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

PART III. CAECUM AND COLON

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

From the Pharmacological Laboratory, Cambridge

(With 8 Figures in the Text)

CONTENTS

I. Introduction

In 1882, Nothnagel, using rabbits, observed that the administration of morphine produced a quietening effect upon the colon which is not so marked as in the case of the small intestine. Local constriction of the colon was sometimes observed. Pal (1900) used dogs under the influence of curare, and dogs anaesthetized with chloroform. He introduced a balloon filled with water into the large intestine, and recorded the movements. The injection of opium or morphine always produced powerful contractions of both longitudinal and circular fibres. Pendulum movements appeared later and were often followed by a persistent contraction of the muscle. Section of the hypogastric and pelvic nerves, or destruction of the spinal cord did not affect the result. In 1906, Magnus, using cats, severed all the nerves from the abdominal ganglion cells. When nerve degeneration had taken place he demonstrated that morphine salts were able to stop milk diarrhoea. He concluded that morphine did not act by stimulation of the inhibitory nerve mechanism. In 1908, when studying the passage of the bismuth meal by means of X-ray methods, he recorded that morphine did not produce any changes in the behaviour of the

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large intestine; he also found no difference in the expulsion time of rectal soap enemata before and after the administration of morphine. From these results he concluded that morphine had little or no effect upon the colon. Schwenter (1912) used X-ray methods on cats and observed a marked relaxation of the colon and diminished peristaltic movements after morphine had been given. Mahlo (1913) used the bismuth meal method on young adults. X-rays showed a delayed passage of food through the colon after the oral administration of tincture of opium. A well marked delay was seen at the sigmoid flexure. The general tone of the colon varied in different subjects; in some it appeared to be contracted, in others dilated. By means of an artificial opening in the ileum of a dog, Schapiro (1913) introduced a bismuth meal into the alimentary canal, and by means of X-rays observed the behaviour of the intestines after morphine had been given. He noticed a delayed passage of food through the colon. Similar results were observed in the human subject where considerable delay occurred at the sigmoid flexure. In some subjects the colon was contracted while in others it showed dilatation. He suggested that a diminished defaecation reflex is responsible for the constipating action of opium. Plant & Miller (1928) investigated the effects of morphine on the colon of dogs. Movements were recorded by means of a balloon placed within a fistula. They made graphic records over long intervals of time and their results showed a constant increase in tone which lasted longer with larger amounts. They also noted that the increase in tone may persist for many hours, even after all evidences of narcosis have disappeared and that it lasted longer than the effects upon the small intestine. They also recorded that the movements of the colon increased but that their amplitude varied inversely with the increase in tone. They extended their experiments to man, and obtained similar results after morphine had been given in three patients with colostomy.

The present communication forms part of a detailed investigation into the effects produced by dilaudid, dicodid, and eukadol, upon the alimentary tract, with a view to comparing their actions with those of morphine, diacetylmorphine and codeine. Dilaudid is the hydrochloride of dyhydromorphinone and is prepared from morphine. Eukadol is the hydrochloride of dihydroxycodeinone; thebaine forms the starting point of its synthesis. Dicodid is the hydrochloride of dihydrocodeinone and is prepared from codeine. Morphine, diacetylmorphine and codeine were included in this study in order that comparisons may be drawn, not only of the effects of all these drugs, but of their relative activities or potencies. This course was found necessary in view of the widely divergent results reported by different workers on morphine, diacetylmorphine and codeine.

II. METHODS

Cats were used exclusively in this investigation. In some experiments decerebrate cats were used, while in others, chloralose was used as a general anaesthetic. A laparotomy was performed, and a sausage shaped balloon, attached to a catheter and filled with water, was introduced into the lumen

of the intestine, through an artificial opening made in the gut wall. The catheter was connected to a small manometer, which was in turn connected to a recorder working on a kymograph. Continuous records were made over many hours. The small pressure exerted by the manometer was never sufficiently great to cause distention of the gut. Most experiments lasted 6 hr. but in a few instances for 8 or 9 hr. In this way the behaviour of the caecum, ascending, transverse and descending colon in response to these drugs was studied. No gross differences were observed in the behaviour of the different portions of the large intestine in response to any one of these drugs. In the following descriptions the behaviour of the caecum and ascending colon will be given.

The drugs were generally administered intravenously through the external jugular or femoral veins. In a few cases, however, they were administered subcutaneously, and the results obtained were in every way comparable to those obtained using the intravenous method, except that the onset was somewhat slower. The doses employed varied between very small amounts (0·005 mg. per kg.), and very large amounts (10 mg. per kg.) which would have produced lethal effects in most normal cats.

III. Experiments

Morphine hydrochloride

The most constant effect produced by morphine, using the range of doses mentioned above, was a marked increase in tone. The onset was immediate, and the maximum tone level was rapidly attained. The peak point was always reached within 5 or 6 min. after the drug had been injected intravenously. When the subcutaneous method was employed this time interval was from 20 to 45 min. The greatest tone effects were not produced by the largest doses; on the contrary, the highest tone levels were obtained when moderately small doses were employed (e.g. 0·05 mg. per kg.). This is well shown in Figs. 1 and 2 where the same apparatus was used and consequently the same degree of magnification obtained in the records on the kymograph.

The duration of the period of increased tone following the administration of the drug was found to vary widely, not only with various doses of the drug, but with the same dose of drug administered to different cats of the same weight. From this it would appear as if individual animals do not respond uniformly. A review of the whole series of experiments, however, clearly showed that the most prolonged tone effects were always produced in response to large doses of the drug. This can be seen by comparing Figs. 1 and 2. In Fig. 1 where 0·1 mg. was injected intravenously into a cat weighing 1·8 kg. the tone returned to normal 15 min. after the injection had been made; whereas in Fig. 2 it will be seen that in a slightly heavier cat, receiving about 10 times the dose given to the previous animal, the period of increased tone was maintained for a much longer interval of time, and the normal tone level was re-established 2 hr. 43 min. after the drug had been injected. In Fig. 1 a secondary

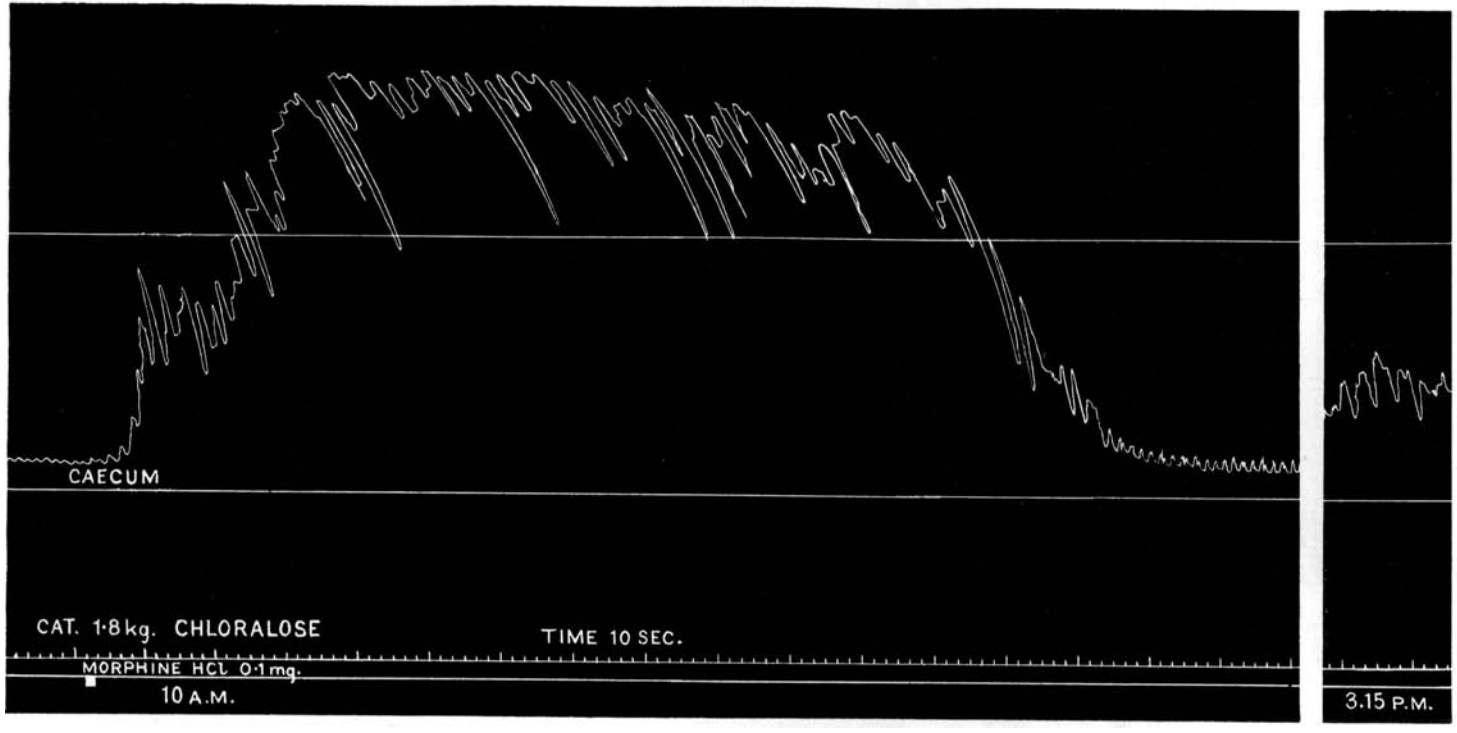

Fig. 1. Cat 1·8 kg. Movements of the caecum. Illustrating the well-marked increase in tone and movements produced by 0·1 mg. morphine HCl. 4½ hr. later there was a second increase in tone and movements, much less than that seen immediately after the administration of the drug, which lasted 3½ hr.

period of slight increased tone is seen, which began 5¼ hr. after the original injection and lasted 32 min. These secondary increases in tone were frequently seen when small doses of morphine were employed and much less often after large doses. Often they were repeated two or three times at hourly intervals.

When very large quantities of morphine (3 mg. or more per kg.) were injected the initial increase in tone of the large intestine and its duration were always much less than when smaller doses were employed.

The influence of morphine upon the peristaltic movements was found to be quite different when different amounts of the drug were employed. Small doses (0·5 mg. or less per kg.), generally increased the amplitude of peristalsis in a most marked degree, setting up a phase of almost continuous peristaltic activity lasting many hours, according to the dosage employed. The frequency became somewhat slower when the movements were increased beyond a certain degree. In Fig. 1, a typical experiment, there is a slowing from 8 to 6 contractions per minute. Large doses of morphine however, were found to decrease the amplitude of peristaltic movements; in some experiments, completely

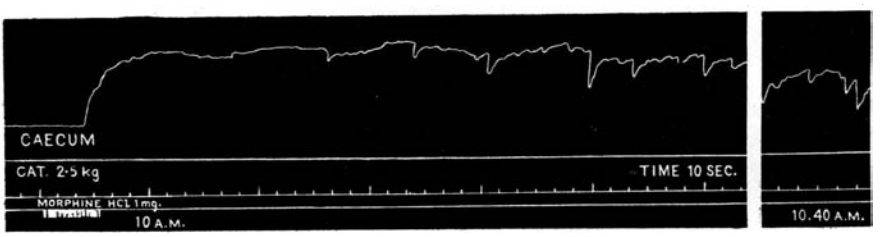

Fig. 2. Cat 2·5 kg. Movements of the caecum. Showing the increase in tone and movements following the injection of 1 mg. morphine HCl.

abolishing them for 10–30 min. It will be seen, therefore, that moderate or small doses of morphine usually increase both tone and peristaltic movements, while large doses produce a spastic contraction of the bowel accompanied by a diminution or suppression of movements lasting for a varying period of time which is dependent upon the dosage employed. The small rhythmical contractions of the colon were not influenced by morphine.

A point of some importance was noticed in the course of these experiments. In a previous paper the effects of morphine and some allied drugs upon the small intestine were described (Myers, 1939). It was therefore possible to compare the effects of these drugs upon the small and large intestines. This comparison has shown clearly that the large intestine is much more sensitive to morphine than the small intestine. Not only are the tone and peristaltic effects greater and more lasting in the case of the large gut, but much smaller amounts of the drug are required to produce them than in the case of the small intestine. The difference in dosage is a marked one; doses small enough to be without effect upon the small intestine were found to be extremely active and produce well marked effects on the large intestine. This was not an observation made in a few individual experiments but was seen clearly in the whole series,

especially where simultaneous records were made on the large and small intestine. The increased tone of the intestine produced in response to the injection of a given dose of morphine was always much more prolonged in the caecum and colon than in the small intestine.

A second or third injection of morphine given to the same animal 30 min. or more after the first dose always produced the same response, but the degree was dependent upon the effects still existing after the previous injection.

The injection of a full dose of atropine always abolished the effects produced by morphine, a second dose of morphine however, given after a short interval of time (20 min. or more) always reproduced the characteristic effects of the drug although they were generally less marked than those seen before the administration of atropine.

Diacetylmorphine (heroin)

The effects of heroin upon the large intestine are essentially similar to those produced by morphine. Smaller doses of heroin than of morphine were required to produce these effects and indicate the greater activity of heroin. A calculation based on these experiments yielded a ratio of morphine : heroin :: 1 : 1·3. This must be regarded only as an approximate figure owing to the small number of animals used for its calculation (18).

Here, as in the case of morphine, the caecum and colon were found to be more responsive to heroin than the small intestine. Simultaneous records of the movements of the duodenum, jejunum, caecum and colon were made and doses too small to produce effects upon the small intestine caused a well-marked increase in tone and movements of the large intestine. The injection of sufficient atropine sulphate to completely "atropinize" the animal at once abolished the peristaltic movements and increased tone of the colon which had been produced in response to heroin. Further injections of heroin given 30–60 min. later were without effect. In this respect heroin differs from morphine. Similar observations were made in the behaviour of the small intestine to heroin, before and after atropine. While heroin resembles morphine in so far as the general effects upon the large intestine are concerned a review of the series of experiments indicates that heroin produces somewhat greater tone effects than morphine, while the increased amplitude of intestinal movements was greatest with morphine.

The effects of posterior pituitary extract (hypophysin) upon the large intestine were found to be enhanced after heroin.

The following is a typical protocol: 0·5 unit of hypophysin injected intravenously into a cat weighing 3·6 kg. produced little effect upon the tone and movements of the colon. 20 min. later 0·25 mg. heroin was injected slowly into the left external jugular vein and produced the typical effects already described. After an interval of 30 min. a second injection of 0·5 unit of hypophysin was given which caused a temporary inhibition of both tone and movements of the colon, lasting approximately 6 min., followed by an

increase in both tone and movements. The movements were so great as to make the recording lever pass 2 in. above the upper limit of the kymograph paper. This condition lasted 33 min. before it showed any signs of diminishing and a further 2 hr. passed before tone and movements were once again normal.

In the case of the jejunum, hypophysin, given after heroin, always produced inhibition of both tone and movements to a subnormal level which required a further 10 min. or more to become normal again. The secondary phase of increased activity seen in the colon was never observed in the jejunum.

Dihydromorphinone hydrochloride (dilaudid)

The effects of this drug upon the caecum and colon were well marked with even very small dosages. The injection of amounts as small as 0·005 mg. per kg. had no effect upon the general tone of the colon but increased the amplitude of the peristaltic waves in a most marked degree. The frequency of the waves was increased slightly in most experiments but remained unaltered in a few. When slightly larger doses were employed (0·04 mg. per kg.) an initial increase in the tone of the large intestine was seen (Fig. 3). This never lasted more than a few minutes and as the tone returned to normal the peristaltic movements began to increase in amplitude. The small rhythmical contractions were not altered appreciably. This phase of increased movements continued for many hours and generally persisted throughout the remainder of the experiment (6 or 7 hr.) when they still appeared to be active and the tone slightly subnormal. Fig. 4 shows the effects upon the descending colon following the injection of 0·6 mg. per kg. It will be seen that no marked changes in the general tone of the colon appeared until approximately 3 hr. after the administration of the drug, when a marked relaxation of the intestinal muscle occurred. The movements now showed an enormous increase in amplitude especially at the 3 hr. stage. The movements continued for a further 4 hr. without much diminution in their amplitude. The frequency of the movements was not much changed at first in spite of the increased amplitude. Later, however, there was a marked slowing in their rate as the amplitude continued to increase. At this stage the rate was reduced from 1 wave per 15 sec. (normal) to 1 wave per 90 sec. (Fig. 4). Similar results were obtained when doses in excess of 1 mg. per kg. were employed. Atropine, when administered during the stage of increased activity produced by dilaudid, caused an immediate diminution of both tone and movements which slowly recovered during the ensuing 15–20 min., after which they both increased again to a stage resembling that seen before the atropine was administered. Further injections of dilaudid given 30 min. or more later were without effect. From these results it is apparent that dilaudid resembles morphine in its action upon the large intestine in so far as they both produce an increase in the amplitude of the peristaltic movements which lasts several hours. Dilaudid is much more potent than morphine in this respect not only in the dosage employed but in the magnitude of the resultant peristaltic waves. On the other hand, however, dilaudid only

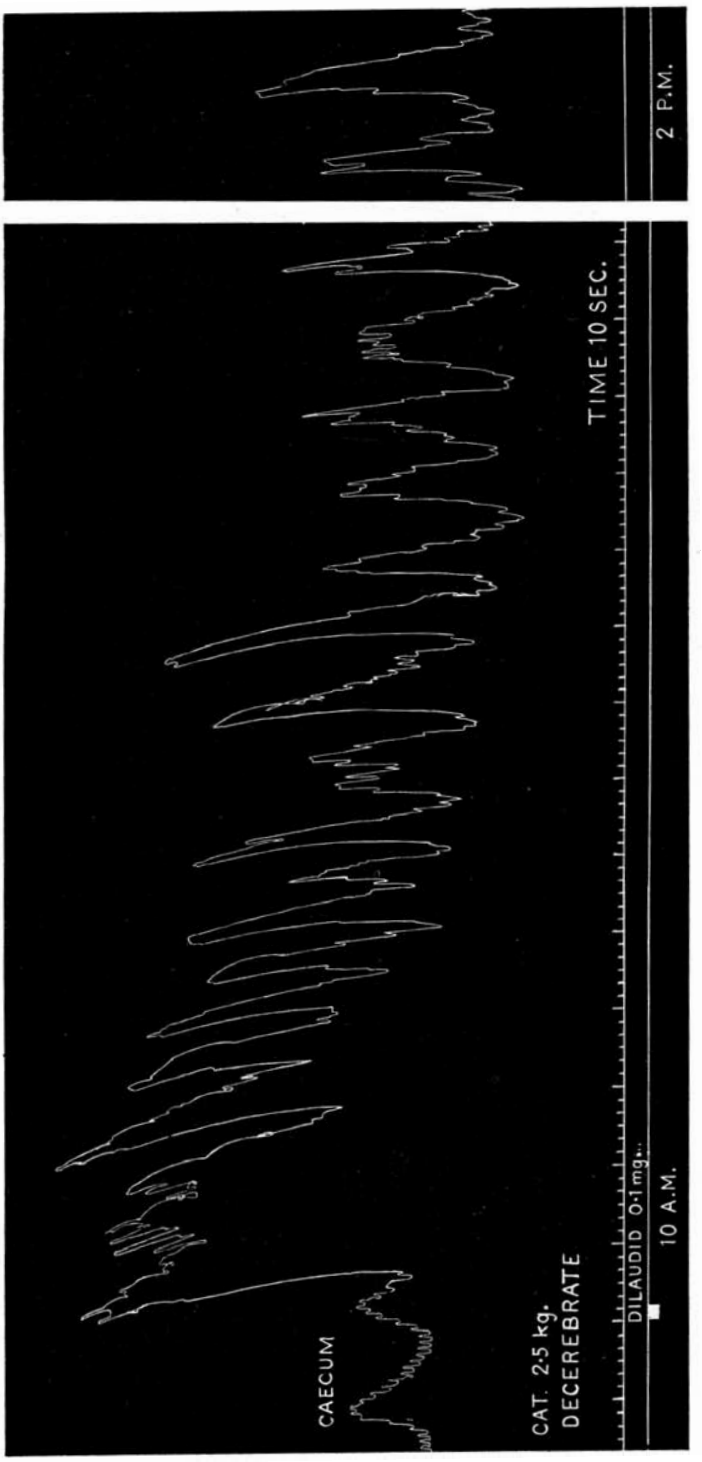

Fig. 3. Cat 2·5 kg. Movements of the caecum. Showing the response to an injection of 0·1 mg. dilaudid. Note the immediate increase in tone and later the increased amplitude of the movements. Small doses (0·025 mg.) do not affect the tone very much but increase the amplitude of the movements enormously.

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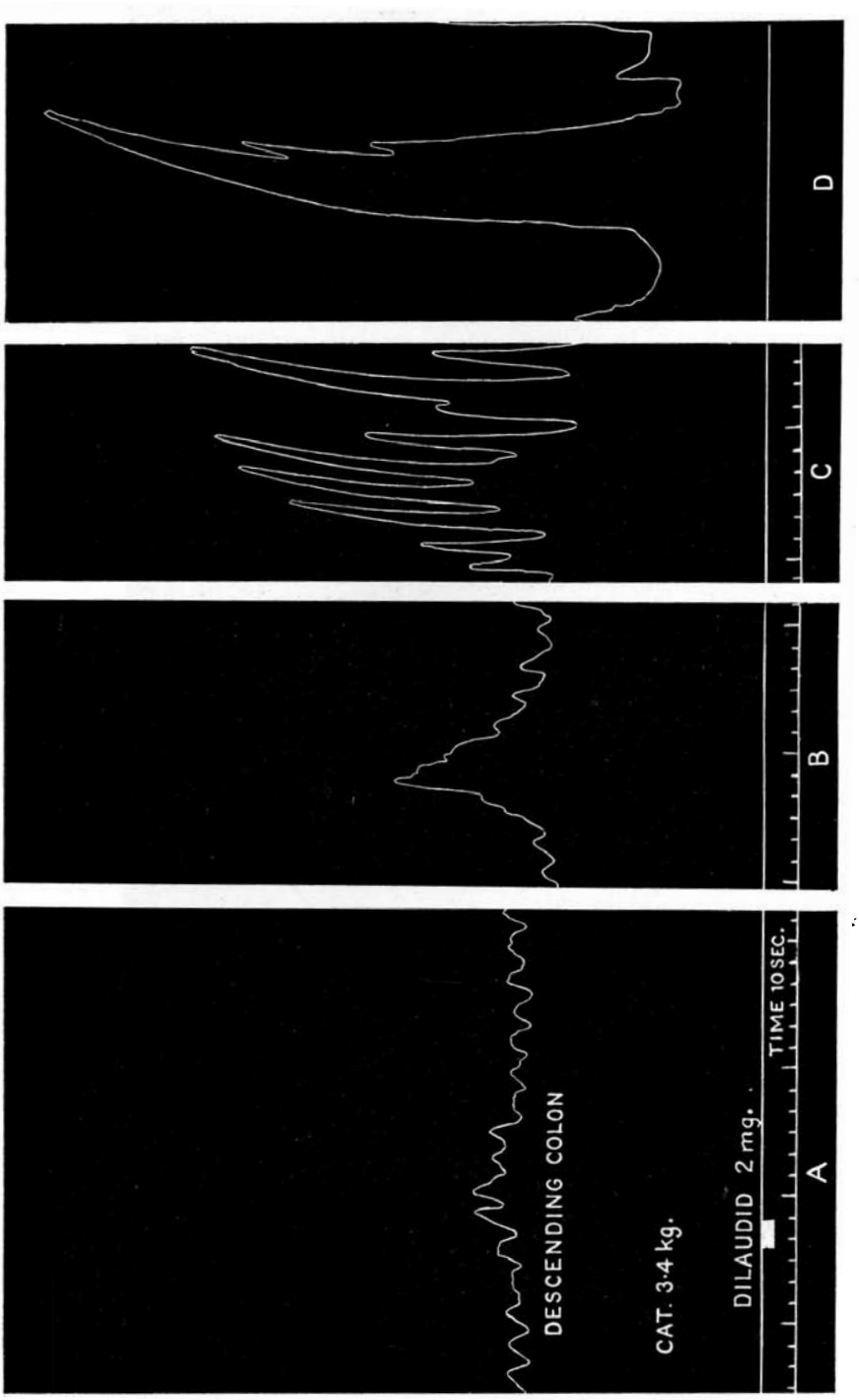

Fig. 4. The effects of 2 mg. dilaudid on descending colon. B is 30 min. after A, C 60 min. after B, and D 80 min. after C.

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causes an increase in the tone of the caecum or colon with small quantities and the effect is very transient. In this respect dilaudid differs from morphine, which constantly increases the tone of both the caecum and colon for many hours. An approximate calculation of the comparative activity of morphine and dilaudid, based upon the doses used in these experiments, indicated a ratio morphine : dilaudid :: 1 : 7·5.

Dihydrocodeinone hydrochloride (dicodid)

The most marked effect of this drug upon the caecum and colon is the increase in amplitude of peristaltic movements which follows its use (Fig. 5). This increase in amplitude is not immediate and only begins to show itself 1–2 hr. after the drug has been given intravenously or 3 hr. after subcutaneous

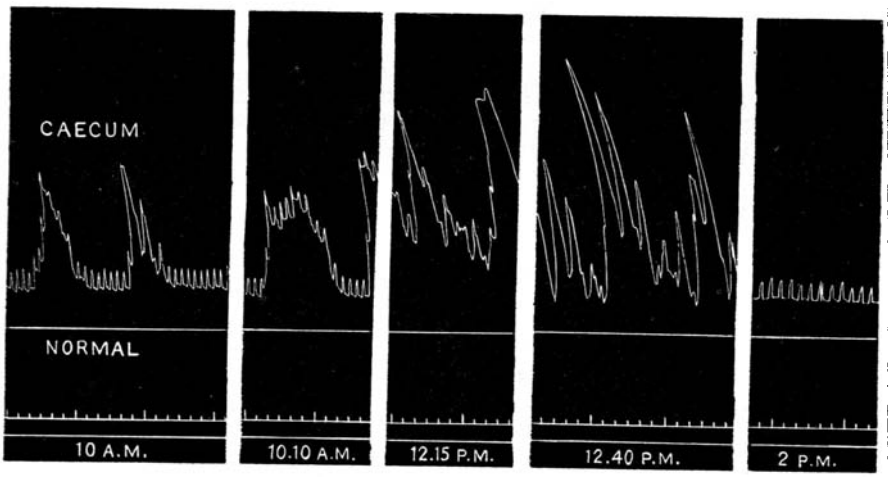

Fig. 5. Cat 2·7 kg. Movements of the caecum. 0·1 mg. dicodid was injected at 10.03 a.m. Time 10 sec.

injection. The maximum movements usually appeared 2 or 3 hr. after intravenous injection, and lasted from 1 to 2½ hr. The general tone level of the large intestine was slightly raised after 1 hr., and rarely lasted longer than 60 min. when the tone began to decline to normal or to a slightly subnormal level. A simultaneous record of the movements of the caecum and jejunum (Fig. 6) showed the greater and more prolonged action of this drug upon the caecum. The enormous increase in the activity of the caecum seen at the 4 hr. stage was continued for a further 2 hr. before it began to decline slowly to normal. The frequency of the peristaltic movements progressively decreased. This slowing is well illustrated in Fig. 6.

Several features of the action of dicodid upon the large intestine bear a resemblance to the effects of morphine and heroin. All these drugs increase both the tone and movements. In the case of morphine and heroin the effects were immediate, whereas with dicodid they only appeared after a latent period

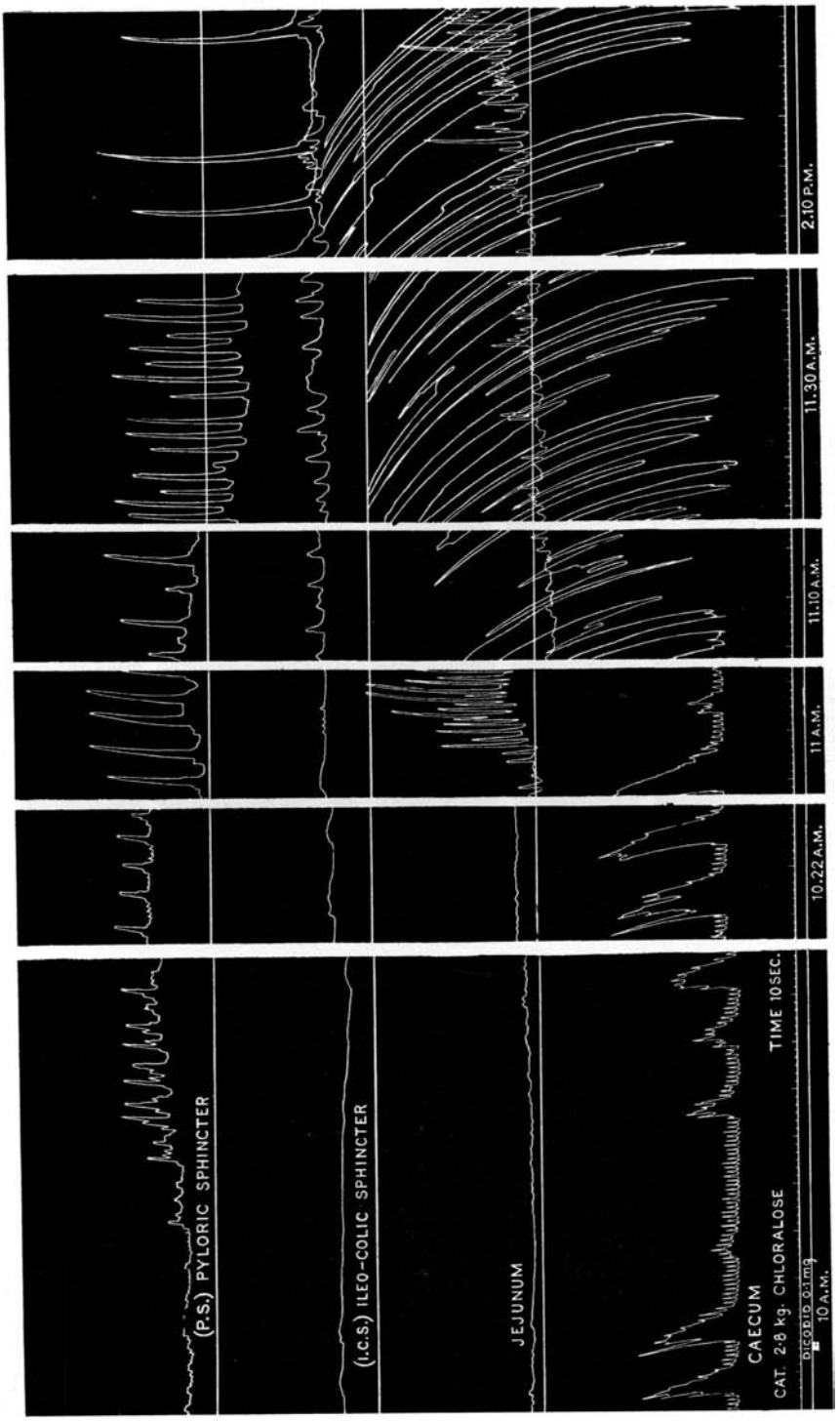

Fig. 6. Showing the effects produced upon the pylorus, ileo-colic sphincter, jejunum and caecum by 0·03 mg. per kg. dicodid, during the first 4 hr. following injection.

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of an hour or more following the administration of the drug, and did not last so long as when heroin or morphine were used.

The effects of dicodid upon the general tone of the large intestine were much less marked than in the case of the other two drugs; but dicodid produced a more marked increase in the amplitude of the peristaltic movements than that caused by either morphine, heroin or dilaudid, although, it may be, of shorter duration.

Methyl morphine phosphate (*codeine*)

With this drug the doses employed ranged between 0·05 and 5 mg. per kg. The most constant effect observed was an increase in the amplitude of the peristaltic contractions. The effects produced in response to the smaller doses, however, were negligible. Even when doses in excess of 1 mg. per kg. were administered the effects were small when compared with those produced by either morphine or heroin. Fig. 7 is a typical tracing, and shows a simultaneous record of various parts of the alimentary tract. The amplitude of the peristaltic movements were slowly increased to a maximum which was reached in 6 min. after an injection was made. 30 min. later the increased amplitude was well maintained although it decreased to negligible proportions 1 hr. afterwards. It will be noticed that the general tone of the caecum remained constant throughout, except for a slight increase when the drug was injected. Doses in excess of 3 mg. per kg., however, sometimes produced a slightly greater increase in tone which was always of short duration and so small as to be negligible.

Qualitatively codeine produces the same effects as morphine upon the large intestine but quantitatively there is little comparison between the two drugs. Reference to Fig. 7 shows how codeine produced an increase in tone of the small intestine, while this effect was almost completely absent in the large intestine.

Dihydroxycodeinone hydrochloride (*eukadol*)

This drug invariably increased the amplitude of the peristaltic movements of the large intestine which was seen best when small doses of 0·01 mg. per kg. were employed. Larger doses produced an increase in the tone of the organ in addition to an increase in the amplitude of the movements. Fig. 8 shows the typical effects produced in response to 0·2 mg. per kg. The tone of the caecum was at once increased to a maximum, but within 2 min. began to decrease again. Normal tone level was re-established 20 min. later. At first as the tone increased, the amplitude of the peristaltic movements was reduced for about 2 min., after which they began to increase to a range greater than normal. This period of increased movements usually continued for 30 min., although in three experiments they were observed over a period of 3–4 hr. before becoming normal once again. The injection of a full dose of atropine always reduced to normal the hypertonic state of the large intestine produced by eukadol. At the same time the amplitude of the movements was reduced,

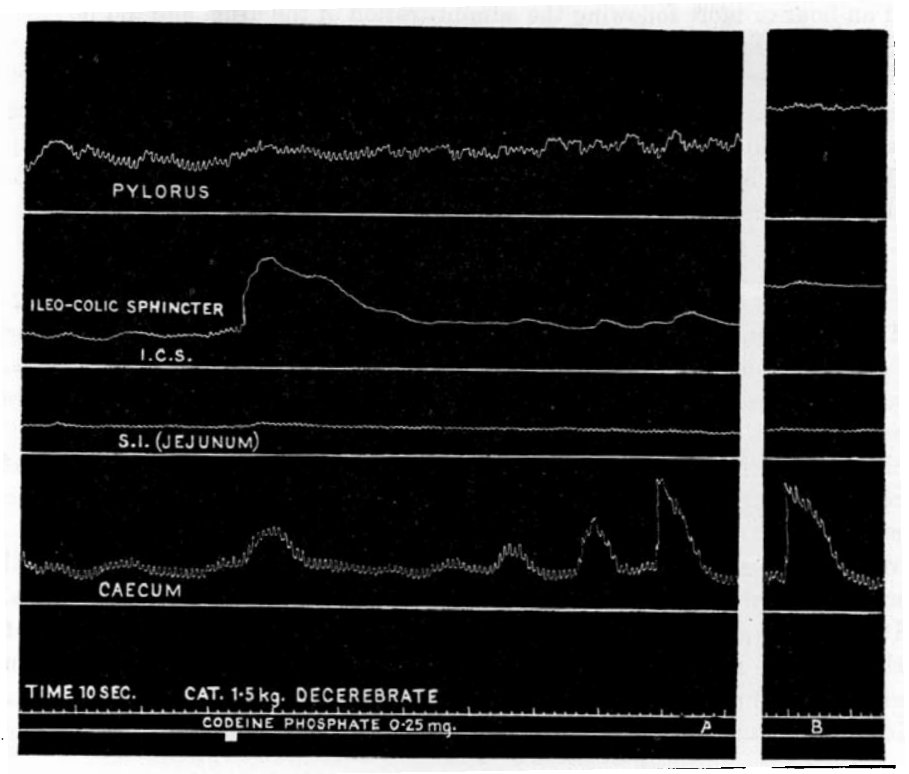

Fig. 7. Illustrating the effect of 0·25 mg. codeine phosphate on the pyloric and ileo-colic sphincters, the jejunum, and caecum. B is 30 min. after A. Time 10 sec.

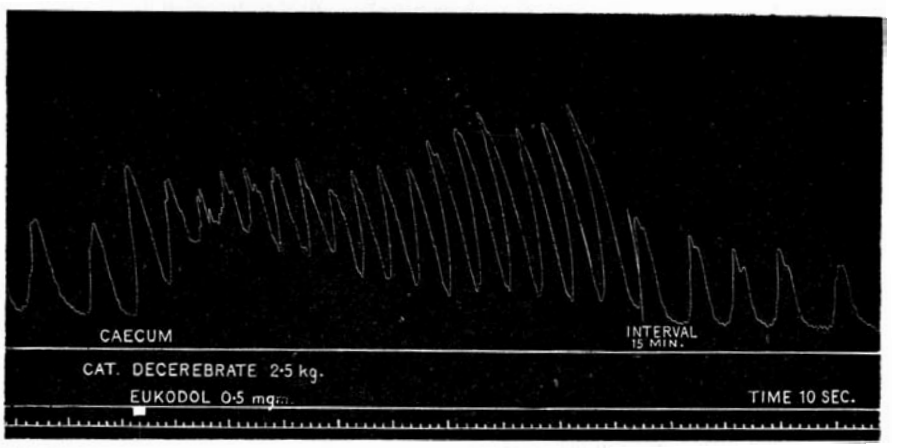

Fig. 8. Cat 2·5 kg. Movements of the caecum. The injection of 0·5 mg. eukadol produces an immediate increase in tone, and later, an increase in the amplitude and frequency of the movements. Recovery to normal is shown. Smaller doses (0·05 mg.) increase the amplitude and frequency of the movements but do not increase the tone.

but rarely to normal, and it was always increased again by further injections of eukadol. In the course of this investigation it was seen that the increased movements of the caecum, which were produced in response to eukadol, were influenced to a lesser degree by atropine than those of the duodenum, jejunum, or ileum. It would appear that the main effect of eukadol is the production of increased peristaltic movements. The increase in gut tone which was produced by large doses of the drug rarely lasted longer than 30 min. The effects upon peristaltic movements were greater than those produced by either morphine or heroin, and were often sustained for several hours without any marked periods of quiescence. On the other hand the tone effects were of much shorter duration than in the case of morphine, heroin, dilaudid, or dicodid.

It will be apparent, therefore, that eukadol resembles morphine in so far as its ability to increase peristaltic movements is concerned but more nearly approaches codeine with its transient effects upon the general tone of the large intestine. Its position in the series of drugs must therefore be regarded as being somewhere between morphine and codeine.

IV. Discussion

All the drugs used in this investigation bear a close relationship to one another in the effects which they produce upon the large intestine. They are all capable of producing an increase in the general tone of the muscular elements of the large intestine in addition to increasing the amplitude of peristaltic movements. Their chief differences are mainly quantitative. It has been shown that the action of morphine is quick in onset. Moderate doses always produce the greatest increase in general tone, although the increase in tone is most prolonged when large doses are employed. The greatest increase in the amplitude of peristaltic movements usually follows the employment of small to medium-sized doses. This increase in amplitude is generally prolonged for many hours. At first the frequency of the peristaltic waves is slightly increased but later it may be decreased when the movements are increased beyond a certain amplitude. There is little or no change in the rhythmical movements of the large intestine. Large doses of morphine generally produce a spastic contraction of the large intestine while the movements are much diminished in amplitude.

The large intestine is much more profoundly influenced by morphine than the small intestine. Smaller amounts of the drug are required to increase the activity of the large intestine and the effects produced are much greater and usually more prolonged than in the case of the small intestine. These effects can be abolished by atropine although subsequent doses of morphine, given after an interval of time, will reproduce them but in a somewhat diminished degree.

The effects of heroin are very similar to those of morphine although smaller amounts of heroin are required, indicating the greater potency of heroin. The amounts of heroin required to produce these effects are about 30 % smaller than those of morphine. Certain differences in the effects of these two

drugs were observed. Heroin usually produces a greater increase in intestinal tone than morphine, while the increase in the amplitude of peristaltic movements is more marked with morphine than with heroin. As in the case of morphine, atropine inhibits the effects of heroin, but the subsequent injection of heroin, even after an interval of 2 hr., is without effect. In this respect there appears to be a difference in the behaviour of the two drugs. The effects of heroin are much greater on the large than upon the small intestine. This is a further point of similarity between morphine and heroin.

The most prominent action of dilaudid is its ability to increase the amplitude and frequency of peristaltic movements even when small amounts are employed. The maximum amplitude is attained about 3 hr. after injection. At first the frequency of the peristaltic waves is slightly increased but later there may be a small decrease when the amplitude of the waves becomes very large. The tone of the large intestine is not easily influenced by small doses. Larger doses, however, may cause an immediate but temporary increase in tone lasting a few minutes. It is common to observe some slight relaxation of the intestinal muscle to a subnormal level at the 3 or 4 hr. stage when the movements are usually enormously increased. Here again, these effects on tone and movements can be abolished by atropine. Further injections of dilaudid, however, are without effect; in this respect it resembles heroin. It is estimated from these experiments that the relative activity of morphine and dilaudid may be expressed as morphine : dilaudid :: 1 : 7·5.

Codeine appears to have a negligible effect upon the large intestine and in this respect is the weakest member of this series of drugs. Small doses produce negligible effects, while larger ones cause a slow but small increase in the amplitude of the movements lasting approximately 1 hr. Very large doses are required to produce even a small increase in the general tone of the organ, which never lasts very long. It is interesting to note that codeine will cause an increase in tone of the small intestine in doses which are without effect upon the tone of the large intestine. From this observation it can be concluded that the large intestine is less sensitive to codeine than the small intestine. This is exactly the reverse to the findings with morphine, heroin, dilaudid and dicodid. Dicodid, like the other drugs, produces an increase in the amplitude of the peristaltic movements of the large intestine. In this respect dicodid is much more active than any of the other drugs. This action is delayed for some time after administration, the latent period before the movements begin to increase being usually 1–2 hr.; the maximum movements being at the 3 or 4 hr. stage. The range of the amplitude of the movements is enormous and may last from 1 to 3 hr. Dicodid is the only drug in this series which does not act immediately upon either the large or small intestine and in this respect it differs from morphine, heroin, codeine, dilaudid and eukodol.

In 1938, Myers & Davidson investigated the effects of dicodid upon the passage of food along the alimentary tract of the human subject by means of

X-ray technique. They observed that the motility rate of the intestine is slightly quickened at the 3 hr. stage but returned to normal at 6 hr. This observation is in complete agreement with the findings outlined in the present communication.

The most important effect of eukadol upon the large intestine is the increase in the amplitude of the peristaltic movements and in this respect it is more potent than either morphine or heroin. This effect is seen best when small doses of the drug are given and may last from $\frac{1}{2}$ to 4 hr., according to the conditions of the experiment. Large doses cause an increase in tone in addition to amplitude of movements. The tone effects take place soon after the drug has been given but last only a short time. In this respect the effects of eukadol are inferior to those of morphine, heroin, codeine, dilaudid, or dicodid. Atropine abolishes the effects of eukadol, but further quantities of eukadol after an interval of time will always reproduce its effects. In this respect it resembles morphine.

The order of decreasing activity of these drugs, as shown by their ability to increase the general tone of the large intestine, may be expressed as follows: heroin, morphine, dilaudid, codeine, dicodid, and finally, eukadol. If expressed by their ability to increase the amplitude of peristaltic movements, then the order would be: dicodid, dilaudid, morphine, heroin, eukadol, and codeine as the weakest member of the series.

V. SUMMARY

1. The effects of morphine, heroin, codeine, dilaudid, dicodid and eukadol upon the caecum and colon are described.

2. Small quantities of morphine produce a rapid increase in tone and amplitude of movements lasting many hours. Large doses result in a spastic contraction of the intestine with diminution of peristaltic movements.

3. The effects of heroin closely resemble those of morphine; it usually produces a greater increase in tone than morphine but the movements are not so great. Heroin is about 30 % more active than morphine.

4. Codeine appears to be the weakest member of the series. It causes a slight increase in tone and peristaltic movements which never last very long.

5. Dilaudid produces effects which closely resemble those of morphine and heroin but it is approximately 7·5 times more potent than morphine. Intestinal tone is increased at first but may be subnormal at the 3 or 4 hr. stage. The maximum amplitude of peristaltic movements is seen at the 3 hr. stage.

6. Dicodid increases the tone, and particularly the peristaltic movements. The effects upon the general tone are moderate, much less than those of morphine, heroin or dilaudid. The increase in the amplitude of the movements is, however, much greater than with any other of the drugs. It differs from the others in producing its effects only after a long latent interval of 1–2 hr.

7. Eukadol increases the peristaltic movements in a marked way and is more active in this respect than either morphine or heroin, but is inferior to dicodid. Its effects upon tone are very transient and never very marked.

8. The effects of all these drugs upon the tone and peristaltic movements are at once abolished by adrenalin or atropine. Except morphine and eukadol, these drugs failed to produce their effects when administered after full doses of atropine.

9. The injection of hypophysin during the phase of increased muscular activity following the injection of these drugs, always causes an immediate abolition or diminution of the peristaltic movements and loss of tone to a subnormal level. There is however a rapid recovery from this state and approximately 5–10 min. later the movements are increased to an amplitude far in excess of that seen prior to the injection of hypophysin.

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