making good the deficiency; the mechanism responsible for the sterilization of the spinal fluid might possibly be assisted.

Precipitation

Zozaya and Wood⁷⁸ (1932) have stated that the soluble specific carbohydrates and "nucleoproteins," obtained from the various types of meningococci and other Gram-negative cocci, have very similar properties and are not type-specific. In their experience the precipitable substance did not appear in the serum of horses undergoing immunization until the fourth month or later. Agglutination and precipitation did not run parallel.

GONOCOCCUS

Toxic Products

Tulloch⁷⁹ (1929), writing in the *System of Bacteriology*, has stated that we have "frankly to admit ignorance of the precise nature both of the invasive mechanism and of the disease-producing mechanism of the gonococcus." Cultures, filtrates, and autolysates are all toxic to laboratory animals, the maximum toxicity being after prolonged incubation—which perhaps suggests that so-called "endotoxins" liberated by autolysis of the cocci are the essential toxic constituent.

Serums and Vaccines

As in the case of antimeningococcus serum, there is no adequate method of titration of the so-called "antibacterial" serum used in the treatment of gonorrhoea and its complications. Satisfactory evidence as to its clinical efficacy is also lacking. Vaccines may be of some value in the prevention and treatment of complications, although the published evidence does not lend itself to statistical analysis.

Precipitation, Agglutination, and Complement Fixation

I have previously mentioned that the soluble specific substances and nucleoproteins of all the Gram-negative cocci have very similar properties and are not type-specific (Zozaya and Wood,⁸⁰ 1932). As regards agglutination, serological types exist for the gonococcus as for the other organisms we have considered, but the difficulties in the technique of the agglutination reaction are considerable, and it is not always easy to reconcile the results of different workers. The complement-fixation test (see Tulloch,⁷⁹ 1929; Price,⁸¹ 1930; Osmond and Oliver,⁸² 1929) is of value in the diagnosis of gonorrhoea, but great care and experience are necessary in the technique of the reaction and in its interpretation. It is generally negative in the early stages of the disease, and positive for some time after cure has been effected. It is almost always positive when complications are present, and is therefore of considerable value in the diagnosis of arthritic and gynaecological diseases. The reaction ceases to be of diagnostic significance if specific vaccine treatment has been employed.

CONCLUSION

It will be seen from this brief review of the serology of the pathogenic cocci that considerable advances have been made of recent years in connexion with the Gram-positive group. As regards the meningococcus and gonococcus, the present position is much less satisfactory, but there are already some indications that more efficient antimeningococcal serums may become available. So far the serologist's most valuable contribution to the gonococcus problem has been the complement-fixation test.

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AN INVESTIGATION ON THE PHARMACOLOGICAL ACTION OF SOME NEW SUBSTITUTES FOR MORPHINE AND HEROIN

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The fact that new substances akin to morphine are always being produced by the chemical industry is due to the desire to find, by means of fresh chemical combinations, a substance which is as useful as morphine but has not its harmful effects. During the past few years three new synthetic drugs have been manufactured and extensively used on the Continent as substitutes for morphine and heroin. These drugs are being manufactured in Germany, and are marketed under the trade names of "dilaudid," "dicodid," and "eukodol" respectively. The clinical literature on these drugs is fairly extensive, but little has been published with regard to their pharmacological action. Eddy,¹ however, gives an extensive survey of the literature bearing on dilaudid. The object of this investigation was to determine some of the more important pharmacological actions of these drugs and to compare them with morphine and heroin.

Dilaudid.—Chemically this is the hydrochloride of dihydromorphine. It is a derivative of morphine, and is manufactured from this source. The chemical relation to codeine, morphine, and dicodid is apparent from the following formulae. Dilaudid is a white amorphous substance which is soluble in water and alcohol but is insoluble in ether. The aqueous solution has a neutral reaction. The name "dilaudid" is a registered trade name patented by Knoll A.-G., of Ludwigshafen-on-Rhine. The

drug is marketed as a substitute for morphine, and the makers claim for it an analgesic action and a quieting effect on the respiration.

Dicodid.—Dihydrocodeinone is the basis of dicodid. It is manufactured by a patent process by Knoll A.-G., of Ludwigshafen-on-Rhine. Its chemical structure shows it to be a derivative of thebaine. Since, however, it can be obtained from codeine, it must be regarded from the standpoint of production as a derivative of codeine, and so of morphine. Dicodid is the bitartrate of dihydrocodeinone. It is advocated as an analgesic and as a sedative of the respiratory tract.

Eukodol.—This drug is the hydrochloride of dihydroxycodeinone and is manufactured by a patent process by E. Merck of Darmstadt. Eukodol is not a derivative of morphine. It is manufactured from thebaine, and as opium contains but a small quantity of thebaine the

amount of eukodol manufactured must therefore be very limited. No process is known for the manufacture of thebaine from morphine or codeine. It is used as a respiratory sedative and as an analgesic.

ACTION ON THE ALIMENTARY CANAL

(a) *Isolated Intestine.*—The small intestine of young rabbits weighing about 800 grams was used. The isolated intestine was suspended by the Magnus method in a Tyrode bath and the movements recorded on a kymograph.

Dilaudid.—In a concentration of 1 in 100,000 the drug causes a gradual increase in movements, which reach a maximum effect after about twelve minutes; no change in tone was recorded. This effect is followed by a gradual depression of both tone and movements. A solution of 1 in 50,000 rapidly produces a temporary initial increase in the movements of the intestine; this is soon followed by depression of movements and loss of intestinal tone. A concentration of 1 in 20,000 causes a rapid depression of both tone and movements.

Dicodid.—A concentration of 1 in 100,000 at first produces an increase in intestinal movements without any change of tone. Later, however, there is a depression of both tone and movements. A concentration of 1 in 20,000 causes an immediate initial increase in tone and movements, which is rapidly followed by a depression of both tone and movements.

Eukodol.—This drug has little effect upon the intestine. A solution of 1 in 100,000 is entirely without effect on the isolated intestine. One of 1 in 20,000, however, produces a gradual increase in intestinal tone, but has no effect upon the movements.

These results show that dilaudid and dicodid have a similar action upon the isolated intestine. Weaker concentrations at first stimulate the movements; this is followed by a depression. Weak solutions of these drugs have no effect upon the tone of the intestine. Greater concentrations, however, cause depression of both the movements. These effects are similar to, but much weaker than, those produced by heroin in the same concentrations. Heroin has a greater effect on the intestinal tone. Eukodol has no marked action on the isolated intestine and, in this respect, differs from dilaudid, dicodid, and heroin.

(b) *Intact Intestine.*—This was studied in pithed cats, which were kept alive by means of artificial respiration. A balloon recorder was placed in the lumen of the intestine and connected to a water manometer and a recording tambour. The drugs were injected intravenously via a cannula ligatured into the external jugular vein.

Dilaudid.—The intravenous injection of 1 mg. of dilaudid produces an immediate but insignificant loss of tone. After a few minutes the gut movements begin to increase. An injection of 10 mg. produces a well-marked increase in tone and movements, which may continue to increase gradually for thirty minutes or more. These increased movements are completely inhibited by an injection of 0.5 c.cm. adrenaline 1 in 20,000, or 0.5 unit of pituitrin.

Dicodid.—This drug in doses as small as 0.5 mg. causes an increase in intestinal tone and movements (Fig. 1), which can be inhibited by the injection of adrenaline or pituitrin. Larger doses of 20 mg. produce an immediate inhibition of movements, an effect which resembles the inhibition caused by adrenaline; complete recovery of both tone and movements follows in about ten minutes.

Eukodol.—Injections of 5 mg. or less have no effect whatever on the intestine; 10 mg., however, cause a marked increase in tone and movements; the intestine recovers to its normal condition fifteen minutes later.

These results agree with those obtained using isolated intestine, and clearly show that dilaudid and dicodid in small doses stimulate the tone and movements of the intestines in the same manner as small amounts of morphine or heroin. Depression of the intestine quickly

follows the injection of large doses. Uhlmann and Abelin,² who studied the action of morphine, hold that the effects on the small intestine are essentially similar in excised intestines and in living animals—namely, that very small doses depress the peristalsis, slightly larger doses stimulate the movements, and still larger doses produce a maximal stimulation, followed by paralysis. It will be seen that the results obtained in this investigation using dilaudid, dicodid, and eukodol closely approximate those of morphine. The early stage of depression described by Uhlmann and Abelin for very small doses of morphine was not obtained with dilaudid, dicodid, or eukodol.

(c) *Pyloric Sphincter and Stomach Movements*.—The movements of the pyloric sphincter were recorded by using a modified form of the apparatus described by Elliott.⁵ Stomach movements were recorded by the balloon method. Cats which had been pithed and kept alive by means of artificial respiration were used, and all injections were given intravenously via the external jugular vein. The abdomen was opened and the recorder passed through an artificial opening made in the wall of the duodenum until the membrane rested in the sphincter of the pylorus.

FIG. 1.—Intestinal movements and blood pressure, showing the effect of injecting 0.5 mg. dicodid.

The stem of the recorder was ligatured to the duodenum so as to prevent the apparatus slipping from the embrace of the sphincter. The abdomen was then closed and a water manometer attached to the pyloric recorder. Another manometer was connected to the balloon in the stomach, each manometer being connected to a recording tambour.

Dilaudid.—The intravenous injection of 0.5 mg. or 1 mg. of this drug produces a gradual well-marked increase in the movements of this sphincter, which reach a maximum effect after about thirty minutes. These increased movements may be continued for a period of two or three hours. At the same time the stomach movements are markedly increased, but the general muscular tone is not altered. The action on the stomach is slow and gradual, and reaches a maximum effect after about forty minutes. Larger doses of 10 mg. produce a similar effect, which is more rapid in onset and not so prolonged.

Dicodid.—The action of this drug upon both the pyloric sphincter and the stomach is so small as to be negligible. The injection of doses of 10 or 20 mg. produces only a slight increase in the tone and movements of the pylorus and the stomach.

Eukodol.—Ten mg., when given intravenously, produce a slight increase in the movements of the sphincter without any change in the muscle tone. The movements return to normal in ten or fifteen minutes. Smaller amounts of the drug have no effect, or an effect which is so small as to be negligible. The action on the stomach is similar to that of dicodid, but it is a little more marked. The movements are only slightly increased with doses of 10 to 20 mg.; the tone is not altered. Smaller doses have no effect. This feeble

action of dicodid and eukodol is very similar to that of codeine.

Dilaudid is the only one of these three drugs which has a marked effect on the pyloric sphincter and the stomach, and in this respect it resembles morphine. Magnus,³ who investigated the passage of the alimentary contents by x-ray methods, found that morphine acts upon the stomach, producing contraction of the sphincter antri pylori, and the pyloric and cardiac sphincters; this caused a delayed passage of food from the stomach to the intestines. Other observers⁴ have shown that morphine tends to produce nausea and vomiting, and that the effect is independent of the mode of administration, the action being central. For comparative purposes it was decided to record the movements of the pylorus and the stomach, produced by morphine hydrochloride in exactly the same way as already described. It was found that an injection of 5 mg. causes a slight increase in the movements of the

FIG. 2.—Upper tracing shows movements of the ileo-colic sphincter. Lower shows intestinal movements. One mg. dilaudid injected, six minutes interval. Time, 10 seconds.

stomach, but has little effect on the muscle tone. The movements and the tone of the pyloric sphincter are, however, increased in a most marked way. This action on the sphincter is slow and gradual, and only begins to take place two or three minutes after the drug has been injected. An injection of 20 mg., however, causes a most marked increase in both the tone and the movements of the stomach, which, when they reach a certain magnitude, result in true vomiting or retching by the animal. The pyloric sphincter shows a gradual but profound increase in tone and movements. Heroin in doses of 5 to 20 mg. increases the movements of the sphincter without altering the general tone of the muscle. This drug apparently has no effect on the stomach movements, as no changes were recorded using injections of 0.5 to 30 mg. These results show morphine to have a most active effect on the stomach and the pyloric sphincter. In this respect dilaudid resembles morphine much more than either dicodid or eukodol, which have a much weaker action.

(d) *Ileo-colic Sphincter*.—The movements of this sphincter were studied in cats which had been pithed and kept alive by means of artificial respiration. The method described by Elliott⁵ was adopted. All injections were given intravenously via the external jugular vein. The method of recording was similar to that employed in the case of the pyloric sphincter.

Dilaudid.—One mg. when injected causes a profound increase in movements and tone, which lasts for ten to twenty minutes (Fig. 2). Larger doses of 10 mg. have a similar but

more marked effect which lasts for a longer period; it is common for the tone to be still increasing as long as thirty to forty minutes after the injection. An injection of 0.25 c.cm. adrenaline 1 in 20,000 inhibits these increased movements, but slightly increases the tone of the sphincter.

Dicodid.—This drug has an action similar to dilaudid; 1 mg. and 10 mg. produce the same effects as dilaudid.

Eukodol.—Injections of 1 mg. have no effect on the sphincter, but doses of 10 mg. cause an immediate increase in tone similar to that produced by dilaudid. These effects continue for ten to fifteen minutes, when the condition of the sphincter returns to normal.

Morphine.—The tone of the sphincter is immediately increased after the administration of 2 to 10 mg. Heroin in similar doses produces the same effects, which were found to last, in some cases, for thirty minutes or more.

These results show that dilaudid, dicodid, and eukodol increase the tone of the ileo-colic sphincter in the same manner as morphine and heroin. It is interesting to note that dicodid, which has such a weak action on the pyloric sphincter, has a well-marked action on the ileo-colic sphincter. Elliott⁵ has shown that stimulation of the sympathetic nerves in the lumbar roots of the spinal column causes the sphincter to contract. He also showed that adrenaline produces the same effect as sympathetic stimulation—that is, constriction of the sphincter. It would appear from these results as if these drugs act either on the sympathetic system or directly on the intestinal muscle.

RESPIRATION

Cats anaesthetized with ether and urethane were used. Respiratory movements were recorded in two ways. First, by means of a ligature from the xiphisternum to a hook in the centre of a tambour, which was in turn attached to a recording tambour. The second method was by means of a tambour placed against the chest. Blood pressure was recorded from the right carotid artery, and the drugs were injected intravenously via a cannula ligatured into the external jugular vein.

Dilaudid.—This drug produces a most profound effect on the respiration, which becomes slower and deeper. The general effect resembles that produced by morphine. Doses as small as 0.25 mg. were found to slow the respiration from a normal rate of 70 or 80 per minute to 16 or 20 per minute, the depth being gradually increased to twice the normal amount. Larger amounts of the drug produce similar effects, but the respiration rate was never slowed to less than 16 per minute without causing complete failure of the respiratory centre in the medulla, which necessitated the use of artificial respiration.

Dicodid.—This drug has an action on respiration which is very similar to that of dilaudid and morphine. When given intravenously the breathing becomes slower and deeper. One mg. was found to slow the respiration from a normal rate of 60 per minute to 16 per minute, while the depth was increased. Similar effects were produced by larger doses.

Eukodol.—This drug has a marked effect upon the respiration. Even small doses cause a slowing and deepening, which is similar to that produced by dilaudid, dicodid, and morphine. An injection of 0.125 mg. has a most marked action; 0.5 mg. was found to slow the respiration of a 2-kilo cat from 40 to 16 per minute, and more than double the depth of respiration.

Heroin.—The action of this drug is similar; 0.5 mg. slowed the respiration from 46 to 16 per minute. The increase in depth with this amount of the drug is not so pronounced as with dilaudid or dicodid.

Toxic doses of any one of these drugs produce a serious progressive depression of the respiratory centre, as shown by the marked decrease in rate, depth, and efficiency of respiration. In each case the respiration is finally arrested before the heart is seriously injured. It is evident, therefore, that dilaudid, dicodid, and eukodol in both therapeutic and toxic doses produce an effect upon the respiration which is similar to that of morphine and heroin. An

interesting observation with regard to the toxicity of dilaudid and eukodol was made as a result of these experiments. It was found that if an initial dose not exceeding 1 mg. per kilo be injected into an anaesthetized cat then the respiration becomes slower and deeper. Much larger doses of 30 to 40 mg. per injection can be now given without having much further effect on the respiration. On the other hand, if an initial dose in excess of approximately 5 mg. per kilo be given, then the respiration ceases and the animal dies. Similar observations were made with eukodol in similar doses. The explanation of this increased tolerance to dilaudid and eukodol after therapeutic doses is not apparent. One might suggest that some form of tissue immunity is quickly developed, or that the tissue cells become more able to detoxicate the drugs, or that excretion is facilitated in some way or other. Further experiments are now in progress with a view to obtaining an explanation of this phenomenon. Large doses of dicodid are tolerated well by anaesthetized cats, it being almost impossible to kill the animal with the drug. Experiments on the bronchioles of cats showed that dilaudid, dicodid, and eukodol have no action on this structure.

ACTION ON VAGUS CENTRE IN MEDULLA

Cats anaesthetized with urethane were used, and the blood pressure and the respiratory movements recorded. Both vagi were cut, and the central end of each stimulated in turn until the minimum current to produce an effect on the respiration was determined. The drug under test was then injected intravenously and the stimulations repeated. Typical protocols are tabulated below.

TABLE I.—Cat (3.4 kilos)
Dilaudid

	Vagus	Coil	Result
Normal	Left	30 27 24 21	— — + ++
1 mg. dilaudid (intravenous)		30	++
10 minutes' interval ...		33 36 39	++ + —

TABLE II.—Cat (2.8 kilos)
Dilaudid

	Vagus	Coil	Result
Normal	Right	21 18 15	— + ++
2.5 mg. dilaudid		21 24 27	++ ++ —
10 minutes' interval ...		27 24 21 18 15	— — — — ++

TABLE III.—Cat (3.6 kilos)
Dicodid

	Vagus	Coil	Result
Normal	Left	30 27 24	— — ++
1 mg. dicodid		27 30 33	++ + —
10 mg. dicodid		27 30 33	+++ ++ +
10 mg. dicodid		36 30 27	— — ++

TABLE IV.—Cat (2.5 kilos)
Eukodol

	Vagus	Coil	Result
Normal	Left	33	—
		30	++
½ mg. eukodol... ..		33	—
		30	++
½ mg. eukodol... ..		30	+
		27	++
1 mg. eukodol		30	—
		27	+
		24	++
		21	++

The results set out in Tables I and II show clearly that the sensitivity of the central vagus is considerably increased after the administration of small doses of dilaudid. Larger doses quickly depress the vagus after a short period of initial stimulation. Table III shows that dicodid in small doses stimulates the vagal centre, while larger doses lead to depression. Eukodol appears to depress the vagus centre from the beginning, even with very small doses. Jackson and Ewing,⁶ Cohn,⁷ and others have shown that morphine increases the reflex excitability of the vagus centre. It is obvious, therefore, that dilaudid and dicodid resemble morphine in this respect, while eukodol is devoid of this action.

THE CORD

Dilaudid and dicodid in large doses have a well-marked action on the spinal reflexes. One large dose of either of these drugs, or several smaller doses given within a short space of time, will produce twitching of the limbs or the whole body. These twitchings, when severe, are of a convulsive nature, and can always be produced in the unconscious, pithed, or anaesthetized animal. A series of intravenous injections of either of these drugs, totalling 20 mg., given within fifteen minutes, was observed to produce increased reflexes with struggles in a pithed cat weighing 2 kilos. Smaller doses of 1 to 5 mg. do not visibly affect the spinal reflexes. Nau⁸ compared the effects of morphine, dilaudid, and heroin on the central nervous systems of tadpoles, frogs, toads, and fishes. He concluded that all three drugs produced paralysis and convulsions. Larger doses per kilo of dicodid than of dilaudid are required to increase the reflexes. It was found by experiment that an average cat weighing 2.5 kilos required a total of 40 mg., given in smaller doses, in a series of intravenous injections, to produce twitchings. The period during which the reflexes are increased may vary from a few minutes to almost an hour, according to the amount of the drug injected. The twitchings can be abolished immediately by injecting curare or by destroying the cord. They never take place with therapeutic doses, but only when these amounts are grossly exceeded. These effects are similar to those produced by morphine hydrochloride, which is much more active in this respect than either dilaudid or dicodid. Injections of 0.5 mg. of morphine hydrochloride will produce the same effects in a cat anaesthetized with urethane as 20 to 40 mg. of dilaudid or dicodid. Heroin produces similar effects. Eukodol, in even large doses of 60 to 100 mg., has no effect on the spinal reflexes. This is not what one would expect in view of the fact that eukodol is manufactured from thebaine, which is a powerful convulsant.

BLOOD PRESSURE

The effect of dilaudid, dicodid, or eukodol on the blood pressure is so slight as to be almost negligible. Injections of 0.5 to 5 mg. of dilaudid produce a slow gradual rise of 10 to 15 mm. of mercury in twenty to thirty minutes. Larger doses, of 20 mg. or more, generally have a reverse effect—a slight gradual fall of 10 to 20 mm. The heart

is generally slowed; this is of central origin. Dicodid or eukodol in doses as large as 30 mg. have little or no effect upon the blood pressure or on the heart's action. With any of these drugs the circulation remains fairly good, even after toxic doses, until death occurs by paralysis of the respiration.

EFFECTS ON THE NORMAL ANIMAL

Dilaudid

(a) *Small Doses*.—A mouse weighing 16 grams was injected subcutaneously with 0.25 mg. dilaudid, and the following effects were observed.

10.40 a.m.—Injection given.

10.43 a.m.—The animal quickly showed signs of restlessness, and commenced to walk around the cage in a regular, monotonous way, with its tail stiff and erect. The respiration is markedly slower and deeper.

10.55 a.m.—There is great difficulty in using the hind limbs, which trail behind. The gait resembles the hyenoid walk seen in the dog under the influence of morphine.

11.5 a.m.—Marked analgesia is present; the animal does not resent pinching of the tail, as do the control mice.

11.40 a.m.—No change.

1.25 p.m.—The animal is walking better, but is still very restless. It walks continuously round the cage in an automatic way, and does not stop to rest like the control animals. It has no interest in food or its surroundings. It does not investigate obstacles placed in its path, but at once retraces its steps without trying to find a way around it. Should the obstacle be another mouse then it persistently pushes against it until it forces a way past.

1 p.m.—The gait is returning to normal, otherwise its condition is as before. The tail is still stiff and erect.

1.30 p.m.—There is a definite improvement. The condition has almost returned to normal. The animal stops to rest, and takes an interest in food. The gait is almost normal again, but the tail is still stiff and erect.

2 p.m.—Condition normal.

These results agree with those of Schoen,⁹ who observed the effects produced in rabbits after the injection of dilaudid. He records slowing of the respiration, analgesia, abolition of postural reflexes, and an increase in general muscular tone.

(b) *Toxic Doses*.—One mg. of dilaudid was injected subcutaneously into a 16-gram mouse.

2.30 p.m.—Injection.

2.43 p.m.—The tail is stiff and erect, respiration is markedly slower and deeper, and the mouse walks around in an automatic fashion without resting.

3.5 p.m.—The animal is now more sensitive to noise than the controls. The restlessness is still present. The hind limbs become stiff and spastic from time to time, which renders walking very difficult.

3.15 p.m.—Walking is becoming increasingly difficult.

3.30 p.m.—The gait is more spastic than before, and the spinal reflexes are enormously increased.

3.45 p.m.—The hind limbs appear to be paralysed. The animal can only move a few inches at a time, and then falls as if intoxicated, with its hind legs stretched out rigidly behind and the tail stiff into the air.

3.55 p.m.—Both hind limbs and fore limbs appear paralysed. The animal is almost unable to move.

4.20 p.m.—Great difficulty is experienced in recovering its posture after having been placed on its back. The reflexes are still very active.

4.23 p.m.—Convulsions, followed by death.

Dicodid

(a) *Small Doses*.—One mg. was injected subcutaneously into a 16-gram mouse:

10.45 a.m.—Drug injected.

10.50 a.m.—Tail stiff and erect. Respiration is slower and deeper. The animal walks around the cage in a manner similar to that described for dilaudid. There is great difficulty in walking. The animal stops from time to time, and rests on its belly with its hind limbs stretched out stiffly behind. There is marked analgesia present.

11.20 a.m.—Condition the same. The restlessness continues. The control mouse sits still most of the time, while the other keeps moving continuously in an automatic way.

12.10 p.m.—The paralysis of the hind limbs is passing away, and the mouse is now running around in an almost normal manner; but restlessness is still present.

2 p.m.—There is now an interest in food, and the animal is eating well.

2.35 p.m.—The condition is now almost normal again, and the animal is washing itself. It is still more active than the controls.

(b) *Large Doses*.—Ten mg. were injected subcutaneously into a 16-gram mouse. Death took place in fifty minutes in a manner similar to that already described for dilaudid.

Eukodol

(a) *Small Doses*.—A subcutaneous injection of 0.25 mg. was given to a 16-gram mouse.

10.40 a.m.—Drug injected.

10.55 a.m.—Respiration slower and deeper. There is a markedly increased activity. The mouse walks or runs continuously around the cage with its ears and tail stiff and erect.

11.10 a.m.—The condition has not changed beyond a pronounced increase in the reflexes.

11.40 a.m.—Food placed in the cage. The mouse immediately investigated it and ate a fair amount. Analgesia is present, as measured by nipping the tail.

12.10 p.m.—Condition as before.

12.45 p.m.—Condition appears normal again.

The effects produced by a subcutaneous injection of 5 mg. eukodol are almost entirely of a depressant character—apathy, stupor, and analgesia. The acute reflexes are heightened, but firm pressure, such as nipping the tail, which would be very painful in normal animals, elicits no response. There is a peculiar clumsiness and lack of co-ordination in the voluntary movements. The animal stands only with difficulty, walks unsteadily, and often drags its hind limbs in a manner not unlike the "hyenoid walk" described for morphine by Claude Bernard. The respiration is markedly slowed, and the tail erected. Complete recovery takes place later without any untoward symptoms. The effects produced in the mouse by dilaudid and dicodid are almost identical. Small doses of either of these drugs produce marked slowing of the respiration, and analgesia. Larger amounts increase the spinal reflexes, in addition. The toxicity of dicodid is very much less than that of dilaudid. Very large amounts of eukodol are tolerated by mice without any lethal effects. The stiff erection of the tail produced by these drugs has been described by Straub, as taking place in mice after the hypodermic injection of morphine or its esters. Rassers¹⁰ described the same effect with other convulsants, but generally only with large doses. Van Leersum¹¹ believes this to be due to intense tenesmus of the anal and bladder sphincters, originating in the medulla and transmitted through the pelvic nerves, while Heinekamp¹² refers it to stimulation of the spinal cord.

DISCUSSION

It has been shown that the pharmacological actions of dilaudid, dicodid, and eukodol are very similar to those of morphine. Dilaudid approximates very closely to morphine, but is much more toxic; smaller amounts of dilaudid than of morphine are needed to depress the respiratory centre. Dicodid, on the other hand, seems to lie midway between morphine and codeine. Dilaudid has a well-marked action on the gastro-intestinal tract. It stimulates the movements of the intestine and stomach as well as those of the pyloric and ileo-colic sphincters. This action on the gastro-intestinal tract resembles that of heroin. Dicodid increases the movements of the intestine and the ileo-colic sphincter, but has little effect on the stomach and the pyloric sphincter. Both of these drugs increase spinal reflexes and general muscle tone. They slow the respiration and increase the amplitude by depressing the respiratory centre in the medulla; they have little or no action on the bronchioles. Eukodol differs from the others in many ways. It has a much feebler action on the movements of the alimentary tract,

and does not increase spinal reflexes. It has, however, a profound effect upon respiration, which is as marked as that produced by either dilaudid or morphine. Considering that this drug is manufactured from thebaine one might have expected some signs of it being a convulsant, but none were found. On the contrary, it produced depression of the respiratory centre and a marked diminution of pain sense. It has no effect on the bronchioles. It is interesting to note that any or all of these drugs when injected into mice produce a stiffening and an erection of the tail similar to that caused by morphine.

SUMMARY

1. Dilaudid, dicodid, and eukodol have an action on the respiration which is similar to that produced by morphine. They have little or no effect upon the bronchioles.

2. These drugs produce marked analgesia.

3. Dilaudid and dicodid have a marked action upon the tone and movements of the alimentary canal. This effect is very much less marked with eukodol.

4. Small doses of dilaudid or dicodid render the vagal centres in the medulla more sensitive; larger doses depress. Eukodol depresses the centre, even in small doses.

5. Toxic doses of dilaudid or dicodid increase the reflex excitability of the cord. Eukodol does not alter these reflexes.

6. The toxicity of dilaudid and eukodol is much greater than that of dicodid. Anaesthetized cats can withstand enormous doses of these drugs provided that they are administered after a smaller therapeutic dose. An initial large dose causes death from respiratory failure.

7. These drugs have only a negligible action on the cardio-vascular system. Dilaudid causes some slight slowing of the heart, which is central in origin.

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THE TREATMENT OF ACUTE OTITIS MEDIA IN ACUTE FEBRILE CONDITIONS*

BY

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We may assume that practically all cases of acute otitis media arising in acute febrile conditions develop as the result of a spread of infection from the nasopharynx along the Eustachian tube to the middle-ear cleft. This is particularly prone to occur in young children who have enlarged adenoids and tonsils when they develop a common "cold in the head," or suffer from any of the acute infectious fevers. It is estimated that the common "cold in the head" and influenza are responsible for more cases of acute otitis media than all the other infectious fevers combined. The percentage of middle-ear infections in influenza varies greatly in different epidemics. This is true also of all the infectious fevers, but probably about 10 per cent. of scarlet fever and measles patients

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