

THE ACTION OF DRUGS ON RESPIRATION.

I. THE MORPHINE SERIES.

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PLATES 5 AND 6.

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These experiments had their inception in an observation that it was possible to control voluntarily the inspiratory phase of the cough reflex in a certain individual and thus partially or completely to prevent the cough resulting from irritation of the pharynx. When the deep inspiration which precedes a typical cough was prevented there was no actual cough, but frequently a series of contractions of the abdominal muscles followed and these were beyond voluntary control; when a deep inspiration was taken a powerful expiratory contraction almost invariably followed. This seemed to indicate that the expiratory phase of the cough reflex in this individual was under less complete voluntary control than the inspiratory, and suggested the possibility that drugs which have a truly selective or specific action in the control of cough—morphine, heroine, and codeine—might act selectively on the expiratory mechanism unless their action is one of pure narcosis.

The conception of a selective action exerted by drugs on inspiration or expiration is not new. Langlois and Richet (1) found that dogs in deep chloral narcosis were unable to expire against a resistance of 10 to 13 mm. of mercury, while inspiration could be maintained against a considerably higher resistance; unpoisoned animals could readily expire against 28 mm. The expiratory mechanism was apparently more seriously affected than the inspiratory.

On the other hand, Aducco (2), working with dogs also, and recording thoracic and abdominal respiration by means of tambours, described stimulation of expiration by laudanum, hydrated chloral, and aconitine, and found that when chloral was given to the point of respiratory failure expiratory efforts were the last to be abolished. The same author (3) found that cocaine, applied directly to the

medulla, caused a respiratory rhythm of long inspiratory pauses broken by active expirations. He believed that these results pointed to the existence of a separate expiratory center, which often continued to function when the inspiratory center was paralyzed. The production of labored breathing, with active expiratory efforts, by means of laudanum, is not in harmony with the general conception that morphine relieves dyspnea, and it seems probable that many of Aducco's results were not due to direct action of the drugs on the respiratory center.

Dreser (4), in his investigation of the action of heroine on respiration, found that rabbits whose breathing had been made slower and deeper by small doses of the alkaloid were able to expire against resistance more efficiently than animals narcotized by hydrated chloral, and he concluded that heroine has a specific action in increasing the depth of breathing without diminishing the efficiency of the respiratory muscles or the ability to expel mucus from the respiratory passages.

In view of the opposing results obtained by these investigators we know of no convincing evidence to indicate either the existence of distinct centers controlling inspiration and expiration, or the possibility of a truly selective action by drugs on one or the other phase of respiration.

Stimulated by the idea stated in the opening paragraph of this paper, we designed experiments intended to study the possibility of such selective action—more specifically, whether drugs which are known to depress cough selectively have a more marked action on expiration than on inspiration.

Methods.

The first requisites for the experiments appeared to be a controllable stimulus for eliciting expiratory movements and an accurate method for recording them. To cause expiratory movements we have made use of inhalations of CO₂-air mixtures of known and constant strength, for a constant period of time; to record them, after unsuccessful attempts to make use of a slip of an expiratory muscle, we depended on a record of intrathoracic pressure, and, to avoid all possible interference with normal conditions, we obtained this record from the mediastinal space, without opening the pleural cavity.

Cats were used in all the experiments on which this report is based. As a rule, they were decerebrated, through a trephine opening, or by the method described by one of us (5); a number of experiments were made on intact animals anesthetized with ether, urethane, luminal, or chloretone. A tracheal cannula

was generally used, for several experiments done without it convinced us that it did not alter the results. Blood pressure was recorded from a carotid artery, with a mercury manometer; injections were made into a saphenous or jugular vein, or into the muscles of the leg. Respiration was recorded by means of Lieb's modification of the Cushny plethysmograph (6), so that minute volume or average depth of breathing could be estimated.

To obtain the mediastinal record, the upper bone of the sternum was exposed and partly freed of its muscular attachments; the lower end of this bone was flattened by paring its surface with a knife where it widens out to meet the cartilage by which it is joined to the second portion of the sternum. By means of a hand drill, a 3 mm. hole was drilled in the flattened portion, as near the cartilage as possible, but in solid bone, exactly in the midline, sudden penetration being prevented by means of a metal guard set about 1 cm. from the tip of the drill. A metal cannula was then screwed into place; this was made with a tapering shaft, 3 mm. in diameter at the tip, with a light thread cut on the shaft, and provided with openings on the side as well as at the tip. Paraffin oil was introduced from a burette and allowed to flow in slowly by gravity, 10 to 20 cc. being used as a rule. The cannula was then removed, cleaned, reinserted, and connected to a small tambour, covered with very thin, tightly stretched rubber; the tambour was calibrated from a mercury manometer at the end of the experiment.

The oil dissects away the loose areolar tissue of the anterior mediastinum, forming a small pocket whose lateral walls are in contact with the pleura. It is not irritant, and the entire procedure does not visibly alter breathing, even in an unanesthetized (decerebrated) animal. It is not absorbed, and, if the tambour is tightly covered, the record is independent of changes in volume of the heart and vessels. The motion of the lever indicates a lower pressure with inspiration and a rise with expiration. The extent and character of the movements practically duplicate those of a similar tambour connected to a pleural cannula, though frequently the mediastinal record is a miniature of the other. Both show corresponding changes during dyspnea, etc., so that it seems justifiable to depend on the mediastinal record in measuring relative changes, and we have used it only for this purpose.

Sometimes the oil dissects upward, appearing around the carotid artery or trachea. To avoid this, it is advisable to confine the neck dissection to the region of the larynx, and not to free the trachea from its posterior attachments.

Occasionally the mediastinal record is so small, and responds so sluggishly to changing conditions, as to be practically useless. This is usually relieved by removing a little oil, and seems to be due to overdistention. Sometimes a flap of tissue acts as a valve in the sternal cannula; this can readily be removed by inserting a feather or a blunt instrument, as there is little danger of damaging the pleura after the oil has been introduced. Rarely, an animal may be encountered whose mediastinal tissues are apparently so rigid that it is impossible to obtain a satisfactory record by this method. (This is always true in the dog.)

Another disadvantage is a frequent failure of the level of the record to return to normal after a deep gasp, especially when breathing is rapid, as during CO₂ inhalation; this is a defect in the method, as a record from a pleural cannula shows nothing like it; it seems to be due to further dissection by the oil, and usually disappears if dyspnea is repeatedly induced.

The chief advantage in the method, for our purpose, lies in the avoidance of opening the pleural cavity, with consequent danger of leakage and partial collapse of the lung. Some of the results to be described cannot be obtained when the lung is incompletely distended, and, even if the pleural cannula does not leak, it is usually necessary to allow partial collapse of the lung to prevent obstruction of the cannula during inspiration; this may be avoided by introducing a small probang through the cannula, and it is only when this is done, and the lung completely reexpanded, that characteristic results can be obtained with morphine and heroine.

Another advantage, theoretical rather than practical, is found in the avoidance of irritation of the parietal pleura, such as may occur when a pleural cannula is fastened in place, and which may give rise to expiratory reflexes if the animal is not narcotized, as was shown by Kohts (7).

As a matter of fact, we have seen no signs of changes in respiration from the presence of a pleural cannula unless the lung was partly collapsed.

All the results from which the present conclusions are drawn have been confirmed by means of a record of intrathoracic pressure, using a pleural cannula. We have been unable to adapt the mediastinal method to rabbits, because of the narrowness of the sternum, or to dogs, because of the rigidity of the mediastinal tissues.

To elicit active expiratory movements, the animal was allowed to breathe a CO₂-air mixture of 4 to 10 per cent CO₂, for 1 minute, as a rule.

The gas was contained in a spirometer large enough to supply a given mixture for any experiment; the spirometer was weighted, so that the gas issued in a gentle stream through a tube which was fitted with a small cup to be held very loosely over the tracheal cannula, or with a small funnel, to be held loosely over the nose and mouth, if no tracheal cannula was used. In this way rebreathing was largely avoided, and there was no mechanical interference with breathing, as shown by control tests with air in the spirometer. This caused a moderate dyspnea, with a marked increase in depth and usually a definite acceleration in rate. A record of intrathoracic pressure from mediastinal or pleural cannula showed a corresponding increase in depth of inspiration, and also a definite rise in pressure with each expiration.

Recovery was usually complete within 2 minutes, and frequent repetitions had no serious effect on the animal. The inhalation was repeated until constant results were obtained, as a control, and again after drugs were applied. After calibrating the tambour, the mediastinal record was translated into millimeters of pressure, the level reached by the lever during expiration just before CO₂ was applied being used as the line of zero pressure; each CO₂ response had its own zero level, and the results are purely relative. Since the record of respiration was a plethysmographic one, it was thus possible to estimate, approximately at least, the relative parts played by inspiration and expiration in producing a given increase in ventilation, in response to the physiological stimulus CO₂.

The degree of activity of expiration was shown, not only by the height to which the lever rose during expiration, but also by the type of the upward movement. In drawing conclusions, we have used only those experiments in which there was a definite increase in the expiratory level and definitely active expiration during the response to CO₂ in the control period, and have taken pains to confirm the recorded increase in expiration by inspection of the animal.

An example of the type of response to be expected is shown in Fig. 1, a tracing from an experiment on an animal during light ether anesthesia; the data obtained from this tracing are given in Table I.

The mediastinal record before CO₂ was applied shows a fairly sharp upward movement of the lever, culminating in a series of sharp peaks, from which inspirations begin; this corresponds to a definitely active expiratory rhythm, and is quite different from the tracing made when expiration is passive (Fig. 2, *B*). CO₂ inhalation caused a prompt and progressive increase in depth of inspiration, but for about 15 seconds there was no corresponding increase in expiration, and no change in rate; then expiration became sharper, the rate increased, and inspiration became still deeper. The maximum rate and depth were seen when expiration was most active—a uniform result of inhalation of CO₂ or nitrogen in our experiments.

By these methods we have tested the effects of morphine, heroine, and codeine on the respiratory response to CO₂. The results are presented in this paper. In the following paper (8) are outlined the results of similar experiments with chloroform, hydrated chloral, urethane, luminal, and magnesium chloride, together with a few observations on the action of caffeine, strychnine, and atropine after the depression of respiration by those drugs.

RESULTS.

Morphine and heroine were found to exert a selective depressant action on the central expiratory mechanism, without producing narcosis, and often without depressing inspiration. Codeine had no constant effect except stimulation of the spinal cord.

Morphine.—Whenever the rate of breathing was definitely slowed after intravenous or intramuscular injection of this drug, expiration became passive, and, if the dose was sufficient, remained so during CO₂ inhalation; inspiration was often deeper than before, and narcosis did not occur. The dose required to produce this effect in decerebrated cats ranged from 1 to 20 mg.; as a rule, 5 mg. produced definite expiratory depression, which was usually overcome by CO₂ inhalation, while 15 to 20 mg. made expiration completely passive. In animals narcotized by ether, urethane, chloretone, or luminal, 1 mg. of morphine usually produced definitely slower breathing and expiratory depression, while 2 or 3 mg. made expiration completely passive both at rest and in response to CO₂ inhalation.

A typical example of the effect of morphine on the CO₂ response of a decerebrated cat is shown in Fig. 2.

The response before morphine is shown in Tracing A. The sharp upstroke of the mediastinal lever before and during CO₂ inhalation and the greater inspiratory and expiratory efforts during the inhalation are well shown.

Tracing B shows the response of the same animal to the same gas mixture after 20 mg. of morphine. The rate was slower and the rounded contour of the top of the mediastinal record indicates completely passive expiration. The latter observation was confirmed by inspection of the animal. This rounding of the expiratory curve persisted during CO₂ inhalation, and there was no tendency to a rise in mediastinal pressure.

The data derived from these tracings are given in Table II.

It is evident that, while morphine had decreased the rate very definitely, the volume of each breath had slightly increased, so that minute volume was not much reduced during air breathing, and, if the dead space be considered, the slower, deeper breathing after morphine may have been quite as efficient as the apparently greater

TABLE II.

	Air.					CO ₂					Air.				
	0	10	20	30	40	50	60	70	80	90	100	110	120		
Time, sec.....															
Expiratory pressure, mm. Hg.....	{ A 0	0	0	+0.1	+0.6	+0.9	+0.8	+0.7	-0.2	-0.4	-0.6	-0.6	-0.6		
	{ B 0	0	0	0	-0.2	0	0	0	0	0	0	0	0		
Inspiratory " mm. Hg.....	{ A -0.8	-0.8	-0.8	-1.2	-1.4	-1.5	-1.6	-2.0	-1.4	-1.2	-1.2	-1.2	-1.2		
	{ B -1.4	-1.4	-1.4	-1.9	-2.1	-2.1	-2.1	-2.9	-1.8	-1.8	-1.8	-1.8	-1.6		
Rate per min.....	{ A 32			32		40	36		48		28		32		
	{ B 24			20		16	20		24		28		28		
Average depth, cc.....	{ A	22	28	47	49	55	62	65	62	54	38	30	30		
	{ B	23	23	26	45	21	33	31	29	29	27	26	24		
Min. volume, cc.....	{ A 706								4,018						
	{ B 538								656						
Blood pressure, mm. Hg.....	{ A 130				136		136		132		134		134		
	{ B 136				138		138		138		138		138		

ventilation before it. During CO₂ inhalation, however, while the mediastinal record indicates greater inspiratory efforts than before morphine, there was no acceleration—in fact a slowing when depth increased—and the increase in ventilation was comparatively insignificant. There was no active expiration at any time after morphine and the response to CO₂ was certainly not dyspnea. This result is typical of the action of morphine in small doses (5 to 20 mg.) in the decerebrated cat with vagi intact.

When the vagi were cut, expiration always became definitely active, whether the animal was decerebrated or narcotized, and frequently respiration became a series of inspiratory pauses, broken by active expirations, as shown in Fig. 3, *B*. During CO₂ inhalation there was a definite, and sometimes very marked increase in expiratory pressure, with a marked increase in depth of inspiration, but there was usually little or no acceleration, as pointed out by Scott (9). Morphine, in 1 or 2 mg. dosage, always definitely diminished this sharp expiratory rhythm and frequently slowed the rate, while 5 mg. made expiration completely passive, even during CO₂ inhalation, and always slowed the rate.

When successive doses of morphine were given, 5 to 10 mg. at a time, to a decerebrated animal, whether vagi were intact or cut, there usually occurred, instead of progressive depression, a return of active expiration and an acceleration in rate. Maximum reduction of rate, with completely passive expiration, usually followed 20 mg. if the vagi were intact, or 5 mg. if they were cut. After about 60 mg. muscular movements or tremors often appeared, accompanied by active expirations, both at rest and in response to CO₂, and the rate was accelerated; in one experiment, tetanic convulsions occurred after 270 mg., following a period of dyspnea. The extremely slow rate, culminating in respiratory failure, which is so characteristic of advanced morphine poisoning in other animals, occurred only if a fairly large dose (30 to 60 mg.) was injected rapidly, and was always accompanied by marked circulatory depression. As long as the blood pressure remained high, it was impossible to produce respiratory failure by morphine alone in the decerebrated cat.

In the anesthetized animal repeated doses of morphine also failed to produce progressive depression of respiration, but the return of

active expiration and signs of increased reflex excitability were not seen. Whether vagi were cut or intact, maximum slowing and complete expiratory depression usually followed 2 to 5 mg., and repeated doses had no further effect on rate or depth until circulatory depression occurred, following rapid injection of a large dose.

A typical example of the effect of progressive doses of morphine in an anesthetized animal is shown in Fig. 3, a series of tracings from an experiment in which urethane was used as the anesthetic; the vagi were cut before morphine was given (between Tracings A and B). The respiratory rhythm before vagotomy was one of brief inspiratory pauses, with active expirations—a characteristic of urethane in our experiments; cutting the vagi accentuated this expiratory rhythm.

From the tracings it is evident that even 1 mg. of morphine diminished the sharp expiratory rhythm, though the rate was unchanged. 2 mg. produced distinct rounding of the expiratory curve, while 5 mg. made expiration completely passive and also caused maximum slowing in rate. Further injections, up to 50 mg., had no effect except a slight increase in depth, until, following a rapid injection of 30 mg., blood pressure fell sharply, and respiration became deeper and a little slower, with prompt recovery as blood pressure rose. At the beginning of the last tracing 10 mg. caused a fall in blood pressure and a slower rate, such as is expected in advanced morphine poisoning, and another 10 mg. produced simultaneous circulatory and respiratory failure. It is quite evident that the fall in blood pressure here could not have been the result of respiratory depression; on the other hand, the appearance is that of respiratory depression as a result of circulatory failure.

Fig. 4 shows a series of CO₂ inhalations taken during the course of this experiment. It is apparent that 1 mg. of morphine completely removed the expiratory response to CO₂, while the response after 50 mg. is exactly the same as that after 2 mg. CO₂ inhalation after the larger dose was continued for 3 minutes in order to insure adequate absorption of CO₂.

In about a quarter of the experiments on decerebrated cats, morphine failed to produce slowing or expiratory depression in any dose, from 0.25 to 100 mg., or more. In the absence of slowing it is obvious that morphine had not exerted its typical effect. Whenever the rate

was decreased after morphine expiration was passive, and when expiration was active there was no slowing.

Heroine.—The effects of this drug on rate and depth of breathing and on the character of expiration in the decerebrated cat were similar to those of morphine, but were produced more regularly and by much smaller doses. A slower rate, usually with increased depth, and with completely passive expiration, regularly followed 0.25 or 0.5 mg. of heroine—effects comparable to those of 5 to 20 mg. of morphine.

The result of heroine action in a decerebrated cat is shown in typical form in Fig. 5, in which Tracing A shows the response to CO₂ before heroine, Tracing B after 0.25 mg., and Tracing C after 0.5 mg. The data derived from these tracings are given in Table III.

It is seen that 0.25 mg. of heroine decreased the rate and increased the depth, making expiration passive, and removed completely the expiratory response to CO₂; 0.5 mg. produced further slowing but no further increase in depth.

When repeated doses of heroine were given to a decerebrated cat, there occurred only progressive circulatory and respiratory failure, death sometimes following a total of 2 mg. There were never any signs of stimulation such as occurred with morphine, and narcosis might follow 0.5 to 1 mg. If blood pressure did not fall respiration was not further affected after expiration had been made passive, and respiratory failure never occurred with a high blood pressure. In those animals in which morphine had failed to produce slowing of the rate, heroine, in dosage up to 40 mg., was also without effect, but apparently did not produce further stimulation. When given alone, however, 0.25 to 0.5 mg. of heroine uniformly produced results such as are described above.

Codeine.—The only constant result of the injection of codeine phosphate in a decerebrated cat was an increase in reflex excitability, culminating usually in tetanic convulsions. In eight experiments, with doses of codeine ranging from 0.125 to 100 mg., there was never any definite slowing of rate or expiratory depression. Doses up to 5 mg. had no effect, while after 10 mg. the rate was accelerated and expiration became more active. Repeated doses caused further acceleration, and the only trace of selective expiratory depression was a failure of the mediastinal lever to rise above the zero level

during CO₂ inhalation after 30 to 40 mg. had been given; the rate was always more rapid at this time than in the control period, and inspiration was definitely diminished, while expiration was still active, but was relatively weakened. After about 50 mg. muscular movements usually appeared and the animal responded violently to slight stimuli, as in the early stages of strychnine poisoning. After 80 to 100 mg. tetanic convulsions usually appeared. At no time was there any sign of respiratory depression or narcosis.

DISCUSSION.

Morphine occupies an unique position as a respiratory depressant because of its ability to relieve specifically cough or dyspnea, and to decrease selectively the rate without affecting the depth of breathing—effects which may be produced without causing narcosis, and sometimes without any other effects than those on respiration.

Existing opinions regarding the action of morphine on respiration were summarized by Cushny (10), who presented additional evidence that the drug has an apparently specific action on the rate of breathing, the result grossly resembling that of vagotomy in that there may be an increase in depth as rate is decreased. Cushny was able to show, however, that stimulation of the central stump of the vagus was at least as effective after morphine as before, so that its action does not depend on a depression of the vagus mechanism; he concluded that it affects the metabolism of the cells of the respiratory center in such a way that the rate of discharge of impulses is decreased, but not their strength.

Cushny and Lieb (6) showed that the CO₂ content of the blood rises after large doses of morphine, indicating depression of the respiratory center to chemical stimuli.

Our experiments have shown that morphine and heroine have an apparently selective action on the expiratory mechanism of the cat, and that whenever the rate is diminished expiration is passive. We wish to emphasize the point that this and the following statements apply only to the cat, for we have been unable, for technical reasons, to complete a series of experiments on other animals sufficiently extended to enable us to speak more generally.

The effect of making expiration passive, when it was active before, might be deduced from the results obtained by Head (11), who found that gentle suction on the tracheal cannula of a rabbit was followed immediately by an inspiratory effort if applied at the end of expiration, as a result of an excitatory vagus reflex aroused by collapse of the lungs. One might expect, therefore, that a slower rate of emptying the lungs would delay this reflex and thus slow the rate of breathing. If this is true, suction on the tracheal cannula during expiration should remove the slowing produced by morphine or heroine.

That this is possible is shown in Fig. 6, a tracing from the same experiment as that from which Fig. 5 was taken. The injection of 0.5 mg. of heroine had decreased the rate from 52 to 20 and expiration became completely passive. Tracing A shows the effect of closing the tracheal cannula at the end of inspiration and expiration; a brief apnea in the expiratory position was caused in the one case, a very deep inspiration in the other. It is apparent that the vagus mechanism was functioning, and that the center was able to respond to impulses aroused by distention or collapse of the lungs.

Tracing B shows the effect of very gentle suction on the tracheal cannula during expiration, so that the lungs were emptied more rapidly. Each suction was followed by an inspiration, and the rate was increased from 20 to 50. (The rate before heroine was 52.) Blowing into the trachea during inspiration decreased the rate from 20 to 15.

These observations have been repeatedly confirmed for morphine and heroine, and it seems certain that the slower rate of breathing which follows the action of these drugs is at least partly due to the slower rate of emptying the lungs, which, in turn, is the result of a selective depression of expiration. When the animal was narcotized this result often was absent, and it could not be obtained regularly with any of the other drugs tried. When very large doses of morphine or heroine were given, and circulation was markedly depressed, with a respiratory rate of 8 or 10 per minute, suction and blowing were usually without effect. When the vagi were cut the rate was not affected by suction or blowing, unless continued long enough to over-ventilate the lungs. It is clear, therefore, that the acceleration which follows more rapid emptying of the lungs is largely, if not wholly, a

vagus reflex, and is removed by depressing the vagus mechanism by narcosis or by asphyxia, or by section of the vagi.

After vagotomy morphine also produced expiratory depression and a slower rate, and usually smaller doses were effective than when the vagi were intact. This indicates that the drug acts centrally, and that the central depression is probably antagonized by excitatory vagus reflexes, the possibility of which is shown by the effect of suction during expiration when the rate was slowed by morphine or heroine (Fig. 6). This probably accounts for the absence of typical morphine action when the lungs were incompletely distended and justifies the use of the mediastinal method for intrathoracic pressure.

A maximum decrease in rate is seen whenever expiration becomes completely passive after morphine or heroine, and when this occurs larger doses have no further depressant effect until circulatory depression takes place (Figs. 3 and 4). This seems to indicate that the drugs either have no depressant action on inspiration, while making expiration completely passive, or, as seems more probable, that the depression of inspiration is overcome by an equivalent increase in the chemical stimulus, such as was shown by Cushny and Lieb (6). We have made a few experiments on decerebrated cats, determining the pH of arterial blood by the method of Dale and Evans (12), just before and just at the end of CO₂ inhalation, repeating the determination after the injection of morphine. The results of one of these experiments are given in Table IV.

In this experiment expiration was made completely passive by 14 mg. of morphine and remained so during CO₂ inhalation; depth of respiration was slightly reduced by morphine, but was increased by CO₂ to practically the same extent as before morphine. The rate of breathing in air was reduced from 44 to 20, and the pH of arterial blood fell from 7.35 to 7.29 after morphine. The most striking difference is seen in comparing the rates during CO₂ inhalation before and after morphine; before morphine CO₂ caused acceleration, after morphine a slowing. The effect of this on the efficiency of ventilation is shown by the figures for pH before and at the end of the two inhalations. Before morphine there was no change; the respiratory mechanism was able to prevent a detectible fall. After morphine,

while depth increased as before, there was retardation instead of acceleration, and pH fell from 7.29 to 7.25 during the inhalation. In this, and in many other experiments, it was evident that if expiration remained passive any marked increase in depth of inspiration would slow the rate, and thus partly defeat its purpose of increasing ventilation.

In decerebrated cats the effect of repeated doses of morphine was complicated by the return of active expiration and an acceleration in rate, after passive expiration and a slower rate had followed smaller doses. At the same time there were signs of increased reflex excitability and actual convulsions might follow very large doses. This points to a stimulant action on the cord, which is well known for morphine,

TABLE IV.

Morphine experiment. November 23, 1921. Cat, female; weight 2.3 kilos. Decerebrated through trephine opening; tracheal cannula; injections into the saphenous vein, completed 45 minutes before the second series of observations.

Period.	Rate per min.		Average depth.		Min. volume.		pH	
	Air.	CO ₂	Air.	CO ₂	Air.	CO ₂	Air.	CO ₂
Control.....	44	48	cc. 35	cc. 45	cc. 1,672	cc. 2,064	7.35	7.35
After 14 mg. of morphine sulfate.....	20	16	31	44	616	706	7.29	7.25

and which apparently overcomes the central expiratory depression which follows smaller doses; this effect is prevented or removed by narcosis. It is also possible that the return of active expiration, and consequent acceleration in rate, are due to spontaneous changes in the condition of the animal, for Macleod (13) has recently shown that a decerebrated cat may develop an acidosis and become dyspneic spontaneously. Against this it may be said that, once expiration was passive, it remained so for a period of hours, with a steady, regular rate, but, if more morphine was given, acceleration and active expiration usually appeared promptly. Furthermore, there were never any signs of stimulation from heroine, no matter how long the experiment was continued, while codeine produced them regularly and after comparatively small dosage. The respiratory effects of

these large doses were similar in all respects to those of effective doses of strychnine; during the period of acceleration and return of active expiration there were signs of increased reflex excitability. It is worth noting that a similar reversal of morphine action by large doses was described for dogs by Wood and Cerna (14), and for rabbits by Filehne (15).

We feel safe in concluding that the typical action of morphine and heroine on the respiration of the cat is limited to a selective depression of the central expiratory mechanism, and that the slower rate, with relatively unchanged depth, is due at least partly to this. It is easy to see how depth is so little affected, or may be increased, for the chemical stimulus is increased, and, though inspiration may be depressed also, it is subjected to a stimulus which may more than overcome the depression. In our experiments, the extremely slow rate, culminating in respiratory failure, which is so typical of advanced morphine poisoning, seemed to be due to depression of circulation rather than of respiration direct, and we do not regard it as part of typical morphine or heroine action on respiration in the cat. Once expiration has been rendered passive by either drug, larger doses have no further depressant effect on the rate or depth until circulatory depression occurs; the latter does not seem to be secondary to respiratory depression, for it usually occurs before respiration is affected, and artificial respiration or oxygen inhalation usually does little good.

A constant and striking relation between blood pressure and respiration has been evident in many of the experiments, and the relation of cerebral blood flow to respiration is now being investigated more fully. The statements made above are justified by the evidence already at hand, and are made at this time in the hope that they may be of some use in the treatment of morphine poisoning in man; we have no evidence that circulatory depression is as prominent a feature in morphine poisoning in other animals, or in man, as it is in the cat, but the subject seems to deserve further investigation, and it is possible that circulatory stimulants, transfusion, or intravenous infusions, may be of value in the treatment of clinical morphine poisoning.

An action of this sort may have occurred in the experiments of Guber (16), who found that, when respiration of a rabbit had been

markedly depressed by large doses of morphine (30 mg.), an injection of adrenalin was followed by temporary improvement of respiration, and when the adrenalin injections were repeated, recovery took place much more rapidly than when the same animal was given the same dose of morphine without subsequent adrenalin injections. Jackson (17) explains the beneficial results of adrenalin in such conditions as being due to relaxation of bronchial spasm, which he has demonstrated after injection of 10 mg. of morphine in a spinal dog. It is probable that such an effect of adrenalin plays a part in the improvement noted by Guber in the rabbit, but the possibility of improved circulation is worth considering.

We are not prepared to state that a selective depression of expiration is responsible for the specific action of morphine and heroine in cough and dyspnea, for our experiments were made on animals which are scarcely to be regarded as fit subjects for the study of the therapeutic action of these drugs. We have made several experiments on dogs, using a pleural cannula, and found that when the lung was completely reexpanded, and when the rate was decreased following 5 or 10 mg. of morphine, a similar selective depression of expiration was evident, and Cushny (10) found that the decerebrated cat reacted to morphine as did the rabbit. If these results are regarded as applicable to the therapeutic use of these drugs, it is at least suggestive that the conditions in which they are regarded as specifics—cough and dyspnea—are characterized by active expiratory efforts, and the response of the cat to CO_2 , after expiration was made passive by morphine or heroine, was certainly not dyspnea.

A comparison of the three alkaloids—morphine, heroine (diacetyl morphine), and codeine (methyl morphine)—shows that morphine is not nearly as specific an expiratory depressant as heroine, while codeine has never shown such action at all. The average minimum dose of morphine required to produce definite expiratory depression and a slower rate was about 5 mg. in our experiments, and practically the same results could be obtained, more uniformly, with 0.25 mg. of heroine. Heroine was, therefore, about twenty times as effective as morphine.

The negative results obtained with codeine were a surprise, in view of the clinical value of the drug, and cast some doubt on the

value of these experiments in explaining the clinical usefulness of the other alkaloids. However, while the experiments have failed to demonstrate any constant action of codeine in the decerebrated cat except stimulation of the cord, it may be that this stimulation was sufficient to overcome a simultaneous depression of expiration similar to that of morphine or heroine, and that this stimulation of the cord is less marked in other animals than in the cat.

SUMMARY.

1. A method is described for recording intrathoracic pressure in cats without opening the pleural cavity; active expiratory movements were elicited by inhalation of a constant CO₂-air mixture for a given time and a study was made of the action of drugs on inspiration and expiration.

2. Morphine and heroine were found to exert a selective depressant action on the central expiratory mechanism, and the slower rate, with relatively unaltered depth, seemed to be due at least partly to the slower rate of emptying the lungs. Codeine had no depressant action on the respiration of decerebrated cats.

3. Larger doses of morphine or heroine had no further depressant effect on rate or depth of breathing after expiration was made passive, unless circulatory depression appeared, and failure of circulation seemed to be the cause of respiratory depression, rather than the reverse relation. In decerebrated animals large doses of morphine and moderate doses of codeine stimulated the spinal cord, and expiration became active, with a faster rate of breathing. The characteristic action of morphine and heroine on the respiration of the cat is apparently limited to a depression of active expiration.

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EXPLANATION OF PLATES.

Upper tracing, mediastinal pressure; down stroke, inspiration. 1 mm. of tracing is equivalent to about 1 mm. Hg. pressure.

Middle tracing, volume of respiration. Up stroke, inspiration. $\frac{1}{4}$ cm. of tracing is equivalent to 20 cc. of air moved.

Lower tracing, blood pressure.

All tracings are to be read from left to right.

PLATE 5.

FIG. 1. Ether experiment. December 17, 1921. Cat, female; weight 2.2 kilos. Ether anesthesia; tracheal cannula; cerebrum and vagi intact; no drugs injected; blood pressure from the right carotid.

The signal line is abscissa for blood pressure and is set at 60 mm. Hg.

Time, 5 seconds. Between the arrows 8.5 per cent CO₂ was inhaled for 1 minute.

FIG. 2. Morphine experiment. December 10, 1921. Cat, female; weight 2.3 kilos. Decerebrated through a trephine opening, under ether anesthesia, with both carotids tied; vagi intact; tracheal cannula; blood pressure from the right carotid; cannula in the left saphenous vein for injections. CO₂, 5.2 per cent, inhaled for 1 minute. Morphine sulfate, 1 per cent in Ringer's fluid.

The signal line is abscissa for blood pressure and is set at 60 mm. Hg.

Time, 5 seconds.

Tracing A, before morphine.

Tracing B, after injection of 20 mg. of morphine sulfate, 5 mg. intravenously, 15 mg. intramuscularly, the last injection 1 hour previously; following the last injection, a transfusion of 100 cc. of whole cat blood was given, with a syringe; no anticoagulant; completed 45 minutes before the tracing was made.

FIG. 3. Urethane experiment. December 6, 1921. Cat, female; weight 2.5 kilos. Anesthetized with chloroform followed by ether; tracheal cannula; urethane, 25 per cent in water, injected slowly into the saphenous vein, to a total of 1.25 gm. per kilo; vagi prepared, but not cut until later.

The signal line is abscissa for blood pressure and is set at 0 mm. Hg.

The numbers just below the time tracing are rates of respiration per minute. The lower numbers indicate the total amount of morphine injected up to that point.

Time, 5 seconds.

Tracing A, air breathing, urethane anesthesia, vagi intact.

Tracing B, the same, 15 minutes after cutting both vagi.

PLATE 6.

FIG. 4. CO₂ inhalations during the course of the experiment shown in Fig. 3. The signal line is abscissa for blood pressure and is set at 80 mm. Hg.

The numbers under the signal tracing indicate the rate per minute, at 15 second intervals.

Tracing A, response to 8 per cent CO₂, inhaled for 1 minute, during urethane anesthesia, with vagi intact; no morphine given.

Tracing B, the same, after cutting both vagi, before morphine. Note the slight but definite increase in the expiratory level of the mediastinal record.

Tracing C, the same, after injection of 1 mg. of morphine sulfate.

Tracing D, the same, after injection of 2 mg. (total) of morphine sulfate.

Tracing E, the same, after a total of 50 mg. of morphine sulfate; this inhalation was continued for 3 minutes.

FIG. 5. Heroine experiment. December 14, 1921. Cat, male; weight 2.8 kilos. Decerebrated through a trephine opening, under ether anesthesia, with both carotids tied; vagi intact; tracheal cannula; blood pressure from the right carotid; injections into the left saphenous vein. CO₂, 4.5 per cent, inhaled for 1 minute.

Time, 5 seconds.

Tracing A, before heroine.

Tracing B, after 0.25 mg. of heroine hydrochloride.

Tracing C, after 0.5 mg. of heroine hydrochloride.

FIG. 6. From the same experiment as Fig. 5, following Tracing C, Fig. 5; 0.5 mg. of heroine has been injected.

Tracing A, Hering-Breuer reflexes; tracheal cannula closed *I*, at end of inspiration, and *E*, at end of expiration.

Tracing B, at *S*, suction on the tracheal cannula during expiration, accelerating the rate from 20 to 50; at *B*, blowing into the tracheal cannula with inspiration, slowing from 20 to 15.

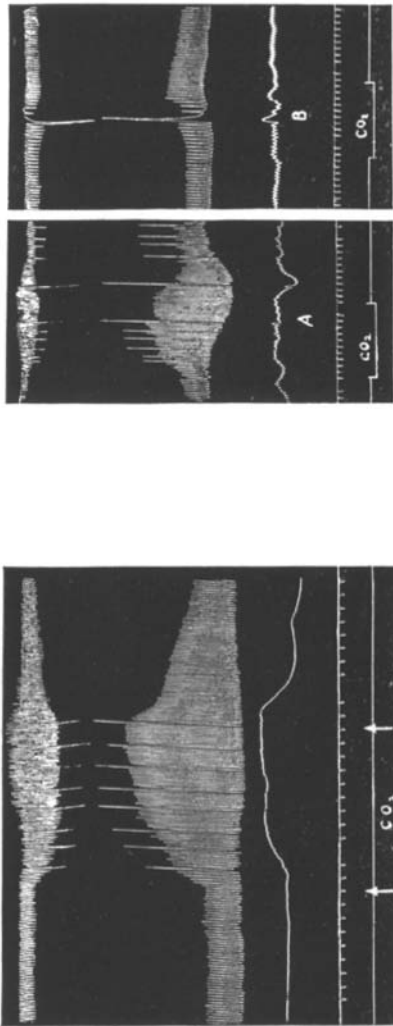


FIG. 1.

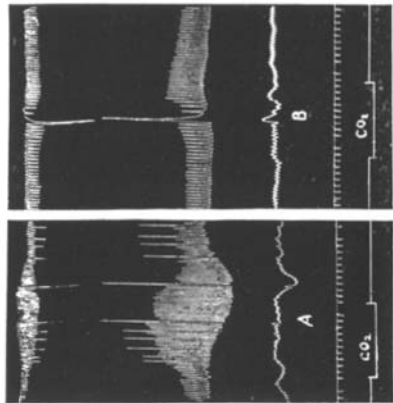


FIG. 2.

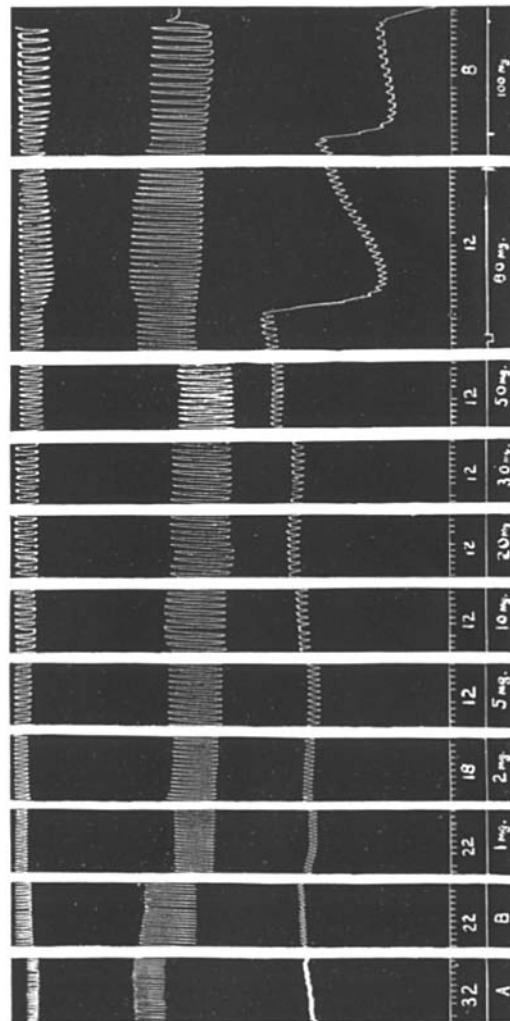


FIG. 3.

