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

PART V. A DISCUSSION ON THE PROBABLE MECHANISM OF THE CONSTIPATING ACTION OF MORPHINE

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

From the Pharmacological Laboratory, Cambridge

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I. Introduction

It has long been known that the administration of the salts of morphine is usually followed by constipation. In certain cases, where the drug has been given regularly over a period of time, this condition may become so serious as to warrant the discontinuation of the drug in order to relieve the abnormal condition of the bowels. As the chief use of morphine is to diminish pain it is not always possible to withhold the drug unless a suitable substitute is available, while to continue with morphine may result in the patient becoming addicted to the drug. It is evident, therefore, that these two undesirable effects, apart from the serious respiratory depression which may follow the use of large doses of morphine have led to a desire to produce allied synthetic drugs possessing marked analgesic properties without any of the harmful effects of morphine. It was with this object in view that research chemists produced several drugs which are synthetic in origin, and closely related to morphine in a chemical sense. Diacetylmorphine, known as heroin, was one of the earliest substitutes to be produced. This derivative was introduced by Dreser in 1898 and is still widely used in medicine although it has a greater toxicity than morphine and is probably a more dangerous drug of addiction than morphine. In more recent years other new substitutes have been produced. Among the most important members are the hydrochlorides of

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dihydromorphinone (dilaudid), dihydrocodeinone (dicodid), and dihydroxycodeinone (eukodol). These new derivatives of morphine and codeine have been used for a number of years and a large clinical literature has grown up around them. They all possess marked analgesic properties which cannot be assessed accurately in relation to morphine because of the difficulty in quantitatively estimating pain experimentally. The effects of these new drugs upon respiration and cough show a close similarity to those of morphine and heroin.

Morphine and heroin are well-recognized drugs of addiction, while opinions are sharply divided on methylmorphine (codeine). Whether dilaudid, dicodid, and eukodol produce addiction is an open question, but the small amount of clinical evidence available, where these drugs have been used over long periods of time, suggests that they are habit-forming drugs. It is perhaps too soon to give a definite decision upon this point in view of the limited use which they give had in clinical practice.

From the clinical point of view there is no doubt that morphine, even when given in small doses, has a constipating action and it is widely used to arrest many forms of persistent diarrhoea. Opium is even more effective in this way, probably because of the added effects of such alkaloids as papaverine which relax the plain muscle of the intestinal wall. Much has been written, and yet a great deal of confusion exists in the many explanations which have been advanced to explain this constipating effect, which is undesirable in the majority of cases, but is sought after in a very few special types of persistent diarrhoea, serious haemorrhage from ulceration of the intestinal wall, etc. This confusion appears to be largely due to the widely divergent interpretations of the effects of the drug upon the alimentary tract, by the many workers in the experimental field.

One of the earliest attempts to explain the constipating action of morphine was made by Nothnagel (1882) who attributed it to a central stimulation of the inhibitory splanchnic fibres. Magnus (1906, 1908) observed that morphine arrested the diarrhoea produced in cats fed on an exclusively milk diet. Division of the intestinal nerves did not influence the result, so he concluded that the action was peripheral. Morphine also increased the peristaltic movements (except when large doses were employed) of the isolated intestine which indicated that the drug did not cause peripheral intestinal depression. He then studied the passage of food along the alimentary tract by means of the bismuth X-ray technique. Morphine produced a prolonged contracture of the sphincter antri pylori, the pyloric and cardiac sphincters. Negligible effects were observed upon the tone and movements of the small intestine. He concluded that the constipating effects are due to the delayed emptying of the stomach. Padtberg (1911) observed that in the diarrhoea produced by colocynth there was exudation and increased peristaltic movements. Both effects were abolished by morphine or opium even when food was present in the intestine and he concluded that the drugs modified the intestinal secretion or absorption. Takahashi (1914) observed that codeine exerted a similar but weaker action to morphine in colocynth diarrhoea. Zunz (1921) found that only the morphine esters produce pre-pyloric spasm and with codeine this action was very feeble. Gordonoff *et al.* (1925), using the X-ray technique on dogs, demonstrated that when morphine is administered at the same time as the food the passage of the food through the small intestine takes place in normal time although food may be delayed in the stomach as long as 5½ hr. If the administration of the morphine is delayed until the food has entered

the small intestine then there is a marked delay in this part of the alimentary tract. He observed similar effects on the stomach and intestines after codeine administration. X-ray observations have been conducted on human subjects and show a delay in the passage of food along all parts of the alimentary tract. Zehbe (1913) found that the time required for the passage of food along the entire tract was twice the normal after opium had been given. The delay in the stomach and the small intestine was increased by 33% of the normal time, while the longest delay was in the colon and rectum. Schapiro (1913), and Mahlo (1913) report a delay or suppression of the defaecation reflex after morphine. Pancoast & Hopkins (1915), however, claim that the longest delay is in the small intestine, while there is but little delay in the colon. Small doses produced a greater delay than large doses. Katsch (1913) made direct observations upon the movements of the caecum in the conscious dog. Morphine produced a marked slowing of the rate of the peristaltic movements. Gordonoff *et al.* (1925), using the same technique, observed a stimulation of the movements after morphine had been given.

In this communication it is proposed to consider the behaviour of the entire alimentary canal, excluding the mouth and the oesophagus, in response to the administration of morphine hydrochloride with a view to an attempted explanation of the constipating action of the drug. The effects of diacetylmorphine hydrochloride (heroin), methylmorphine phosphate (codeine), dihydromorphinone hydrochloride (dilaudid), dihydrocodeinone hydrochloride (dicodid) and dihydroxycodeinone hydrochloride (eukodol) will be discussed in a similar way and attention drawn to the main points of difference in the behaviour of these drugs upon the alimentary tract. It is hoped, in this way, to find any important effects of these drugs which may modify the normal passage of the intestinal contents along the alimentary tract. With this information and the knowledge that morphine produces constipation it may be possible, by comparison, to predict which of these drugs might, or might not, have a similar constipating action. There are many factors which may be conducive to constipation and these will be studied in turn.

There are many physiological factors which are known to influence the rate of progress of food along the course of the alimentary canal. Among the more important are the chemical and physical characters of the food taken, individual variations in the activity of the muscle of the alimentary tract, and variations in the absorptive functions of the colon leading to variations in the consistency of the alimentary contents. The state of fullness of the alimentary canal is believed to influence the rate of travel along the gut. After a fast or after the bowels have been emptied by a purgative, the contents move along much more quickly. The rate of movement can also be increased by muscular exercise or by emotional states.

Morphine can also modify the passage of food along the alimentary tract and produce constipation. The mechanism of the constipating effect has never been satisfactorily explained although morphine produces many effects which may be regarded as constipating factors. The first is a prolonged closure of the pyloric sphincter leading to a delayed emptying of the stomach. Normally all the meal has left the stomach in approximately 3 hr. Morphine delays it 6 hr. or more. The second factor is the degree of muscle tone, and the amplitude

of the movements of the small intestine, both of which can profoundly modify the rate of passage of food from the pyloric to the ileo-colic end of the small intestine. The third factor is the state of the ileo-colic sphincter. Any prolonged closure of this sphincter would delay the passage of food into the caecum with a consequent excessive dehydration of the mass in the small intestine. When the sphincter relaxes greater force would then be required to force the plastic material into the caecum, and the requisite force may not be available at that moment, which may result in a prolonged delay at this point. The same factors which affect the small intestine can also affect the large intestine. A marked increase in tone with a restriction in the amplitude of the gut movements would retard the progress of the meal, whereas a condition of normal tone accompanied by a marked increase in movements would hasten the food onwards. Any drug which causes a prolonged diminution in the tone of the rectal muscle may set up a condition of rectal stasis should the movements be diminished at the same time. All these factors can be studied in the experimental animal and may contribute towards the solution of this most difficult problem of morphine constipation.

In addition to these peripheral effects, the effects of morphine upon the central nervous system may play an important part in producing this condition. Morphine diminishes the attention of the subject to rectal sensations. This decreases the sensitivity or response to the defaecation reflex and is probably central in origin.

The effects of morphine, heroin, codeine, dilaudid, dicodid, and eukodol upon the different portions of the alimentary tract of cats have been studied in detail and have been published in the earlier parts of this investigation (Myers, 1933, 1939*a*, *b*, *c*, 1940). A brief summary of the effects of these drugs upon the alimentary tract is outlined here and their possible effects upon the passage of food along the alimentary tract discussed. In this way a composite picture of the progress of food from the stomach to the rectum, in response to each of these six drugs, has been obtained.

II. Discussion

(*a*) *Morphine hydrochloride*

The effects of morphine upon the pyloric sphincter of the cat were found to be remarkably constant no matter what dosage was employed. The tone of the sphincter was always rapidly increased while the amplitude of the sphincter movements was often increased at the same time. The rate of onset, the magnitude and the duration of these effects was found to be more or less proportional to the dosage employed. With small doses (0·01–0·25 mg./kg.) the onset was slow, even when the intravenous route was employed, and a latent period of 10–30 min. was usually recorded before any visible effects took place. The maximum tone level was generally recorded within 30 min. while the action persisted for a period of 1–4 hr. Larger doses always produced immediate effects which lasted as long as 7 or more hours according to the dosage employed.

The effects of morphine upon the stomach were found to be very variable. The commonest effect observed was a gradual relaxation of the general tone of the organ accompanied by

a diminution in the rate and amplitude of the gastric movements. These effects lasted from 1½–4 hr. In some experiments, however, the gastric tone showed a marked increase lasting 30 min. or more and was accompanied by four or five slowly moving contractions of great amplitude. In a few experiments the drug produced no effects whatever upon the stomach.

These effects upon the pyloric sphincter and the stomach would automatically cause a marked delay in the passage of food from the stomach to the duodenum. This result is in agreement with the findings of Magnus (1908) and Myers and Davidson (1938). The latter workers demonstrated the slow emptying of the stomach in the human subject after the administration of morphine and noted the presence of a portion of a barium meal in the stomach more than 7 hr. after the meal had been swallowed and the morphine had been injected. This figure agrees closely with the time delay recorded in cats in the present communication.

That the pylorospasm is intermittent in character, so allowing food to leave the stomach from time to time, was recorded by Myers & Davidson (1938). Best & Taylor (1939) give the normal time for complete emptying of the stomach as 3–4½ hr. Taking these figures as an average it would appear as if morphine approximately doubles this figure. Certain variations must occur in individual cases depending upon whether the stomach tone decreases or increases in response to the drug. A relaxation of the stomach might reasonably be expected to lead to a longer stay of the food in the stomach than would be the case where the stomach increased or even maintained its normal tone. The question of dosage, too, is of some importance, for it has been clearly shown that the duration of the effects of morphine is approximately proportional to the size of the dose. Within limits, the larger the dose the more prolonged are the effects and so the delay caused to the passage of the stomach contents into the duodenum, when large doses of morphine are administered, may be much greater than 7 hr.

The intravenous injection of small doses of morphine HCl (0·05 mg./kg.) in the cat always produced a gradual but marked increase in the tone of the small intestine, which reached a maximum in about ½ hr. and lasted from 3–8 hr. before any signs of a decrease to normal level began to take place. As the tone of the intestine increased the amplitude of the peristaltic movements slowly increased in amplitude. This increase in amplitude was always greatest when the initial movements were small. With small doses the increase in the amplitude lasted from 1–2 hr.; with larger doses (1 mg./kg. or more) 3–5 hr. The frequency of the movements was generally slightly increased at first but later, when the movements were large, there was always a decrease in frequency.

Morphine HCl always produced a well-marked and immediate increase in tone of the ileo-colic sphincter indicating a closure of the sphincter. At the same time the movements became regular in rhythm and were increased in amplitude. These tonal effects were found to be dependent upon the dosage of the drug employed. The greatest degree of increased tone was always obtained in response to large doses (1 mg./kg. or more). Small doses (0·05 mg./kg.) maintained this effect for ½–2 hr. while the effects of larger doses lasted much longer.

In the normal animal the passage of the alimentary contents from the duodenal side of the pyloric sphincter to the caecum is dependent upon three

Table 1. *Showing the principal effects of morphine and some*

	Morphine HCl	Diacetylmorphine HCl (heroin)	Methylmorphine phosphate (codeine)
Stomach	(*a*) Usually { − Tone { − Amplitude of movements { − Frequency of movements Lasts 1½–4½ hr. Duration is proportional to dose (*b*) Occasionally + tone lasting ½ hr. accompanied by 4–5 large movements, each one of 15 sec. duration (*c*) No effects in a few experiments	(*a*) Usually { Small + tone { Amplitude of movements unchanged { Frequency of movements unchanged Tone subnormal 15–30 min. later (lasts 2–3 hr.) (*b*) Sometimes there is an initial and continued relaxation	Effects less marked than those of morphine or heroin { Slight + amplitude of movements { Slight − frequency of movements Normal tone level (These conditions last 15–20 min.) passing to − tone level for 30–40 min. returning to normal tone later
Pyloric sphincter	{ + Tone { + Amplitude of movements { + Frequency of movements Lasts 2–7 hr. Degree and duration are proportional to dose	{ + Tone { + Amplitude of movements { + Frequency of movements Maximum effects within 5–10 min. Tone effects greater than morphine Amplitude of movements less than morphine	Effects less marked than morphine or heroin (*a*) Small doses + Tone (5–10 min. duration) passing to subnormal for 30 min., returns to normal later No change in amplitude or frequency (*b*) Large doses Greater initial tone, maximum at 30–40 min. lasting 30–90 min., returns to normal
Small intestine	{ Gradual + tone (maximum at ½ hr.) (lasting 3–8 hr.) { + + Amplitude of movements, lasting 1–2 hr. { + Frequency of movements diminishing later	Effects similar to morphine { + Tone (maximum at 3 min.) { + + Amplitude of movements Tone usually subnormal at 10–20 min. Secondary periods of + tone 2–3 hr. later, each wave lasting about 2 min.	Effects similar to morphine but less marked Much larger doses of codeine required than morphine
Ileo-colic sphincter	{ + Tone (maximum at 2–30 min.) { + Amplitude of movements Tone returns to normal in 30–120 min.	{ + Tone (lasts 30–60 min.) (later becomes subnormal) { + Amplitude of movements (lasts 1–4 hr.) Amplitude is greatest after small doses when the tone is not excessive	Slow + tone (maximum at 10–15 min.) of short duration (30 min.) Small + amplitude of movements
Colon	(*a*) Moderate doses: Immediate + tone (maximum in 5–6 min.) (lasts 3 or more hr.) Secondary periods of + tone begin at 5½ hr. Each wave of 30 min. duration. Waves repeated at 1 hr. intervals (*b*) Small doses: { + + Amplitude of movements { − Frequency of movements (*c*) Large doses: { + + Tone { − Amplitude of movements	Effects similar to morphine	Small + tone at first but negligible + Amplitude of movements (large doses required). Maximum movements at 6 min. maintained 30 min. Negligible at 1 hr.
Rectum	+ Tone (lasts 20–45 min.) Returns to normal or slightly + tone Secondary waves of + tone during next 3–4 hr. Each wave of 30 min. duration Tone subnormal at 5–6 hr. stage { + + Amplitude of movements (maximum at 3 hr. stage) { − Frequency of movements	Effects similar to morphine. Tone usually greater than normal at 5–6 hr. stage	Effects similar to morphine and heroin { Small + tone (maximum at 15 min.) { Small + amplitude of movements (over at 30–45 min.) Tone never subnormal at 5–8 hr. stage

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allied drugs upon the different portions of the alimentary tract

Dihydromorphinone HCl (dilaudid)	Dihydrocodeinone HCl (dicodid)	Dihydroxycodeinone HCl (eukodol)
Effects variable (*a*) 0·02 mg./kg. { − Tone { − Amplitude of movements Returning to normal after 20 min. 10–20 min. later { − Tone { + Amplitude of movements Lasts 2–4 hr. (*b*) 0·15 mg./kg. { − Tone { + Amplitude of movements Lasts 2–4 hr. (*c*) Large doses { + Tone { + Amplitude of movements Lasts 30–70 min.	Resembles codeine 0·5 mg./kg. gives small + tone (gradual) maximum at 25 min. returns to normal after 6–12 min. followed by four tonal waves each of 20 min. duration, later becomes subnormal for 2 or more hr. Movements show small + amplitude lasting 6–7 hr. maximum at 3 hr. returning to normal again	Similar to dicodid Eukodol is slightly more active when equal doses are employed
Effects more marked than morphine, heroin or codeine With dose of 0·025 mg./kg., an immediate { + Tone (maximum at 2 min.) { + Amplitude of movements { − Frequency of movements Tone returns to normal level 3 hr. or more later Large doses give similar but more prolonged effects Three experiments with 3 mg./kg. showed: { − Tone { + Amplitude of movements { − Frequency of movements 0·01 mg./kg. dilaudid ≡ 0·1 mg./kg. morphine	(*a*) 0·25–1·0 mg./kg. Immediate + tone (maximum 15 min.) lasting 30 min. becomes subnormal and remains so many hours Later + amplitude of movements (maximum at 5 hr.) (*b*) Larger doses: Similar effects but of shorter duration, and not so marked *Note.* Secondary loss of tone is greater than with morphine	Resembles dicodid and codeine 0·1 mg./kg. { + Tone (gradual in onset) lasts 10–20 min. { + Amplitude of movements (for 6 hr.) 20–40 min. later tone becomes subnormal for 4–5 hr.
Effects almost identical with morphine Dilaudid much more effective in smaller doses 0·005 mg./kg. dilaudid ≡ 0·05 mg./kg. morphine	Small slow progressive + tone (maximum at 50 min.) Alternate periods of inhibition and excessive activity followed over a period of 1½–2½ hr. Large doses produced a short-lived inhibition	{ + + Amplitude of movements (lasts 3–4 hr.) { + Tone (negligible) 30 min. later passing to − tone (negligible)
Immediate { + Tone (maximum at 2–6 min.) { + Amplitude of movements (lasts 12 min.) Tone slightly + normal for 1–1½ hr. *Small intestine very active every* 10–20 min. at this period	{ + Tone (maximum at 20–40 min.) { + Amplitude of movements (maximum at 3 hr.) + Amplitude effects last for about 6 hr. with bouts of + tone and + + amplitude during 1st hr.	Slight + tone, becoming normal 30 min. later. Tone markedly subnormal after 2–3 hr. + Amplitude of movements (*maximum after 3–4½ hr.*) becoming normal ½–1½ hr. later
(*a*) Small doses: { No change in tone { + + + Amplitude of movements { + Frequency of movements (usually) This condition lasts 6–7 hr. or more (*b*) Moderate doses: { Slight − tone at 3 hr. { + + + + Amplitude of movements at 3 hr. continued a further 4 hr. During the last hour pronounced slowing of frequency occurred The peristaltic effects are much greater than those produced by morphine, heroin, or codeine	Very marked + + + amplitude of movements at 1–2 hr. stage (maximum at 3 hr.). Continued another 2–3 hr. the frequency becoming slowed + Tone at 1 hr. Later becoming subnormal	(*a*) Small doses: { + Amplitude of movements { Normal tone (*b*) Large doses: { + Amplitude of movements (lasts ½–4 hr.) { + Tone (maximum at 2 min.) { Normal again at 20 min.
(*a*) Small doses: Increase in tone rather than movements + *Tone lasts 30–40 min. passes to* normal within 70–90 min. (*b*) Large doses: { + Tone { + Amplitude of movements lasting 30 min. Tone subnormal at 6–8 hr. stage (resembles morphine)	Enormous increase in activity of rectum, greater than morphine, heroin, codeine or dicodid + *Tone (maximum at 3–5 min.)* Slight − amplitude of movements passing to + amplitude of movements and + frequency of movements Secondary + tone waves every 15–25 min. during next 4½ hr.; effect like morphine Tone never subnormal at 8 hr. stage (resembles heroin)	Marked increased activity { + Amplitude of movements (maximum at 3–3½ hr.) { + *Tone (becomes subnormal* at 3–3½ hr.) Secondary waves of increased tone (each wave 18–25 min.) over a period of 2½–3 hr. Tone subnormal at 8 hr. Amplitude of movements still greater than normal but decreasing

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main factors. First the amplitude of the peristaltic movements of the small intestine, second the general tone of the intestinal muscle, and lastly the tone of the pyloric sphincter. When the tone is moderate, the movements large and the sphincter relaxed, then there is little or nothing to prevent the normal passage of the food along this part of the alimentary tract which should arrive at the hepatic flexure about 4 hr. after it has been swallowed. When morphine has been administered the consequent marked increase in the tone of the small intestine, in spite of the increase in movements which also takes place, would delay the normal passage of the food along the small intestine. Lead salts produce an increase in intestinal tone resulting in a condition of spastic tonus of both large and small intestine. This hinders the free passage of the alimentary contents and is undoubtedly an important factor in the production of constipation in chronic lead poisoning. Lead, however, does not increase the amplitude of the peristaltic movements but generally diminishes it considerably because of the imperfect relaxation of the gut during the condition of spastic tonus. In the case of morphine, the increase in intestinal tone would similarly delay the passage of the alimentary contents but the delay would not be so great as with lead salts because morphine salts do not influence the tone to such a marked extent, and so the lumen of the gut would not be narrowed to the same degree as with lead. On the other hand, morphine always increases the amplitude of the peristaltic movements, a factor which would promote the passage of the intestinal contents along the tract and so partially offset the delay caused by the increase in intestinal tone. Plant & Miller (1928) explained the constipating action of morphine on the basis of the prolonged increase in intestinal tone, but while the results of Plant & Miller are in close agreement with those published in this communication the general conclusions are slightly different.

In so far as the ileo-colic sphincter is concerned, small doses of morphine always produced a well-marked increase in sphincter tone, indicating a closure of the sphincter. At the same time the normal movements of the sphincter became regular in rhythm and increased in amplitude. The tonal effects were dependent upon the dosage employed and were always much greater with larger than small doses, although in all cases the effects were prolonged over many hours.

As in the case of the pyloric sphincter, the closure of the ileo-colic sphincter was seen to be intermittent in character, but there appears to be no doubt that this mechanism would delay the passage of any food residues, already in the lower portion of the small intestine, from the ileum to the caecum. It is doubtful, however, whether any food, taken at the same time as small amounts of the drug were administered, would be held up at this point very long because the spasm of the sphincter would probably have passed away by the time the food reached this point. With larger doses (1 mg./kg. or more), however, where the sphincter spasm has been shown to be prolonged beyond 3 hr., some delay might be expected here provided that the delay at the pyloric sphincter and in the small intestine is not too long. In any case, the delay at the ileo-colic

sphincter would retain the food residues for an abnormally long time in the small intestine where they would be subject to prolonged dehydration and absorption processes. This would render them more plastic and consequently more difficult to propel along the alimentary tract than more liquid material. This would be an added cause of any further delay from the ileum into the caecum and later along the colon to the rectum.

The most constant effect produced by morphine upon the caecum and the various sections of the colon was a well-marked increase in tone. The onset was always immediate and the maximum level rapidly attained. When the intravenous route was employed the maximum tone level was always reached within 5–6 min., while this time was increased by 20–45 min. when the subcutaneous method was used. The greatest tone effects were not produced by the largest doses; on the contrary, the highest tone levels were generally recorded when moderately small doses were employed (0·05 mg./kg.). The duration of the period of increased tone was found to vary widely, not only with different doses of the drug, but with the same dose of drug administered to different cats of the same weight. It would therefore appear as if individual animals do not respond uniformly. A review of the whole series of experiments indicated that the most prolonged tone effects were always produced in response to large doses of morphine. Normal tone level was usually re-established in 15–20 min. when a dosage of 0·05 mg./kg. was injected intravenously. When the dose was increased to 0·5 mg./kg. this time interval was extended to 3 hr. or more. Secondary periods of increased tone of the large intestine were frequently seen when small doses of morphine were employed, and much less often after large doses. The first of these periods of secondary increased tone usually began about 5½ hr. after the injection has been made, and lasted about 32 min. They were generally repeated two or three times at hourly intervals.

Moderate doses of morphine (0·5 mg. or less per kg.) increased the amplitude of peristaltic movements in a most marked degree, setting up a phase of almost continuous peristaltic activity lasting many hours, according to the dose employed. The frequency of the movements was diminished as the amplitude increased. Large doses of morphine usually produced a spastic contraction of the bowel accompanied by a depression, or complete suppression of peristaltic movements lasting 3 or more hours.

The effects of morphine upon the caecum and colon were found to be much greater than upon the small intestine. Not only were the tone and peristaltic movements greater and more lasting in the case of the large gut, but much smaller amounts of the drug were required to produce them than in the case of the small gut. Doses small enough to be without effect upon the small intestine usually produced very marked effects upon the colon.

It is doubtful whether the initial increase in the tone of the caecum and colon which is produced by morphine has a marked effect upon the passage of the alimentary contents of food recently swallowed. Any residues present in this section of the alimentary canal would, however, be delayed for a period not exceeding 1 hr. after which their passage may be speeded up by the enormously large and slow-moving peristaltic movements which follow the initial period of increased tone. Whether this speeding up can make up for the initial delay would depend upon the dosage of the drug employed. The initial period of increased tone of the caecum and colon was always shortest when small amounts of the drug were used, and so the delay to the passage of the alimentary contents would not be more than about 10–30 min., and it is possible that this delay might be later made up by the increased movements which follow. This delay would be correspondingly greater when larger doses of the

drug are employed, and peristaltic movements may be diminished or even suppressed. It must also be remembered that the food residues would probably be more plastic following the delay in the small intestine and that such plastic material would be more difficult to propel along the lumen of the gut than more fluid contents. This factor may be a further cause of delay and is probably of some importance.

The secondary phases of increased tone which morphine produces in the colon might also be expected to cause a further stagnation of the alimentary contents for periods of 15–30 min. every hour so long as these phases recur. It is evident, therefore, that a multiplicity of factors must be taken into consideration when the alimentary contents reach the large bowel and it seems as if the delay here may be well marked no matter whether large or small doses of morphine are employed.

Small doses of morphine always produced a well-marked increase in rectal tone which was rapid in onset and lasted 20–45 min. when the tone level became normal once again or was slightly raised. At this stage the amplitude of the movements was greater than normal. A secondary phase of increased tone and much greater movements began during the next 5 min. and lasted 20–40 min., when both the tone and the amplitude of the movements declined to normal during the next 10 min. The rectum usually remained in this condition for approximately 1 hr. or more. About 3 hr. after the administration of the drug by the intravenous route, another sudden increase in tone and movements occurred. The maximum tone effect was recorded within a few minutes and was soon followed by a rapid decline to a subnormal level during the next 30 min. when another period of renewed activity began. This active phase consisted of a series of enormous contractions and relaxations, each one lasting about 2–5 min. These very large movements continued for a period of 1–1½ hr. 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 rectum remained relaxed at a markedly subnormal level with very small movements for a further period of 3 or more hours when the experiments were usually terminated. Similar results were obtained using doses ranging from 0·05 to 1 mg./kg.

From this account it will be seen that when morphine is administered the rectum behaves in a similar fashion to the colon except that the general tone of the rectum becomes markedly subnormal and inactive 5–6 hr. after the drug has been administered by the intravenous route. Similar effects were produced when the subcutaneous route was employed but there was a general delay in the time required for their onset and the consequent train of effects was generally later although their magnitude was not altered within any measurable limits.

In so far as the passage of the alimentary contents is concerned there would be some slowing in the upper rectum from the same causes which have been discussed already in the case of the colon. In addition, the relaxation of the rectal muscle seen at the 5–6 hr. stage would allow the rectum to become loaded to a most marked degree, while the much diminished movements would give little incentive to the rectum to empty itself. This might be an important point in the constipating action of the drug.

All the factors tending to slow down the passage of the alimentary contents have been discussed but there is a further important aspect to be considered. It is well known that morphine diminishes the attention to both external stimuli and internal afferent impulses. There seems little doubt that such

a state would diminish the attention to the rectal reflex and so the impulses calling to stool would pass unheeded. Such a condition if prolonged over many days or weeks would cause the subject to become seriously constipated quite apart from the complicated series of events which take place in the alimentary tract.

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

The effects of this drug upon the stomach and pyloric sphincter were found to be very similar to those produced by morphine. Small doses of heroin (0·2 mg./kg. or less) were usually without effect upon the stomach. Larger doses, however, sometimes caused some slight increase in the tone of the stomach with little or no increase in the amplitude and frequency of movements. 15–30 min. later the tone was subnormal and remained so for 2–3 hr. In one-half of the experiments 1 mg. of heroin per kg. caused an immediate slight loss of gastric tone accompanied by a diminution of both the amplitude and the frequency of contractions which was present for 2–3 hr.

In so far as the pyloric sphincter is concerned, small doses of heroin always produced an immediate increase in sphincter tone which is similar to that produced by morphine. During the next few minutes the amplitude and the frequency of the movements increased to a maximum which was attained in 5–10 min. The increase in tone was nearly always much greater than that produced in response to morphine whereas the increase in the amplitude of the movements was usually not so great as with morphine.

From these results it is apparent that heroin must cause a well-marked delay in the emptying of the stomach contents into the duodenum which must be even more marked than that seen after the administration of morphine, because of the more pronounced closure of the pyloric sphincter produced by heroin. This conclusion is supported by the observations of Myers & Davidson (1938) who studied the effects of morphine and a number of allied drugs upon the passage of food along the alimentary tract of the human subject. By means of X-ray technique they demonstrated a pronounced delay in the passage of the stomach contents produced by morphine. A fair proportion of the meal was observed to be still present in the stomach 6 hr. after it had been swallowed. In the case of heroin, 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.

The effects of heroin upon the small intestine were substantially the same as those of morphine, and differed only in one or two details. The effects of heroin were always immediate. The amplitude of the movements was increased and the general tone of the intestine increased at the same time. Both of these effects, especially the increase in the amplitude of the movements, were more marked after heroin than morphine. The increased tone produced by heroin never lasted so long as that which followed the administration of morphine. In many of the experiments where heroin was employed, the tone of the small intestine had relaxed to a subnormal level 10–15 min. after the drug had been injected by the intravenous route. During the next 2–3 hr. the tone increased and relaxed again continuously in periods lasting approximately 2–3 min. each. Like morphine, heroin increased the amplitude of the rhythmical contractions while the rate remained practically unaltered.

Heroin always produced an increase in the tone and movements of the ileo-colic sphincter. The increase in tone was profound when large doses (1 mg./kg.) were injected and was less marked when very small doses (0·005 mg./kg.) were employed. With the small doses, however,

the movements were generally increased to a much greater amplitude than when large doses were used. In all cases the increase in tone rarely lasted longer than 30–60 min., after which the tone level became either normal or very slightly subnormal, whereas the increased movements continued for a further 1–4 hr.

In so far as the small intestine is concerned it will be seen that the increased tone which follows the administration of heroin is often much greater but always more short-lived than that seen after morphine, and rarely lasted longer than 15 min. Such a narrowing of the lumen of the small intestine would undoubtedly impede the progress of the contents of the alimentary canal but only for a period of 10–15 min., after which they would be free to travel on to the ileo-colic sphincter unhindered. Owing to the marked increase in peristaltic movements which was always seen when the period of increased tone had passed away, the contents of the intestine would now be hurried along the lumen towards the sphincter. In view of this, it is doubtful whether heroin would cause any increase in the total time required to traverse the length of the small intestine because any initial delay caused by the increased tone would probably be made up by their later swift passage produced by the increased movements. It will be seen, therefore, that whereas morphine probably causes a marked delay in this section of the alimentary tract, heroin may not.

The effects of heroin upon the ileo-colic sphincter are such as to cause a definite delay in the emptying of the contents of the small intestine into the caecum. It is doubtful whether there would be much delay, at this point, to the passage of food which had to be taken by mouth at the same time as the heroin was administered, because the effects of the heroin upon the sphincter would probably have almost passed away by the time such food had reached the sphincter. This would, however, depend upon a number of factors such as the dosage of the drug employed, because the duration of the effects has been shown to be more or less proportional to the size of the dose administered, and the route by which the drug is administered. This may be of some importance. When the oral route is used the onset of the effects is delayed by the time required for the absorption of the drug, and then prolonged for a similar period. This would allow food present in the stomach and small intestines to travel freely until the effects of the drug had become manifest, and so delay their further passage. When the intravenous route is employed, the effects are immediate and so the delay begins at once. It will be seen, therefore, that the mode of administration will have an important bearing upon whether or not the contents of the upper or lower portion of the small intestine would be arrested at the ileo-colic sphincter. The delay at this point is from 30–60 min. when small doses of heroin are employed but is increased when larger amounts are administered. The delay is intermittent in character rather than absolute. It is, however, not so prolonged after heroin as after morphine when the delay may be 3 hr. or more. It is evident, therefore, that in the case of heroin there should be less dehydration of the alimentary contents than in the case of morphine, consequently the food residues would be more

normal in consistency and more easily moved along the lumen of the large intestine than after morphine.

The effects of heroin upon the large intestine are very similar to those produced by morphine. Here, as in the case of morphine, the caecum and colon were found to be more responsive than the small intestine to small doses of heroin.

For the same reasons which were discussed in the case of morphine, some delay in the passage of the alimentary contents would be expected in the large intestine itself. When heroin has been employed it seems reasonable to assume that the faecal mass would be more fluid than after morphine and that such material would be more easily propelled along the colon to the rectum. It is probable, therefore, that there is less delay in the large intestine after heroin has been administered than when morphine has to be used. In this argument no account has been taken of any change in the intestinal secretion which may follow the use of either of these drugs. Direct observations, made on the experimental animals used in this investigation, have shown that any alteration in the amount of the secretion of the large intestine which may take place is never very great and probably does not influence any comparative conclusions which may be drawn from the general results.

The effects of heroin upon the rectum are somewhat similar to those of morphine. The greatest difference recorded 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 some experiments relaxation below normal tone level was never observed, even after a space of 7 hr. Both drugs, however, always produced a well-marked increase in the tone of the rectum shortly after their administration. After heroin, the tone level usually returned to normal within 30–45 min. after which there were periods of secondary rectal activity, such as have been described in response to morphine.

This question of rectal tone at the 1–2 hr. stage may be important because it indicates quite clearly that after morphine administration the rectum is dilated and is probably overloaded with very plastic faeces whereas, after heroin, a more or less normal state exists which is not conducive, in itself, to constipation. From this account it will be seen that heroin arrests the progress of the alimentary contents at two main points, the pyloric and ileo-colic sphincters, whereas morphine causes a general slowing along the entire intestinal tract as well as at these two sphincters.

Myers & Davidson (1938), in their studies upon the human subject, observed that the effects of heroin were similar to those of morphine. They observed that heroin produced a more marked closure of the ileo-colic sphincter than morphine. This was so marked that, in most of the subjects, none of the meal had entered the caecum at the 6 hr. stage. On the other hand, heroin increased the activity of both the large and small intestine to a much greater extent than morphine. From these observations it would appear as if heroin produces a more prolonged effect upon the ileo-colic sphincter of the human subject than in the cat, otherwise the effects are almost identical.

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

The effects of codeine upon the stomach and pyloric sphincter are considerably less marked than those produced by morphine or heroin, but bear a similarity to the effects of these two drugs.

No effects upon the stomach were produced with doses of codeine less than 1 mg./kg. and doses in excess of this figure were required to produce even small effects. 2 mg./kg., or more, produced a slight increase in the amplitude with diminished frequency of the movements lasting 15–20 min. The tone was then reduced very slightly to a subnormal level. Normal tone was usually established 30–45 min. later. In a few experiments a slight increase in tone was recorded as well as increased movements. These effects never lasted longer than 40 min. The effects upon the pyloric sphincter were similar to, but much less marked, than those of morphine and heroin. Small doses (0·05 mg./kg.) slightly increased the tone of the sphincter for a period of 5–10 min., after which it decreased to a slightly subnormal level. Normal tone was usually re-established 30 min. later. Larger doses (0·25 mg./kg. or more) produced similar but more marked effects. The maximum tone effects were generally seen 30–40 min. after the drug had been given intravenously. The duration of this phase of increased tone was found to be dependent upon the dose employed and lasted 30–90 min. before the sphincter tone was normal again. No changes in the rate or amplitude of the sphincter movements were recorded.

From these results it will be seen that the effects of small amounts of codeine upon the stomach and pyloric sphincter are not sufficiently great to cause any appreciable increase in the emptying time of the stomach. Large doses, however, may cause a slight delay at the pyloric sphincter lasting for a period of 1–2 hr.

The effects of codeine upon the small intestine and ileo-colic sphincter were found to be qualitatively the same as those of morphine. Quantitatively, however, the effects of codeine were extremely small in comparison with those of morphine or heroin. The duration of the effects of codeine upon the small intestine was roughly proportional to the dose employed, but even large doses rarely increased the tone of the ileo-colic sphincter for a period longer than 30–60 min.

It is very doubtful whether the effects of codeine would have any influence upon the normal passage of food through the length of the small intestine. Some small delay at the ileo-colic sphincter might be expected, but only when large doses of the drug are employed. This would be more in the nature of a braking or retarding action rather than an absolute stoppage and would rarely be in operation for more than 1 hr. Any delay at this site, produced by codeine, would be almost negligible in comparison with the delay caused by morphine and it seems doubtful whether this small delay would produce any alteration in the normal consistency of the alimentary contents entering the caecum.

Codeine, in doses ranging from 0·05 to 5 mg./kg., always increased the amplitude of the peristaltic contractions of the caecum and colon. The greatest effects were produced by the larger doses but were always much smaller than those seen after morphine or heroin administration. With codeine these increased movements reached a maximum at 6 min. and were well maintained for $\frac{1}{2}$ hr. after which they declined to negligible proportions 1 hr. later. Codeine had little effect upon the tone of the large gut except when very large doses were

employed (3 mg./kg. or more) which produced a negligible increase in tone lasting a few minutes.

Moderate doses of codeine (0·25 mg./kg.) always produced a slow progressive increase in the tone of the rectum. The maximum level was attained about 8–12 min. after intravenous injection of the drug, and was never very marked. Movements were increased in amplitude for 10–20 min. Normal tone was always re-established about 30 min. after the drug had been injected and no further changes were observed during the next 8 hr. Secondary phases of increased rectal activity were never observed.

From these results it is possible that the effects of codeine upon the caecum and colon might promote the passage of the alimentary contents to the rectum in a normal period, or slightly shorter time. The conditions in the rectum would be more or less normal. The effects of codeine upon the alimentary tract, therefore, do not deviate very much from the normal and would not produce a constipating action.

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

Like morphine, the effects of dilaudid upon the stomach are variable. With small doses (0·02 mg./kg.) most animals showed an immediate relaxation of the stomach accompanied by a decrease in the amplitude of gastric peristalsis. 20–40 min. later the tone had recovered to normal while the movements were more regular and increased in amplitude in excess of the normal. A second decrease in tone with increased movements followed in 10–20 min. and was sustained for 2–4 hr. In some experiments no changes in the amplitude, or rate of movements were recorded.

Dilaudid produces more marked effects upon the pyloric sphincter than either morphine, heroin, or codeine. The tone and amplitude of the movements are both increased, while the frequency of the movements is reduced. These effects immediately follow the administration of the drug by the intravenous route and are delayed 10–20 min., when the subcutaneous method is employed. Very small amounts of the drug are extremely active (0·025 mg./kg.). The increase in sphincter tone is followed by a slow but gradual decline to normal. Only in rare instances was normal tone re-established in less than 3 hr., even when small amounts of the drug were administered. The increased sphincter movements usually terminated after 30 min. when the tone level was still greater than normal. From time to time during the next 4 hr. the movements returned for a few minutes every 30–40 min. In some experiments, however, the increased movements were seen over a long period of 30–120 min. before they disappeared. Larger doses of the drug did not usually produce greater effects, but rather prolonged the period of increased activity.

From this evidence it will be seen that the general relaxation of the stomach and the closure of the pyloric sphincter would delay the emptying of the stomach contents into the duodenum. This mechanism is similar to that produced by morphine. The delay, however, would not be so prolonged after dilaudid as after either morphine or heroin.

The effects of dilaudid upon the small intestine and the ileo-colic sphincter were seen to be almost identical with those of morphine. The chief differences between the effects of these two drugs upon the small intestine is quantitative, dilaudid being approximately ten times more potent than morphine.

Dilaudid always produced an immediate increase in the tone of the ileo-colic sphincter which reached a maximum in 2–6 min. when the intravenous route was adopted. Simultaneously, the amplitude of the sphincter movements increased for a period of 10–20 min.

At the end of this time the movements had almost disappeared, while the tone was still well above normal, although below the maximum level recorded immediately after the drug had been injected. At the same time as these sphincter effects were recorded the small intestine became extremely active resulting in an enormous increase in the amplitude of the peristaltic movements. This activity lasted from 1 to 2½ hr.

From this account it will be seen that the effects of dilaudid upon the ileo-colic sphincter are similar, but not so pronounced as those of the pyloric sphincter. This indicates only a moderate obstruction to the progress of the alimentary contents at the ileo-colic sphincter. Owing to the increased peristaltic movements in the small intestine produced by dilaudid it is obvious that little delay would take place in traversing the small gut, while the delay at the ileo-colic sphincter must be intermittent, and moderate compared with morphine.

The caecum and colon were observed to produce most marked effects in response to even small amounts of dilaudid. Very small doses (0·005 mg./kg.) produced no effects upon the general tone of the colon but increased the amplitude of the peristaltic movements to a most marked degree. The frequency of the waves was generally increased at first but later slowed. Larger doses (0·04 mg./kg.) produced similar effects but there was always an immediate increase in tone which never lasted more than a few minutes. This phase of increased activity lasted 6–7 hr. when the tone became subnormal.

The effects of dilaudid upon the rectum were variable. In some animals 0·02 mg./kg. produced only a negligible increase in both the tone and the amplitude of the rectal movements which lasted 14–20 min., after which no further effects were observed. In other experiments, the same dosage produced marked activity of the rectum. There was always a progressive increase in tone during the first 4–6 min. following the intravenous administration of the drug, 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. 40 min. later the tone of the rectum was markedly subnormal and continued to decline to its lowest level which was reached 80 min. after the administration of the drug. It remained at this level for 6 or more hours. The amplitude of the movements remained constant throughout the experiments. Similar results were recorded using larger doses of dilaudid. The most constant effect of the drug upon the rectum was an increase in muscular tone which never lasted longer than 45 min. Later the tone always became subnormal and remained so for many hours. In this latter respect dilaudid resembles morphine.

It is obvious that the effects of dilaudid upon the passage of the alimentary contents through the large bowel are similar to those of morphine. The progress through the small intestine would be influenced by the same factors which cause delay in the subject under the influence of morphine. The effects of dilaudid upon the pyloric and ileo-colic sphincters do not appear to be prolonged so long as those of morphine or heroin and so the delay at these two points would be shorter. The contents in the small intestine would, therefore, be subject less to dehydration and so enter the caecum in a more fluid state than would be the case with morphine. Dilaudid produces conditions in the large intestine which are such as to cause a marked quickening in the passage of the contents into the rectum.

The subnormal condition of the rectal musculature, which takes place one or more hours after the drug has been administered, would cause an overloading

of this viscus. In the human subject Myers & Davidson (1938) recorded the entry of the barium meal into the caecum 3 hr. after dilaudid had been injected subcutaneously. This indicates that the effects upon the ileo-colic sphincter do not markedly delay the passage of food which is swallowed at the same time as the drug is injected by the subcutaneous route. They also observed the delayed passage of the stomach contents into the duodenum which was caused by a pylorospasm of the intermittent type. 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 morphine or heroin. These observations are supported by the results of the present experimental investigation.

This evidence suggests that dilaudid is probably a constipating drug although this effect may not be so marked as that produced by morphine.

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

In many ways the effects of dicodid upon the stomach resemble those of codeine. The intravenous administration of 0·5 mg./kg. dicodid into cats always produced a small gradual increase in tone which reached a maximum in about 25 min. when it slowly declined to normal again during the next 6–12 min. Periods of increased tone, followed by a gradual return to normal level were frequently seen at this stage. Each wave lasted approximately 20 min. Three or four such waves in succession were usually recorded, after which they ceased and the tone diminished to a subnormal level. This relaxation of the stomach usually lasted a further 2 hr. Large doses of dicodid caused a more prolonged period of relaxation. Stomach movements usually increased in amplitude, reaching a maximum at 3 hr. This was maintained a further 3–4 hr. before they began to return to normal again.

Small amounts of dicodid (0·25–1 mg./kg.) always increased the tone, and later, the amplitude of the movements of the pyloric sphincter. The maximum tone was reached in 15 min., after which it declined to subnormal during the next 30 min. This relaxation became increasingly more marked during the next few hours while the movements showed increased activity. Larger doses of dicodid (5 mg./kg.) produced similar effects but they were never so marked or so prolonged as when smaller doses were employed. This is a point of marked difference between the effects of dicodid on the one hand and morphine, heroin, and dilaudid on the other.

These effects of dicodid upon the stomach and pyloric sphincter would not offer any resistance to the normal passage of stomach contents into the duodenum and in this respect the effects of dicodid differ markedly from those of morphine, heroin, and dilaudid.

The injection of 0·4 mg./kg. of dicodid intravenously produced a very small increase in the tone of the small intestine, which required nearly an hour to attain its maximum level. 5 min. later the tone had relaxed to normal while the activity of the peristaltic movements increased to a very short period of 2 min. During the ensuing 7–10 min. the intestines were quiescent and then suddenly became active again for 3 or 4 min. During this period, both tone and amplitude of the movements were increased. A sudden decrease in tone to a subnormal level then occurred while the movements almost disappeared. This inactive state of the small intestine was continued for 15 min. when a further period of renewed activity in movements at normal tone level took place and lasted about 6 min. These alternate periods of inhibition and excessive activity continued over a period of 1½–2¼ hr. Similar effects were obtained using larger doses (1–2 mg./kg.). Very large doses (5–10 mg./kg.) produced an immediate inhibition of movements and marked loss of tone of the small intestine.

The ileo-colic sphincter always showed a decided increase in tone and movements within a few minutes of the drug being injected. The maximum tone level was reached in 20–40 min. after which it slowly relaxed to normal during the next 5–10 min. As the tone relaxed, the movements showed a decided increase in amplitude and their frequency diminished. This phase of normal tone was maintained for only about 5 min. when it began to increase again, and relax to normal once more after a further 20–30 min. During this period the movements were increased. About 60 min. after the dicodid had been injected the tone became slightly subnormal and remained so during the next 6–7 hr. The peristaltic movements reached a maximum at 3 hr. and were maintained for a further 3 hr., after which they began to diminish in amplitude.

From this account it will be seen that dicodid causes little or no delay to the passage of food from the stomach to the duodenum. At the 30 min. stage when the tone of the pyloric sphincter was subnormal and the gastric movements increased in amplitude, the conditions should favour a better filling of the upper coils of the small intestine from the meal in the stomach than under normal control conditions without the use of the drug. Once the food is in the duodenum it would be hurried onwards to the ileo-colic sphincter by the increased activity of the small intestine where it should arrive in a shorter time than that normally required to traverse this section of the alimentary tract. The delay at the ileo-colic sphincter would not be greater than about 30 min., even to the residues present at this point when the drug is administered. No delay would be caused to any food swallowed at the same time as the drug is injected because the tonic effects of the drug on the ileo-colic sphincter would have passed away long before the meal would be able to reach this point. Consequently the meal would be unhindered in its passage into the caecum which it would enter ahead of normal time. When large doses of dicodid are employed there may be some delay in the small intestine owing to the inhibition of intestinal tone and movements.

The most marked effect of dicodid upon the caecum and colon is the increase in the amplitude of the peristaltic movements which follows its use. This effect is not immediate and only begins to show itself 1–2 hr. after the intravenous administration of the drug or about 3 hr. after subcutaneous injection. The maximum movements usually appeared 2–3 hr. after the drug had been injected into a vein, and was ½–1 hr. later when the oral route was used. The effect lasted 1–2½ hr. The general tone of the large intestine was slightly raised after 1 hr. and rarely lasted longer than 60 min. after which it declined to a normal or subnormal level. The effects of dicodid upon the general tone of the large intestine were much less marked than those produced by morphine or heroin but it increased the amplitude of the peristaltic movements to a much greater degree than the other two drugs.

Dicodid caused a marked stimulation of the rectum which was greater and more prolonged than that seen following the use of either morphine, heroin, or dilaudid. Small amounts of the drug (0·08 mg./kg.) always produced a marked increase in the tone of the rectum reaching a maximum at 3 min. when it declined during the next 6 min. to a level slightly above normal. Within 1 min. the tone level quickly increased again but never reached the previously recorded maximum level. At this stage the movements invariably began to increase in amplitude while their rate increased as well. 15 min. later the amplitude and rate of the movements were normal once again while the tone was still slightly greater than normal. 2 min. later the tone began to increase once more. These periods of increased tone followed by relaxation recurred regularly every 15–25 min. during the next 4½ hr.

At the end of the 8 hr. stage the rectal tone was still slightly greater than normal, which is a contrast to the condition of the rectum seen at the same stage following the use of morphine.

This experimental evidence suggests that the effects of dicodid upon the large intestine would not delay the passage of the alimentary contents along this part of the alimentary canal. On the contrary, if any deviation from the normal rate were to take place, it would be in the nature of a quickening of their passage into the rectum. Here, the rectal activity set up by the drug would be very favourable to a rapid emptying of the rectum, while the slightly increased tone of the rectal musculature produced by the drug would not favour any overloading of the rectum with a subsequent stagnation of faeces in this position. From these deductions it would appear that dicodid, in moderate doses, promoted the passage of the alimentary contents along the tract and that no factors are produced which would lead to constipation. These conclusions agree with the findings of Myers & Davidson (1938) in the case of the human subject.

(*f*) *Dihydroxycodeinone hydrochloride* (*eukodol*)

The effects of eukodol upon the stomach were seen to be very similar to those of dicodid but in this respect eukodol appears to be a little more active than dicodid.

The effects of these two drugs upon the pyloric sphincter bear a close resemblance to one another. Small doses of eukodol (0·1 mg./kg.), given intravenously, always produced an immediate gradual increase in tone while the movements increased in amplitude. The sphincter continued to increase in tone for 10–20 min. after which it declined to normal during the next 20–40 min. The sphincter continued to decrease to a subnormal tone level and remained at this level for 4–5 hr. During the whole of this period the amplitude of the sphincter movements was greater than normal.

From these results it will be seen that the effects of eukodol upon the pyloric sphincter are such as to cause a delay of approximately 15–60 min. in the passage of the stomach contents into the small intestine, according to the dosage employed.

Quite small doses of eukodol (0·01 mg./kg.) always increased the amplitude of the movements of the small intestine without much alteration in the muscular tone. Any change in tone was always a negligible increase followed by a very slight decrease to a subnormal level. Larger doses (0·5 mg./kg.) generally produced a small increase in tone as well as movements. The small increase in tone persisted for 30 min. or more before becoming normal again, whereas the increased movements continued for 3–4 hr.

Eukodol, in doses as small as 0·05 mg./kg., always produced a slow progressive increase in the tone of the ileo-colic sphincter which was never very marked. 30 min. later the tone was normal again and remained at this level for many hours (8–9 hr.). In a few animals a marked relaxation of the sphincter lasting 2–3 hr. was recorded following the initial period of increased tone. The movements of the sphincter were always increased.

From this evidence there appears to be nothing to delay the passage of food from the duodenum to the caecum; on the contrary it is possible that the increased peristalsis produced in the small intestine may promote its passage

in a time somewhat less than normal. The delay at the ileo-colic sphincter would be intermittent and not exceed 30 min. It might be inferred, therefore, that there would be no excessive dehydration of the fluid contents of the gut during their stay in the small intestine and so their passage into the caecum should be relatively easy.

Even small doses of eukodol (0·01 mg./kg.) caused a marked increase in the amplitude of the movements of the large intestine. No increase in the tone of the colon was observed except when much larger doses were employed. This increase in tone was rarely excessive and was never prolonged more than 15–30 min. The period of increased movements usually continued for approximately 30 min. although in a few experiments they continued as long as 3–4 hr. before becoming normal again. This increase in the movements was much greater than the increase seen following the administration of morphine or heroin.

The effects of eukodol upon the rectum showed a resemblance to those of morphine on the one hand and those of dicodid on the other. Eukodol, 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 lasting 18–25 min. and separated from the next one by an interval of 8–15 min., were observed throughout the first $2\frac{1}{2}$–3 hr. following the administration of the drug. The effects of eukodol upon the rectal movements were extremely marked. The maximum increase in 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 still decreasing in both rate and amplitude. When moderate doses of eukodol are employed there appears to be little reason why the contents of the colon should not pass into the rectum in normal time. When larger doses are employed, and should the increased movements continue as long as 3–4 hr., as was observed in a few experiments, then the time may be less than normal. In any case there appears to be no reason for any delay beyond that caused by the closure of the pyloric sphincter. The loss of rectal tone which was always seen at the 6 hr. stage would present conditions favourable for the overloading of the rectum, whereas the increased amplitude of the rectal movements, which were declining, but still greater than normal, at this 6 hr. stage would be favourable for the emptying of the rectum. Should the defaecation reflex, however, be postponed beyond this time then it is possible that the conditions may not be so suitable for the emptying of the rectum. In such circumstances it may be possible for constipation to follow. Myers & Davidson (1938) observed a well-marked pylorospasm in the human subject following the subcutaneous injection of eukodol. This caused some delayed emptying of the stomach. At the 3 hr. stage, however, the stomach was empty and the meal was lying 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 the 6 hr. stage, however, the meal had advanced well into the hepatic flexure and was practically the same as the control at this stage. The short delay seen at the 3 hr. stage is therefore

probably due entirely to the delay produced by the closure of the pyloric sphincter. These results are support for those of the present communication.

It is interesting to observe the effects of the individual drugs upon the rectum 8 hr. after their administration by either the intravenous or subcutaneous routes. In so far as the tone of the rectum is concerned they fall into two main groups. First those which produce a subnormal tone level and this group includes morphine, dilaudid in moderate or large doses, and eukodol. The second group leaves the rectum either at a normal or slightly increased tone level and embraces heroin, codeine, dilaudid in small doses, and dicodid. It will be seen that morphine, which is definitely a constipating drug, leaves the rectum dilated, whereas heroin, which does not produce constipation, never leaves the rectum in a dilated condition.

Codeine produces the smallest increase in the amplitude of the rectal movements, whereas dicodid and eukodol produce the greatest increase in amplitude and duration of this increased activity.

Some of these drugs produced secondary waves of increased tone followed by relaxation. The drugs producing these waves, and the periods of duration were: eukodol $2\frac{1}{2}$–3 hr., dicodid $\frac{1}{2}$–$4\frac{1}{2}$ hr., morphine $\frac{1}{2}$–$4\frac{1}{2}$ hr., heroin $\frac{1}{2}$–4 hr. No secondary waves of increased tone of the rectum were observed following the administration of codeine, or dilaudid.

In this discussion no account has been taken of the defaecation reflex. Normally, this is probably governed by two centres. The first lies in the floor of the 4th ventricle close to the vomiting and respiratory centres, while a second centre is believed to exist in the spinal column at the level of the 2nd, 3rd, and 4th sacral segments. Morphine, heroin, codeine, dilaudid, dicodid and eukodol, depress the respiratory centre in a greater or lesser degree (Myers, 1933). In view of this, it is possible that these drugs may depress the defaecation centre in the medulla, and so abolish the reflex. It is doubtful whether this action would account for the constipating effects of morphine, otherwise all these other drugs would produce constipation.

In so far as the spinal centre is concerned, destruction of this region need not lead to faecal incontinence because the rectum, like the bladder, is capable of controlling evacuation through its intrinsic nervous mechanisms. It is probable, therefore, that the constipating action of morphine is due to the mechanical causes which have been outlined in this communication, coupled with the diminished attention to internal stimuli which the drug produces. Barclay (1933) suggests that three types of constipation exist. The first, and most frequent type, being due to an absence of mass movement and inertia of the colon, the second type being caused by a stagnation of the alimentary contents in the caecum and ascending colon while the third type is due to a stagnation in the rectum. Hurst (1909) regards the last type as a fault of defaecation often acquired through persistent neglect of the call to stool rather than to true constipation. In this condition the rectum is ballooned and

atonic, even when emptied. The effects of morphine show a close relationship with this third type.

In conclusion, it will be interesting to see how these results agree with those obtained by the clinicians in medical practice.

III. Summary

1. The mechanical effects of morphine, heroin, codeine, dilaudid, dicodid, and eukodol upon the alimentary tract are discussed and contrasted.

2. The results of these mechanical effects upon the passage of food along the alimentary canal are discussed.

3. The constipating action of morphine is explained upon an almost purely mechanical basis.

4. From experimental evidence it is concluded that dilaudid is probably a constipating drug although this effect may not be so marked as that produced by morphine.

5. There is no experimental evidence to suggest that the administration of dicodid would ever produce constipation.

6. It is suggested that small doses of eukodol are not constipating, whereas large doses, in certain circumstances which are discussed, may produce a mild degree of constipation.

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