AN INVESTIGATION OF THE EFFECTS OF CERTAIN SUBSTITUTES FOR MORPHINE AND HEROIN UPON THE PASSAGE OF FOOD ALONG THE ALIMENTARY TRACT OF THE HUMAN SUBJECT

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(With Plates XIV–XVI)

Introduction

The harmful effects of morphine and heroin upon the human subject have long been recognized and given rise to a keen desire upon the part of the medical practitioner to eliminate these extremely toxic drugs of addiction from general use. This desire can only be attained when suitable substitutes have been produced, possessing all the desirable actions of these two drugs without their disadvantages. With this object in view scientific experts in the chemical industry are constantly striving to produce, by means of fresh chemical combinations, substances which would be as useful therapeutically as morphine and heroin but without any of their deleterious effects. Within recent years a number of synthetic drugs have been manufactured and are now undergoing extensive therapeutic trials in the fields of medicine and surgery. In this country, however, their use has been somewhat restricted until more is known of their general and special effects upon the various systems of the human subject.

Several new drugs have been manufactured in Germany by various firms, and three of them are marketed under the trade names of Dilaudid, Dicodid and Eukodol. In each instance the drug is manufactured by a secret process which is covered by extensive patents.

Dilaudid is the hydrochloride of dihydromorphine and is manufactured from morphine. The chemical relationship to codeine, morphine and Dicodid is clearly shown in the formulae on p. 433. Dilaudid is a white amorphous compound which is soluble in water or alcohol, but is insoluble in ether. An aqueous solution has a neutral reaction. It has a quietening effect upon respiration and produces analgesia. It is manufactured by Knoll A.G., of Ludwigshafen-on-Rhine.

Dicodid is a product of the same firm. The basis of this drug is dihydrocodeinone, and its chemical structure shows it to be a derivative of thebaine.

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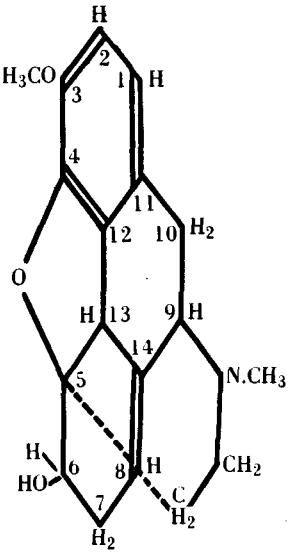
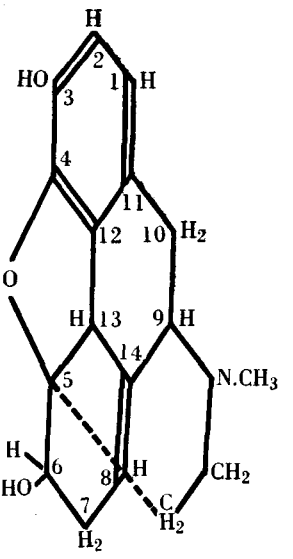
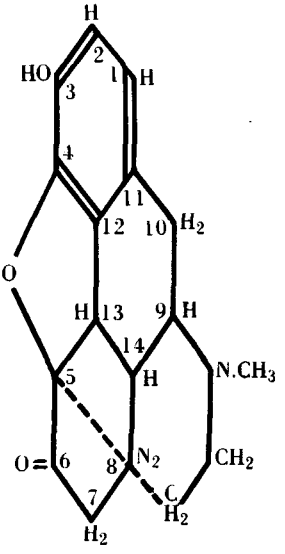
It can, however, be obtained from codeine, and so, from the standpoint of production, must be regarded as a derivative of codeine, and so of morphine.



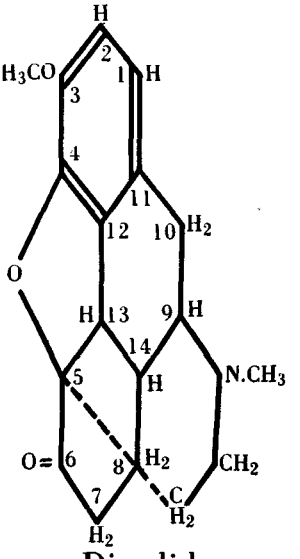
Codeine



Morphine



Dilaudid



Dicodid

Dicodid is the hydrochloride of dihydrocodeinone. It is advocated as an analgesic and a sedative of the respiratory tract.

Eukodol is manufactured by E. Merck of Darmstadt. It is the hydrochloride of dihydroxycodeinone and is not a derivative of morphine. It is

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prepared from thebaine, and as opium contains only small amounts of thebaine the amount of Eukodol manufactured must therefore be limited. No process is known for the manufacture of thebaine from morphine or codeine. It is a drug having analgesic properties and is a respiratory sedative.

Previous literature

The clinical literature, based mainly upon the observations of continental practitioners, is gradually growing, and an excellent survey of that concerning Dilaudid is given by Eddy (1933).

The object of this investigation was to determine the effects of these three drugs upon the human alimentary tract and to compare them with the actions of morphine and heroin. In an earlier investigation, one of us (Myers, 1933) carried out a lengthy research on the pharmacological actions of these drugs upon isolated tissues and intact animals. Many systems were investigated, including the effects upon the alimentary tract.

It is well known that morphine salts produce constipation in the human subject, an action which is a cause of great discomfort to subjects who are addicted to the drug. Numerous workers have attempted to elucidate this problem by various methods, and it would appear as if the mechanism is one of spastic tonus of the gastro-intestinal tract, probably produced by a direct action upon the muscle or nervous mechanism of the intestinal wall. Many views, however, have been expressed by the numerous investigators in this field, and the explanation is still an open question.

Nothnagel (1882) injected morphine, subcutaneously, into etherized rabbits and concluded that moderate doses of morphine stimulate the splanchnic nerves to the intestine and so produce inhibition, and that large doses paralyse these nerves. He attributes the constipating action to splanchnic stimulation. These results were later confirmed by Spitzer (1891), who also found evidence of a decrease in peripheral irritability of the intestinal wall. Curarized dogs were used by Pal (1900), who recorded intestinal contractions, by the balloon method. Intravenous injections of morphine produced an increase in the tone and stimulated rhythmical contractions. These effects were not abolished by section of the nerve fibres to the intestine which led him to conclude that the effects were due to stimulation of ganglion cells in the intestinal wall.

Magnus (1906) applied a solution of morphine to the superior cervical ganglion in rabbits and cats but found no evidence of paralysis. Using cats suffering from milk diarrhoea he demonstrated that the constipating action of morphine is mainly due to its effects upon the stomach. In a later investigation (1908), by means of X-ray methods he observed that constipating doses of morphine and opium produced only negligible effects upon the small intestine, although a slight delay of the contents was noted. Marked delay in the emptying of the stomach was seen to be caused by a strong contraction of the pyloric antrum. He concluded that the constipating effects are due to

delayed emptying of the stomach, and that there is no marked effect upon the intestines.

Rodari (1909) states that the principal action of opium on the intestines is a decrease in peristaltic waves.

Schwenter (1912), using X-ray methods, obtained evidence of relaxation and decreased motility in both small and large intestines. He records delayed emptying of the stomach, but seldom was there any constriction of the pyloric antrum.

A similar technique was employed by Schapiro (1913), who studied the emptying time of the stomach in human subjects after the administration of morphine, opium or Pantopon. Some of his subjects were normal, about half of them were children, while some had disturbances of intestinal function, and a few had fistulae of the small or large intestine. About 50% of his subjects showed delay in the emptying of the stomach, while others showed some acceleration; a number showed no change. The contractions of the small intestine and the passage of food was not affected in many cases, some showed an increase in intestinal tone and movements; still other cases showed delay in emptying. This delay was probably due to contraction of the ileo-colic sphincter. There is no record of gastric peristalsis

He introduced a bismuth mixture into the alimentary tract of a dog by means of a fistula in the ileum. X-rays revealed that morphine slowed the passage of the food through the colon.

In human subjects, both with normal and irritated colons, morphine and opium slowed the passage of the food through the colon. There appeared to be some delay at the sigmoid flexure. In a few cases the colon was dilated, in others contracted.

Mahlo (1913) gave 20–30 drops of tincture of opium orally to young adults. Skiagrams and screen observations revealed considerable delay in the passage of food through the small and large intestine. The meal was also delayed in the stomach. He records contraction of the pyloric antrum in one case only, and this subject showed no delay in stomach emptying. The majority of his cases showed relaxation of the wall of the stomach. He noted that the food made a prolonged stay in the colon, even when castor oil was given after the meal had reached the small intestine. Uhlmann & Abelin (1920), using anaesthetized rabbits and guinea-pigs, found that very small doses of opium decrease the tone and movements of the small intestine. Larger doses caused a marked increase in both tone and movements.

Zunz (1909), using animals, and Zehbe (1913), using human subjects, were able to demonstrate, by means of X-ray technique, a closure of the pyloric sphincter. This delayed the passage of food from the stomach to the intestines. Plant & Miller (1926) state that the primary effect of morphine on the small intestine is stimulation of muscular activity and tone, while frequency of rhythmical contractions remains unaltered or slightly decreased. This frequency is later decreased while the tone remains greater than normal. In

man, they found similar effects to those observed in dogs, while heroin, codeine, papaverine, narceine and narcotine produce reactions which are similar to morphine. With the exception of heroin, larger doses were required to produce an equivalent effect. Zehbe (1913) noted that the time required for the passage of food through the entire alimentary tract was twice the normal. He believes that the delay is mainly in the colon and the rectum, but that the delay in the stomach and intestinal canal was each increased by one-third. Pancoast & Hopkins (1915), however, are inclined to the view that the delay is not so much in the colon as in the small intestines when morphine is given at the same time as the test meal and the food does not pass on until the effects on the intestine have passed away.

Methods

All the subjects used in this investigation were young healthy men who were studying medicine. They all played the usual outdoor games such as rugby, tennis, etc., as a relaxation from their studies and their general physique was good. At the outset of the investigation they were given a rough outline of the regime to which they would be subjected, and they all volunteered to co-operate closely in spite of any discomforts which might be experienced by them.

Before the tests were commenced they were informed that a drug would be introduced by the subcutaneous route at a certain point in the procedure, but they were quite ignorant of the name or type of substance used until the investigation was finished. After the usual preparation, each subject was given a preliminary barium meal, and screened at intervals in order to ascertain the normal passage of food, etc., through the alimentary tract. Screening and skiagrams were carried out at 12, 30, 180 and 360 min. after the meal had been taken. This preliminary test was of great importance and was done to ensure the rejection of any subject who had a wide deviation from the normal. All the subjects chosen showed no abnormalities, and the results of these tests are given in brief.

Results

G. O. R. Age $22\frac{7}{12}$ *years*

The control examination of this subject revealed a normal stomach, duodenum, jejunum, small intestine and ascending colon. Gastric peristalsis was at the rate of 4 waves in 72 sec. The emptying time of the stomach and duodenum and the motility rate in the small and large bowel at $\frac{1}{2}$, 3 and 6 hr. were normal.

Three weeks later a further barium meal was given. The gastric peristaltic rate was 4 waves in 85 sec. $\frac{1}{6}$ grain of morphine hydrochloride was then given subcutaneously, and the gastric peristaltic rate observed after a few minutes' interval. The waves were vigorous and at the rate of 4 waves in 84 sec. The meal was seen to be rapidly leaving the stomach.

At 3 *hours* there was a slowing of peristaltic movements as shown by the presence of a slight trace of the barium meal in the stomach and the situation of the remainder of the meal in the jejunum and upper coils of the small bowel. The corresponding stage in the control examination showed the head of the meal at the hepatic flexure and the stomach quite empty.

At 6 *hours* there was still a trace of barium meal in the stomach. The head of the meal had advanced to the hepatic flexure, with the caecum and ascending colon well filled with the barium. There was also some of the meal in the middle coils of the small bowel and in the distal 12 in. In the control examination at this stage the head of the meal had reached the descending colon and the middle coils of the small bowel were empty.

From this examination it would appear as if the morphine caused some delay in the emptying of the stomach. The delay was intermittent rather than continuous, as was suggested by the way in which the meal was divided up in the small intestine with a trace in the stomach even at 6 hr. The meal had not advanced so far along the large intestine as in the control at 6 hr.

There seems little doubt that this drug produced a well-marked action upon the pyloric sphincter causing intermittent spasm and also peristalsis in the small bowel. It is significant that the gastric peristaltic rate was unaltered by the drug.

M. W. M. Age $21\frac{6}{12}$ *years*

The control barium meal examination revealed a normal stomach, duodenum, small bowel, caecum and ascending colon. Gastric peristalsis was at the rate of 4 waves in 80 sec. The emptying time of the stomach and the motility rate of the meal in the bowel at $\frac{1}{2}$, 3 and 6 hr. were within normal limits.

A further barium meal was given 3 weeks later and gastric peristalsis was seen to be at the rate of 4 waves in 92 sec. A hypodermic injection of $\frac{1}{12}$ grain of heroin hydrochloride was given 7 min. after the meal had been swallowed and the rate of peristalsis 6 min. later was at the rate of 4 waves in 52 sec.

3 *hours*. The rate of emptying of the stomach and the passage of the meal into and through the small intestine was slowed to such an extent that the radiographic appearances were almost identical with those noted at $\frac{1}{2}$ hr. in the control examination, namely one-third in the stomach and the remainder in the upper and middle coils of the small intestine, but had not reached the terminal ileum.

At 6 *hours* there was still about one-quarter of the meal in the stomach, but the reduction in the amount may be due, in part at least, to bouts of vomiting which occurred after the 3 hr. examination. There was a slight advance in the position of the meal in the small intestine. Some of the lower coils were seen to be unusually contracted as if by spasm. The head of the meal was in the terminal ileum, but no barium had entered the caecum. In the

control examination, at 6 hr., the meal had advanced to the hepatic flexure; the terminal coils of the ileum were full and the stomach empty.

The effects of the heroin appeared to be upon the stomach where there was well-marked spasm of the pyloric sphincter which caused a definite retention of stomach contents for longer than 6 hr. The slow passage of the meal through the bowel is probably due to pylorospasm as well as the spasm in the region of the lower ileum which was observed during the examination. The increased rate and vigour of gastric peristalsis was well demonstrated.

H. G. M. Age $21\frac{9}{12}$ *years*

The control examination revealed a perfectly normal stomach and duodenum. Gastric peristalsis was at the rate of 4 waves in 75 sec. The motility rate was within normal limits at $\frac{1}{2}$, 3 and 6 hr.

After an interval of 3 weeks a further meal was given. Immediately before the injection of $\frac{1}{24}$ grain Dilaudid the rate of peristaltic waves in the stomach was 4 waves in 73 sec. A few minutes after the drug had been given the rate was 4 waves in 67 sec. Examination after $\frac{1}{2}$ hr. showed that peristalsis was very poor and almost abolished for a time. The barium meal had not advanced as far along the small intestine as in the control examination at the same stage.

At 3 *hours* there was a small but definite gastric residue and a continuous barium shadow through the duodenum, jejunum and middle coils of the small intestine. No barium was present in the lower coils of small intestine, but a small isolated collection was seen in the caecum. At the 3 hr. stage in the control examination the stomach, duodenum, jejunum and upper and middle coils of small intestine were empty. The meal was mainly in the lower coils of small intestine and continuous with a collection in the proximal part of the caecum.

At 6 *hours* there was a minute trace of barium in the stomach, but the duodenum, jejunum and upper coils of small intestine were empty. The meal was in the middle and lower coils of small intestine, but there was no addition to or advance in the position of the barium in the caecum.

In the control examination at this stage the stomach, duodenum, jejunum, and upper and middle coils of small intestine were empty. There was barium in the distal 6 in. of ileum and the head of the meal had advanced to the hepatic flexure.

It is interesting to record that 43 min. after the injection of the Dilaudid this subject complained of nausea, went extremely pale and nearly vomited. After lying down for a time he stated that he felt better, but the nausea continued for 6 hr. afterwards. On three further occasions he nearly vomited.

The effect of the drug is to delay the emptying time of the stomach with a consequent slowing up of the passage of the meal through the intestine.

G. A. S. Age $21\frac{9}{12}$ *years*

The control examination revealed a normal stomach, duodenum, jejunum, small bowel, caecum and ascending colon. Peristalsis was at the rate of 4

waves in 80 sec. The emptying times of the stomach and duodenum and the motility rate in the small and large bowel at ½, 3 and 6 hr. were within normal limits.

A normal phenomenon was noted in the form of mass emptying of the distal 6 in. of small intestine. The contents passed swiftly into the caecum and ascending colon almost as far as the hepatic flexure at the 6 hr. examination.

A further barium meal was given after 3 weeks. The peristaltic rate was 4 waves in 92 sec. A hypodermic injection of $\frac{1}{24}$ grain Dilaudid was administered 8 min. after the meal had been swallowed. Five minutes later the gastric peristaltic rate was 4 waves in 52 sec. The pylorus showed definite spasm and the meal was interrupted in its flow into the duodenum.

At 3 *hours* the stomach contents had been reduced considerably by vomiting. Only small amounts of barium were seen in the upper coils of small intestine, and none had entered the middle and lower coils.

In the control examination at this stage the stomach and duodenum, and middle and upper coils of small intestine were empty. The meal had collected in the lower coils of small intestine.

At 6 *hours* there was a much reduced residue in the stomach and the barium was seen in a continuous shadow through the jejunum, and middle and upper coils of small intestine.

The control examination at this stage showed the stomach, duodenum, jejunum, and upper and middle coils of small intestine to be empty. The head of the meal had advanced to the hepatic flexure with a good demonstration of the caecum and ascending colon.

The last two subjects, who had the same dose of Dilaudid, each complained of nausea after the injection of the drug, and one case actually vomited. These effects were accompanied by a closure of the pyloric sphincter.

S. C. Age $21\frac{6}{12}$ *years*

The control examination by a barium meal revealed a perfectly normal stomach, duodenum, jejunum, small bowel and caecum. Gastric peristalsis was at the rate of 4 waves in 80 sec. The emptying time of the stomach and duodenum and the motility rate in the bowel at ½, 3 and 6 hr. were within normal limits.

After an interval of 3 weeks a further barium meal was given and the gastric peristalsis recorded at the rate of 4 waves in 100 sec. Three minutes later $\frac{1}{24}$ grain of Dicodid was injected hypodermically. Four minutes afterwards the peristaltic rate was almost unchanged, being 4 waves in 98 sec. Twenty minutes later the rate was 4 waves in 74 sec.

After 30 *min.* the tone of the stomach was good and the meal was emptying well. The upper coils of small intestine were better filled than in the control examination and some barium had reached the middle coils.

At 3 *hours* the meal was mainly in the lower coils of small intestine with

traces in the middle coils. The stomach, duodenum, jejunum and upper coils of the small intestine were empty.

The control examination at this stage showed that the general advance was the same as above, but the whole of the upper and middle coils of the small bowel were fully demonstrated by barium.

At 6 *hours* the meal had advanced to the hepatic flexure, filling the lower coils of small bowel, caecum and ascending colon. The position of the meal was practically identical with that seen in the control examination.

From these results it appears as if the injection of $\frac{1}{24}$ grain of Dicodid had no influence upon the motility rate at 6 hr. but hastened it slightly at the 3 hr. stage. The gastric peristaltic rate was unaltered until 20 min. after the administration of the drug when a decided quickening of the rate was observed.

E. I. T. Age $19\frac{5}{12}$ *years*

The control examination revealed a normal stomach, duodenum, jejunum, small intestine, caecum and ascending colon. Gastric peristalsis was at the rate of 4 waves in 77 sec. The emptying time of the stomach and duodenum, and the motility rate in the bowel at $\frac{1}{2}$, 3 and 6 hr. were within normal limits. A very long vermiform appendix was seen to lie on the medial aspect of the caecum and ascending colon as high as the hepatic flexure.

A second barium meal examination was made 3 weeks later and $\frac{1}{6}$ grain Eukodol administered hypodermically 3 min. after the meal had entered the stomach. Just prior to the injection the gastric peristaltic rate was 4 waves in 92 sec. For some time the pylorus appeared to be in a state of spasm and the peristalsis was very active, being at the rate of 4 waves in 52 sec. No food was leaving the stomach.

At 3 *hours* the stomach was empty but barium was present in the duodenal loop, jejunum, and upper and middle coils of small intestine. The terminal portion of the ileum was empty.

In the control examination all the meal had collected in the lower coils of the ileum at this stage.

At 6 *hours* the meal had advanced well into the hepatic flexure and was practically the same as seen in the control at this stage.

The appendix was not demonstrated on this occasion.

Discussion

The results of this investigation have shown quite clearly that the subcutaneous injection of morphine hydrochloride, when food has just been taken, produces a well-marked slowing of the passage of food along the alimentary tract. The first delay was observed to take place in the stomach where the food was retained for an abnormally long period. Traces of barium were observed here more than 6 hr. after the meal had been swallowed. No changes in the tone of the stomach were observed, such as a relaxation, which might have accounted for such a delay; but a pronounced increase in tone of

the pyloric sphincter was seen a few minutes after the administration of the drug. Relaxation of the sphincter was seen from time to time, and was accompanied by the passage of food from the stomach to the duodenum. It will thus be seen that the delayed emptying of the stomach is of the intermittent type.

The slow advance of the meal which was observed at the 6 hr. stage is not wholly due to the increased tone of the pyloric sphincter because the ileo-colic sphincter was also seen to be in a similar state of increased tone causing a further delay at this point. The position of the head of the meal after 6 hr. was approximately the same as that seen in the control at 3 hr., and shows a delay of about 3 hr. which is considerable over a 6 hr. period. All these features were recorded in animal experiments (Myers, 1933). No change in the rate of gastric peristalsis was observed in the human subject, but the waves were much more vigorous than normal. In view of the fact that active peristalsis was seen in both the small intestine and the caecum throughout the investigation, we believe that the delayed passage of food following the injection of morphine salts is mainly due to the increased tone of the pyloric and ileo-colic sphincters causing obstruction at these two points. Although constipation was not observed after the injection of a single dose of morphine, it is possible that the constipation which follows repeated injections may be partly due to the delay caused by the ileo-colic sphincter, resulting in a greater dehydration of the alimentary contents thus rendering them more plastic. It is difficult to ascertain how far diminished attention to stimuli, such as that set up by the defaecation reflex, which is produced by morphine, is responsible for the constipation; but it may be a factor of some importance.

Heroin appears to act in a similar way to morphine but with a few minor differences. Generally, its effects are much more powerful in the doses employed. The action upon the stomach is such as to produce not only an increased rate of gastric peristalsis but extremely vigorous peristaltic waves. The pyloric sphincter is increased in tone and movements, which are intermittent in character, causing a more pronounced delay in the passage of the stomach contents than with morphine. One-quarter of the meal was present in the stomach at the 6 hr. stage, being a much larger amount than with morphine at the same stage. Heroin, too, produced a more marked closure of the ileo-colic sphincter than morphine. This was so marked that none of the meal had entered the caecum at the 6 hr. stage. On the other hand, heroin increased the activity and tone of the small and large intestines to a much greater extent than morphine. From these observations one might believe that heroin would be a more constipating drug than morphine owing to its more pronounced effects upon the sphincters, but in practice this is not so, consequently one is left to speculate how far the rectal sphincter is involved and what part is played by the depression of the central nervous system which follows the use of these drugs. Further research upon these points is required to clear up the problem.

Dilaudid appears to be a drug which readily produces nausea and vomiting

in the human subject when given in doses of $\frac{1}{24}$ grain. These effects are very prolonged, and in the cases described lasted for about 5–6 hr. after the administration of the drug. The observations made in the first case show that gastric peristalsis may not be greatly affected and may even be reduced in strength. In the second subject, however, there was an immediate quickening of the rate of gastric peristalsis. Pylorospasm of the intermittent type is a constant feature of the drug, causing a delayed passage of the stomach contents to the duodenum. Some of the meal was seen in the stomach 6 hr. after it had been swallowed, but the delay caused by the sphincter was not so prolonged as with heroin and morphine. The effects upon the ileo-colic sphincter are similar, but not so pronounced as in the case of the pyloric sphincter. This is indicated by the presence of a small amount of barium in the caecum at the 3 hr. stage. The slow progress in the advance of the head of the meal in the caecum between the 3 and 6 hr. stages may indicate a condition of decreased activity in the large bowel produced by the drug.

The action of Dicodid upon the pyloric sphincter is not a marked one, as is shown by the stomach emptying well after the drug has been administered. Gastric peristalsis is unaltered in rate for about 20 min. when it shows a decided quickening, being increased about 30% above the normal rate. Dicodid does not cause a delayed emptying of the stomach, and in this respect differs markedly from heroin, morphine and Dilaudid. It does not produce any appreciable effects upon the ileo-colic sphincter, consequently there is no obstruction to the meal at this point. The motility rate of the intestine is slightly quickened at the 3 hr. stage but returns to normal at 6 hr. Constipation was not observed following the use of a single dose of Dicodid, and the result of this investigation shows no reason why it should ever be a sequel to its use when used in this way. The drug was seen to produce marked analgesic effects, and it might prove to be a valuable drug to allay pain in conditions where constipation would be very undesirable in the course of a disease.

Eukodol produces an immediate but not powerful spasm of the pylorus which is accompanied by an increased rate of gastric peristalsis. The result is to cause a slight delay in the passage of the meal through the sphincter. This delay is well demonstrated at the 3 hr. stage, but at the 6 hr. stage there is a condition resembling the normal passage of food. Previous experiments on animals showed that the action of the drug upon the pyloric sphincter was not prolonged beyond 10–15 min., which would explain the delay seen at the 3 hr. stage. A similar short-lived effect at the ileo-colic sphincter was also recorded in animal experiments.

It will be readily seen from these results that all these drugs produce similar effects, in a lesser or more marked degree, upon the stomach and pyloric sphincter. The greatest effects are produced by heroin, with morphine as a good second. Of the three substitutes used in this investigation, Dilaudid has the most marked effect upon these structures and in this way closely

resembles morphine. A similar conclusion can be drawn from their effects upon the ileo-colic sphincter.

Eukodol resembles morphine and heroin in many respects, but its action is much less pronounced.

Dicodid has the least effect in delaying the passage of food along the alimentary tract. It causes a slight quickening of motility rate at first, but the passage of food later becomes normal. Eukodol causes only a negligible slowing, while heroin, morphine and Dilaudid produce a marked delay. The actions of Dicodid and Eukodol upon the human alimentary tract least resemble those of heroin and morphine, while a close resemblance exists between Dilaudid, morphine and heroin.

Grubner *et al.* (1936) studied the effects of morphine sulphate and Dilaudid upon the antrum, pyloric sphincter and duodenum in dogs. Four dogs were used having permanent gastric and duodenal fistulae. Simultaneous graphic records of gastric, pyloric and duodenal tonus and activity were made. Their results showed that morphine and Dilaudid cause a temporary spastic contraction and a prolonged increase in the general tonus of the pyloric sphincter and duodenum. The response of the antrum was variable to both of these drugs. In some dogs increased tonus was recorded, in others decreased tonus and amplitude of contractions. They associate the decrease in general tonus with nausea produced by both of these drugs. Their results closely approximate our observations on the human subject which are outlined in this communication, except that we observed nausea and vomiting in subjects showing increased gastric activity as well as those in whom it was greatly reduced.

In 1933, Myers described a stiff erection of the tail in mice following a single injection of any of these drugs. A similar condition was noted by Rassers (1916) following the use of other convulsants. Van Leersum (1918) believes this to be due to intense tenesmus of the anal and bladder sphincters, originating in the medulla and transmitted to the pelvic nerves. Heinekamp (1923), however, refers it to stimulation of the spinal cord. In view of these observations a careful check was made upon any rectal symptoms which might have been experienced by any of the human subjects used in the present investigation. Nothing unusual was reported, and none of the subjects experienced constipation afterwards.

SUMMARY

1. The effect of heroin, morphine, Dilaudid, Dicodid and Eukodol upon the human alimentary tract are described from observations involving the use of the barium meal and X-ray methods.

2. The effects of Dilaudid closely resemble those of morphine. Dilaudid produces a condition of increased tone in the pyloric and ileo-colic sphincters resulting in delayed emptying of the stomach contents into the duodenum and a delayed passage of the intestinal contents into the caecum.

3. Dicodid has a much weaker action upon the pyloric and ileo-colic sphincters than either morphine, heroin, Dilaudid or Eukodol. It causes only a negligible delay in the passage of food up to the 3 hr. stage, it being normal at the 6 hr. stage owing to a hastening of the motility rate.

4. Eukodol has an action resembling that of morphine and is described.

5. All these drugs possess well-marked analgesic properties.

6. No gross rectal symptoms were observed in any of the subjects under observation.

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EXPLANATION OF PLATES XIV–XVI

PLATE XIV

G. O. R.

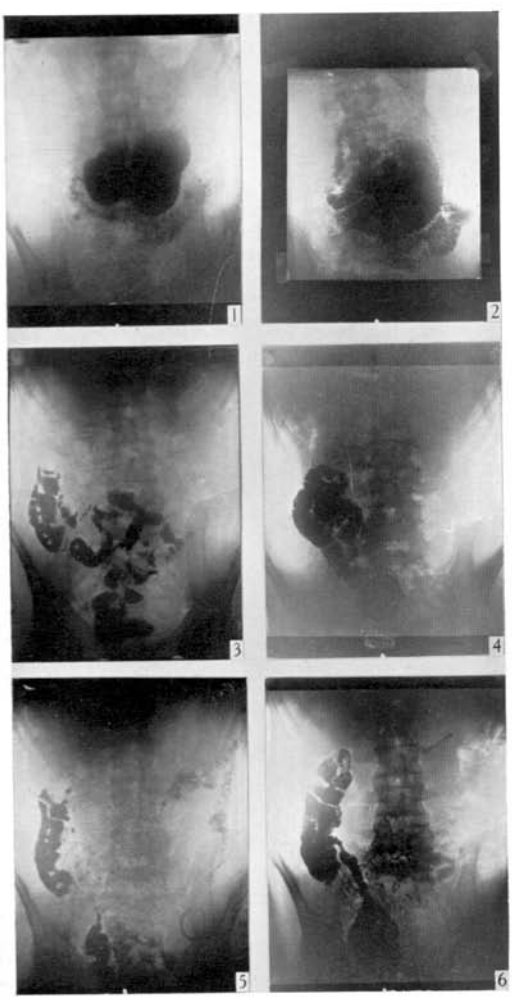
1, 3 and 5. Showing the position of the control meal 30 min., 3 hr. and 6 hr. respectively after swallowing.

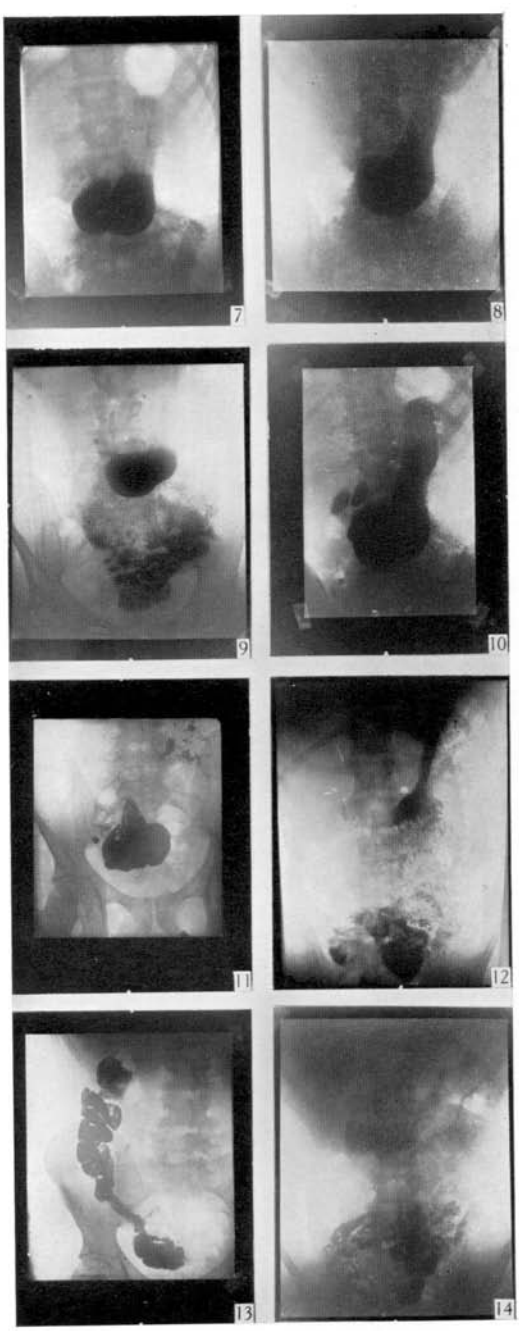
2, 4 and 6. Showing the progress of a meal at 30 min., 3 hr. and 6 hr. respectively after the injection of $\frac{1}{8}$ grain of morphine hydrochloride.

7, 9, 11 and 13. Illustrating the position of the control meal at 15 min., 30 min., 3 hr. and 6 hr. respectively.

8 and 10. Were recorded immediately before and immediately after the injection of $\frac{1}{12}$ grain heroin.

12 and 14. Showing the position of the meal at 3 and 6 hr. respectively after the heroin had been administered.





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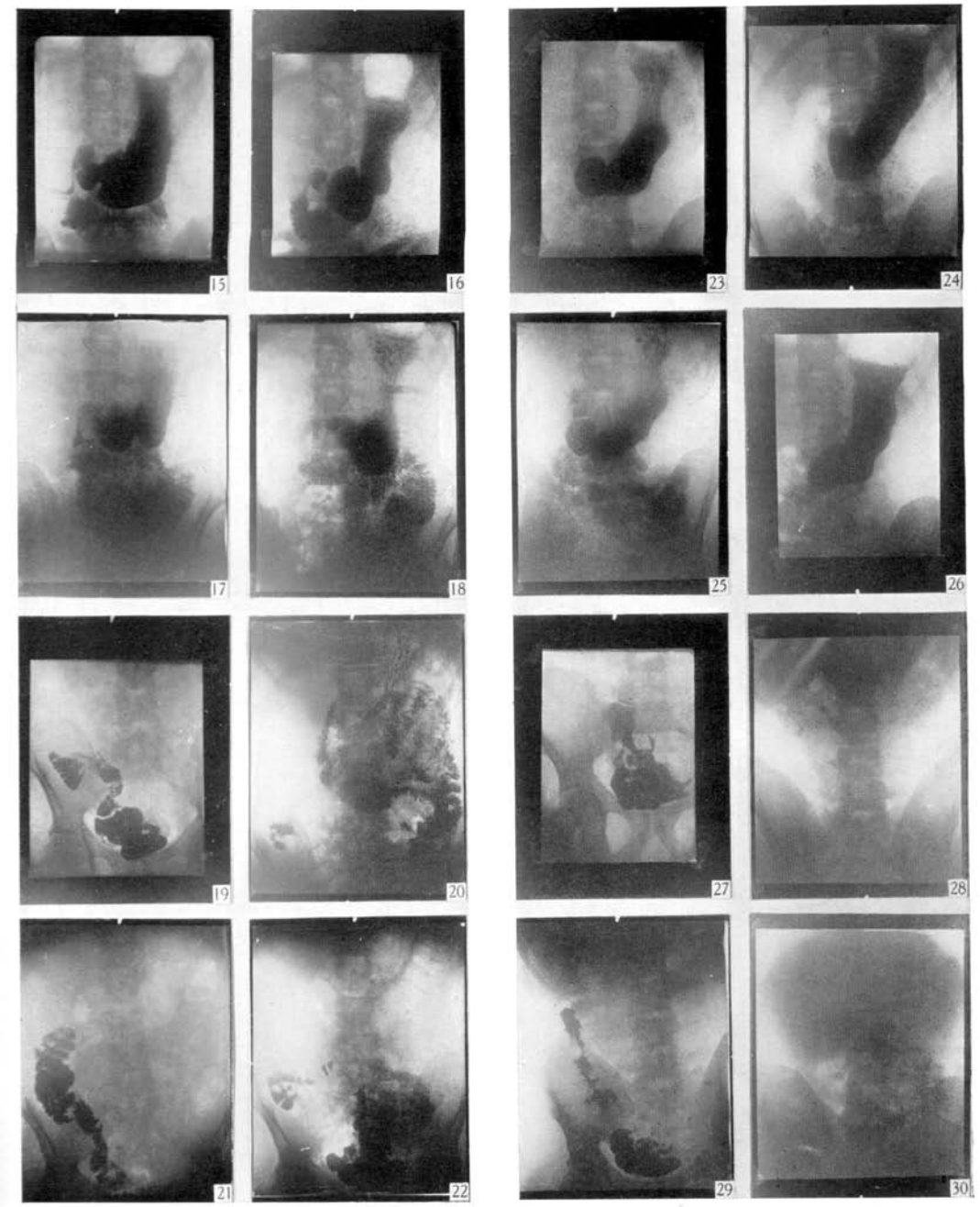

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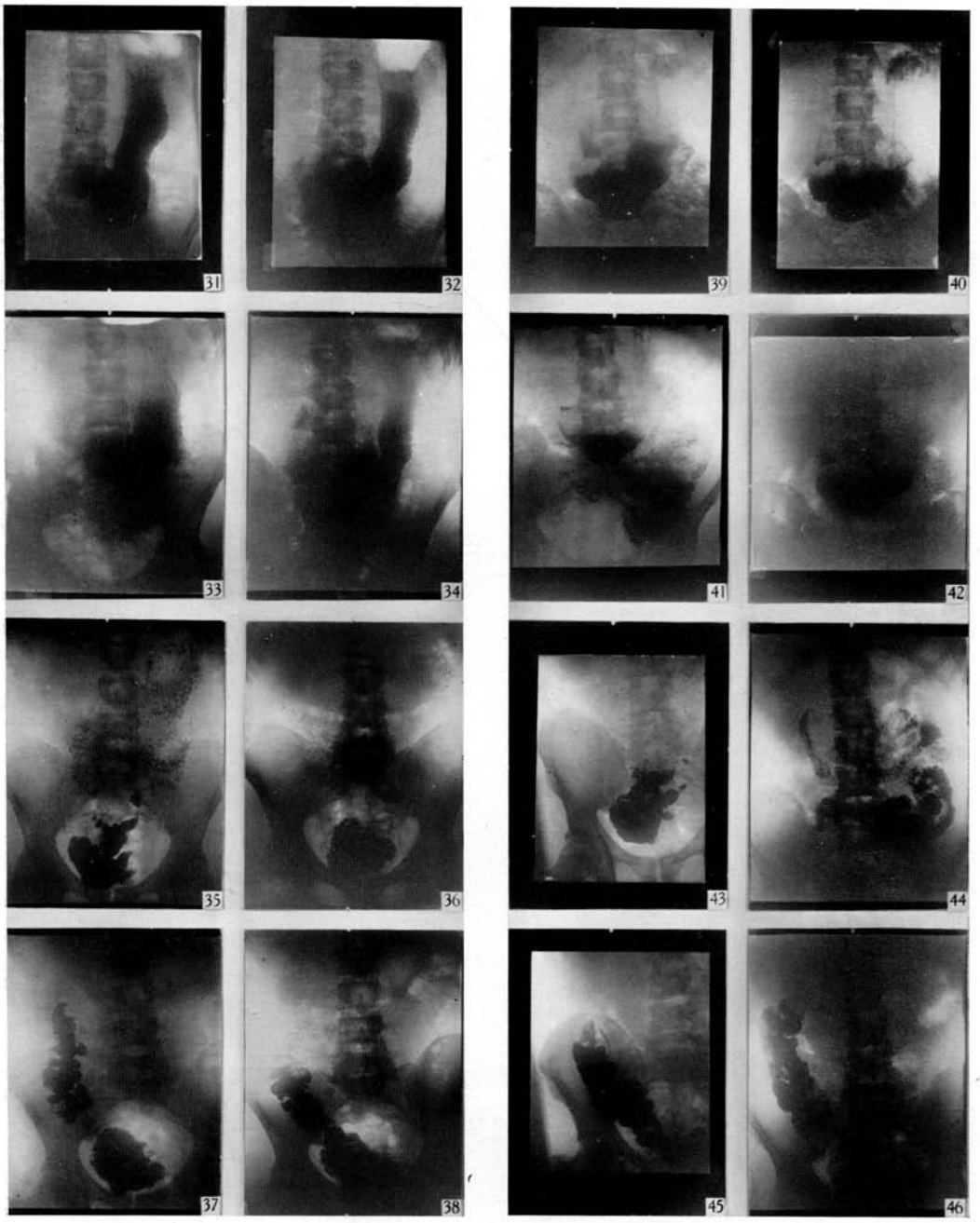

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PLATE XV

H. G. M.

15, 17, 19 and 21. Showing control examinations taken 10 min., 30 min., 3 hr. and 6 hr. respectively after the meal.

16, 18, 20 and 22. Illustrating the position of a meal at 5 min., 25 min., 3 hr. and 6 hr. after the injection of $\frac{1}{24}$ grain Dilaudid.

G. A. S.

23, 25, 27 and 29. Control examinations at 10 min., 30 min., 3 hr. and 6 hr.

24 and 26. Showing the position of a meal immediately before and immediately after $\frac{1}{24}$ grain of Dilaudid.

28 and 30. The same meal at 3 and 6 hr. later.

PLATE XVI

S. C.

31, 33, 35 and 37. A control meal. Skiagrams taken at 11 min., 30 min., 3 hr. and 6 hr. respectively.

32, 34, 36 and 38. Showing a meal at 6 min., 30 min., 3 hr. and 6 hr. after the administration of $\frac{1}{24}$ grain Dicodid.

E. I. T.

39, 41, 43 and 45. The control examination at 11 min., 30 min., 3 hr. and 6 hr.

40, 42, 44 and 46. The position of a meal 13 min., 30 min., 3 hr. and 6 hr. after $\frac{1}{8}$ grain Eukodol.

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