude of the rectal movements is slowly increased, reaching a maximum about 3 hr. later, when they are usually very large and much slower than normal. Later the movements decline to a subnormal amplitude. These effects are abolished by the administration of atropine, and subsequent injections of morphine hydrochloride given within a few hours fail to reproduce them.

3. The effects of diacetylmorphine hydrochloride (heroin) are similar to those of morphine hydrochloride, except that it rarely leaves the rectum in a subnormal state of tone at any time during the first 8 hr. following the injection of the drug. In two experiments a slight relaxation beyond the normal limits was observed at the 5 hr. stage, but it was so small as to be negligible.

4. Methylmorphine phosphate (codeine) produces effects upon the tone and movements which resemble those of morphine, but they are always less marked in degree and of shorter duration than those of morphine. With codeine the effects never lasted longer than 30–45 min.; secondary waves of increased tone, such as were seen after the administration of morphine, diacetylmorphine, dicodid or eukadol, were never observed following the use of codeine. The tone level of the rectum was never subnormal at the 5 hr. stage or later. The effects of codeine were always immediately abolished by atropine, after which codeine was ineffective.

5. Diacetylmorphinone hydrochloride (dilaudid) is a very potent drug, producing very marked effects upon the rectum even when very small doses were employed. Small amounts of the drug cause an immediate increase in tone without any change in the character or rate of the movements. Normal tone was re-established 30–45 min. later, when it declines still further to a subnormal level, reaching its lowest level at 70–90 min. Larger doses of

dilaudid produced an increase in the amplitude of the movements in addition to increasing the tone. These effects lasted approximately 30 min., when both tone and movements were normal again. The tone level was generally markedly subnormal at the 6–8 hr. stage. The effects of dilaudid were immediately abolished by atropine, after which dilaudid was ineffective.

6. Dihydrocodeinone hydrochloride (dicodid) is a very active drug which produces an increase in the activity of the rectum which is far greater than that produced by morphine, heroin, codeine, or dilaudid. The immediate effect of dicodid is an increase in rectal tone, accompanied by some decrease in the amplitude of the movements. Later the tone decreases far in excess of normal. Secondary waves of increased tone, each one of 15–25 min. duration, were observed to recur during the first $4\frac{1}{2}$ hr. following the administration of the drug. The tone level of the rectum was never subnormal, even at the 8 hr. stage. The effects of dicodid were always inhibited after the administration of atropine, while the subsequent injection of dicodid always produced its usual effects, which were, however, modified and of shorter duration.

7. Dihydroxycodeinone hydrochloride (eukadol) at first increases the tone of the rectum to a marked extent and later the amplitude of the movements. Secondary waves of increased tone, each one of 18–25 min. duration, and separated from the next by an interval of 8–15 min., were observed through the first $2\frac{1}{2}$–3 hr. following the administration of the drug. The effect of eukadol upon the rectal movements is extremely marked. The maximum increase in their amplitude was generally observed at the 3–$3\frac{1}{2}$ hr. stage, when the tone was subnormal. At the 8 hr. stage the tone was always subnormal, while the movements were decreasing in both rate and amplitude. Atropine immediately inhibited the action of eukadol upon the rectum, while the subsequent administration of eukadol always produced a marked increase in tone without much change in the amplitude of movements.

8. Codeine phosphate is undoubtedly the weakest member of this series in so far as the effects produced upon the rectum are concerned, while dihydrocodeinone (dicodid) and dihydroxycodeinone (eukadol) are the most active.

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