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DEPRESSION OF THE COUGH REFLEX BY PENTOBARBITONE AND SOME OPIUM DERIVATIVES

BY

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Experiments on the cough reflex (Larsell and Burget, 1924; Widdicombe, 1954a and b) have shown that two afferent nervous mechanisms are present. One has receptors lying in the trachea and is excited by mechanical stimuli, whereas the other extends throughout the tracheobronchial tree and is sensitive chiefly to irritant gases; the two types of cough stimulus give somewhat different motor responses. The central nervous pathways for coughing have not, however, been investigated, and little is known of the interactions between the respiratory centre, the cough reflexes, and other respiratory reflexes. The experiments described in this paper were carried out to see whether drugs that depress the cough reflex, and that are believed to act centrally, have quantitatively different effects on these reflexes. At the same time a new morphine derivative, pholcodine (2'-morpholinoethyl ether of morphine), became available, and, since it had not been directly tested against coughing, its action was compared with those of morphine and codeine.

METHODS

Tracheal cannulae were inserted into 28 cats, anaesthetized with pentobarbitone sodium, 32 mg./kg. intraperitoneally. The cats were enclosed in the body plethysmograph described by Dawes, Mott, and Widdicombe (1951), from which respiratory volume changes were recorded on a smoked drum, using a float recorder. The method permitted measurement of tidal volume and of changes in expiratory volume (functional residual volume). Blood pressure was measured by a Hg manometer from a carotid artery. Intratracheal pressure was measured by a tambour, and intraoesophageal pressure by an electrical condenser-manometer and displayed on a cathode-ray oscilloscope.

Coughing.—Coughing was induced in two ways: firstly, by passing a polythene catheter down the trachea until it touched the carina, after which it was immediately withdrawn; and secondly, by blowing air containing SO_2 into the trachea. The SO_2 was generated by adding 50 ml. of N-HCl to 5 g. of sodium thiosulphate in a conical flask; to excite coughing, a measured quantity of air (0.5–1 ml.) was bubbled through the mixture into the tracheal cannula at the beginning of an inspiration. Both types of stimulus (mechanical and chemical) were applied once only to produce a cough, and they were repeated at intervals of 5–10 min. With the mechanical stimulus control experiments showed that refractoriness did not develop for at least an hour; with SO_2 the respiratory responses sometimes decreased slightly during that period, but never by more than 25%. The latter reflex became refractory if large amounts of SO_2 were administered.

The cough in response to a mechanical stimulus was expressed as the ratio of the volume of the initial *expiratory* effort after the stimulus to the average of ten preceding tidal volumes. The percentage changes in this ratio after administration of drugs were calculated. SO_2 did not always cause an initial expiratory effort, but one or more deep gasps were invariably seen; the depth of the first *inspiratory* effort was therefore used as an index of reflex activity, and the ratio of this inspiration to the average preceding tidal volume was calculated. The inspiratory activity after a mechanical stimulus was measured similarly.

Hering-Breuer Inflation Reflex.—This was elicited by inflating the lungs with 50–100 ml. of air, and maintaining the distension. The inflation was made at the beginning of an expiratory pause, and delayed the next inspiratory effort. The next inspiration caused a fall in intratracheal pressure, and the distension of the lungs was then released. The ratio of the consequent inspiratory pause to the average of ten preceding respiratory intervals was calculated and the percentage change in this ratio was taken to indicate either an increase or a decrease in reflex activity. This method takes into account the rate of respiration and its slowing by the Hering-Breuer inflation reflex, but not tidal volume and respiratory muscle tone. It is possible that large changes in the spontaneous respiratory cycle would invalidate the use of this index, but in most experiments the results were unequivocal.

Bronchoconstriction.—The intratracheal pressures at the beginning of the maintained inflations of the lungs were used to indicate changes in the resistance to inflation. Changes might be due to several factors of which the chief is bronchial tone, but, since the cats had intact chests, the influence of expiratory muscle tone must be considered.

Drugs.—Morphine and pentobarbitone were administered at 5 min. intervals, and codeine and pholcodine at 10 min. intervals. The drugs were given in increasing doses, and since each experiment took less than 1 hr. the doses were assumed to be cumulative. In calculating the total dose of pentobarbitone the initial anaesthetic dose was not included. All injections were made into the external jugular vein. After each injection several minutes were allowed to elapse and then the three respiratory reflexes were each elicited once, in turn, so that the experimental procedures were carried out immediately before the next injection. Provided the respiratory disturbance from the preceding stimulus had subsided before the next reflex was tested, no interaction between the reflexes was observed. Pentobarbitone and morphine were each given to five cats, and pholcodine to seven; codeine was given to eleven cats, since its actions were rather variable.

Carbon dioxide was administered by making the cat rebreathe from a 10 l. flask through which 5% CO_2 in air was being circulated.

Results

Some of the results are shown in Table I.

Cough Reflexes.—The expiratory effort due to an endotracheal mechanical stimulus was reduced by each of the four drugs; Fig. 1 shows the mean dose-response curves, compared with the changes in minute volume. Pentobarbitone abolished the reflex only in doses associated with profound respiratory depression or death; the other drugs never caused death in the doses used. Morphine was the most active; pholcodine was more active than codeine, the difference being significant (Table I).

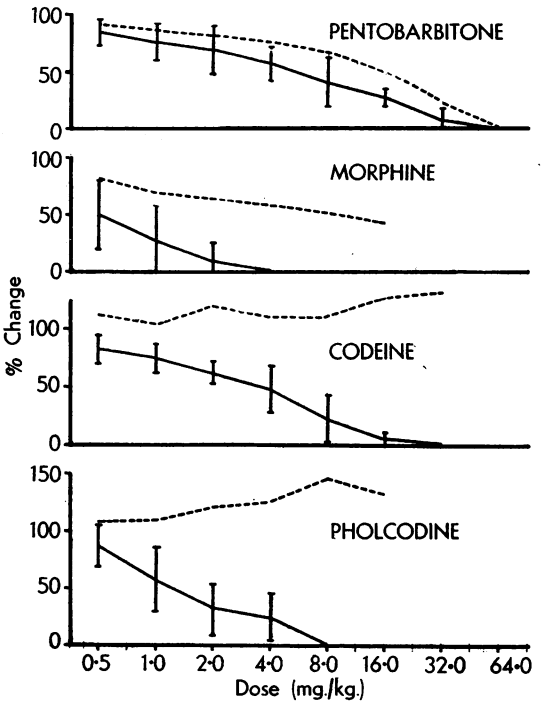

FIG. 1.—Dose-response curves showing the action of pentobarbitone and of opium derivatives on minute volume (interrupted lines) and on the expiratory efforts caused by an endotracheal mechanical stimulus (continuous lines). The control values before administration of the drugs are expressed as 100%. Each line represents means for the cats used with the appropriate drug. Vertical lines show standard deviations for the cough reflex; for clarity, they have not been given for minute volume or in Fig. 2, but these were of the same order of size.

When SO_2 caused coughing, pentobarbitone and morphine were significantly *more* active in blocking the reflex than for an endotracheal mechanical stimulus. On the other hand, pholcodine was significantly *less* active against chemically induced coughing, and was the least potent of the opium derivatives (Table I). There was little difference in the actions of codeine on the two cough reflexes.

The usual patterns of the two types of cough differed; a mechanical endotracheal stimulus caused an initial expiratory effort followed by a gasp (e.g., Figs. 3 and 4), while after a noxious chemical stimulus inspiratory efforts predominated, although they were often preceded and followed by forced expirations. The response to a mechanical stimulus was first assessed from the size of the *expiratory* effort, while for the chemical stimulus the *inspiratory* gasp was measured. It was noticed, however, particularly with morphine, that after a mechanical stimulus the inspiratory

TABLE I

APPROXIMATE DOSES OF DRUGS THAT ABOLISH THE COUGH REFLEX

For each drug the mean doses and standard deviations are given

Drug	Doses (mg./kg. Body Wt.) to Abolish				Mean % Changes in Respiration and Reflexes with Doses that just Abolished the Expiratory Efforts after a Mechanical Stimulus		
	Expiratory Efforts after Mechanical Stimuli	Inspiratory Efforts after Mechanical Stimuli	Inspiratory Efforts after Chemical Stimuli	Respiratory Movements	Minute Volume	Inflation Reflex	Resistance to Inflation
Pentobarbitone	33·1±4·5	20·5±4·5	25·7±2·1	41±9	−80	−84	−20
Morphine	2·3±1·4	0·4±0·2	0·5±0·3	—	−38	+120	+35
Codeine	16·3±7·8	7·6±4·1	11·2±4·0	—	+24	+240	+56
Pholcodine	5·3±1·8	17·1±7·5	15·1±8·5	—	+27	+50	+37

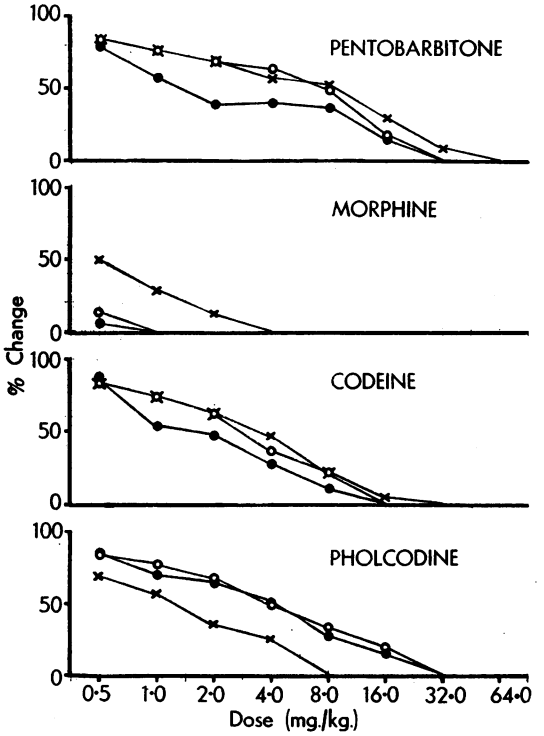

FIG. 2.—Dose-response curves showing the actions of the four drugs on the expiratory efforts after a mechanical endotracheal stimulus (—X— as in Fig. 1), the inspiratory efforts after a mechanical stimulus (—●—) and the inspiratory efforts after inhalation of SO_2 (—O—). Presentation of results as in Fig. 1.

gasp was blocked by smaller doses than was the primary expiratory effort. In Fig. 2, therefore, the doses that blocked the inspiratory and expiratory components of the mechanical cough reflex are compared, together with the doses that blocked the inspiratory gasps after SO_2. The actions of the drugs on the expiratory efforts due to SO_2 have not been included, since there was considerable irregularity in this response. With pentobarbitone and codeine there is little difference between the three curves. With morphine, however, the inspiratory components of both types of coughing were abolished by doses significantly smaller than those which inhibited the expiratory efforts of the mechanical cough reflex (Table I). Fig. 3 illustrates such an experiment with morphine. Pholcodine blocked the expiratory effort caused by a mechanical stimulus in doses significantly smaller than those which abolished the inspiratory components of the two cough reflexes; the curves for these last almost coincide. A typical response to pholcodine is seen in Fig. 4. Thus morphine and pholcodine have a quantitatively different effect on the inspiratory and expiratory components of both cough reflexes. The fact that expiratory efforts predominate after a mechanical stimulus, and inspiratory gasps after a chemical stimulus, seems to be largely responsible for the impression that morphine is more active against

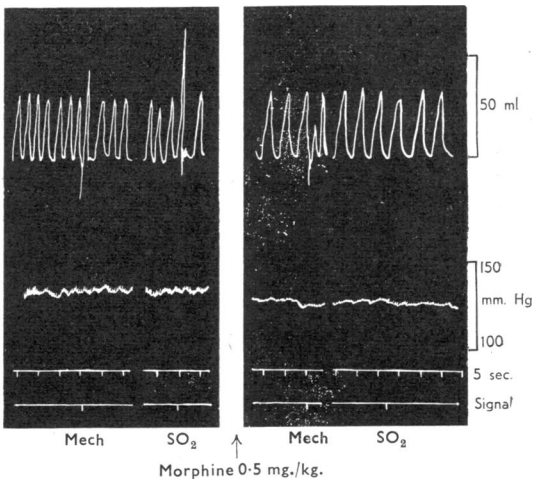

FIG. 3.—Cat 3.2 kg. The action of morphine on coughing induced by a mechanical stimulus and by SO_2. Upper trace: volume record of respiration. Lower trace: blood pressure. Administration of 0.5 mg./kg. morphine at the arrow resulted in complete depression of the cough due to SO_2, and inhibition of the inspiratory gasp (but not the expiratory effort) due to a mechanical stimulus. This and subsequent kymograph records have been retouched.

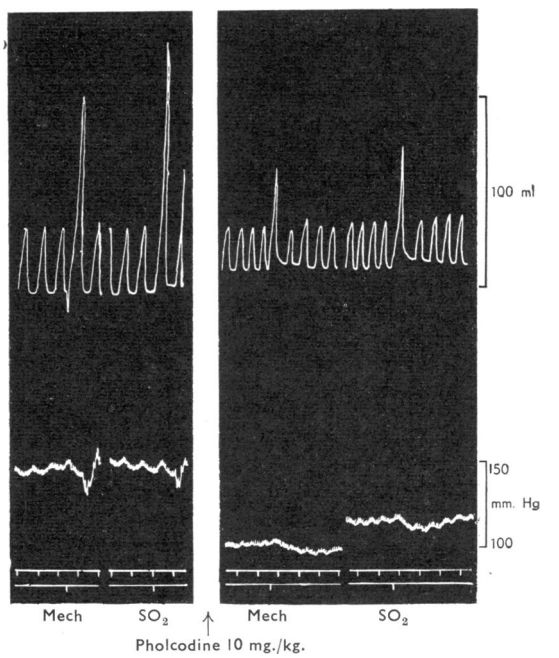

FIG. 4.—Cat 2.1 kg. The action of pholcodine (10 mg./kg. at arrow on coughing induced by a mechanical stimulus and by SO_2.

the chemical than the mechanical reflex, and *vice versa* with pholcodine.

Respiration.—The respiratory actions of the drugs are well known. Pentobarbitone and morphine depress respiration (tidal volume and rate), whereas codeine sometimes causes rapid shallow respiration with an increase in minute volume (Kreuger, Eddy, and Sumwalt, 1941). In our experiments codeine was variable in its action; respiratory depression was seen in six cats, and stimulation in three; the mean change in the nine animals was an increase in minute volume. Pholcodine resembled codeine rather than morphine, but caused a small decrease in minute volume on one occasion only. In vagotomized cats equivalent doses of codeine and pholcodine caused little change in respiration, so that the effect was probably not central.

Hering-Breuer Inflation Reflex.—The opium derivatives cause bronchoconstriction, and this might influence respiration both by a direct mechanical hindrance to airflow and by modifying respiratory reflexes. Since the inflation reflex is known to alter with changes in bronchial tone (Widdicombe, 1954c), the activity of this reflex was measured before and after administration of the four drugs. Pentobarbitone depressed the inflation reflex, except for a transient increase in activity in one cat. When doses sufficient to block the mechanical cough reflex had been given the inflation reflex was on average only 16% active (Table I). The other three drugs enhanced the inflation reflex, occasionally as much as tenfold. An example is seen in Fig. 5, where codeine has increased the inflation reflex 460%. The effect is apparent even when the reflex is assessed as the *absolute* delay in the respiratory cycle, taking no account of the increase in respiratory rate (190%) caused by codeine. The latter increase might alone be expected to decrease the delay in inspiration due to inflation. A possible explanation of these results was that the respiratory responses to hypercapnia and anoxia were depressed by the drugs, for the time of the first inspiratory effort after artificially maintained inflation of the lungs must be partly dependent on the strength of the chemical stimulus to respiration. This was tested by observing the action of codeine and pholcodine on the hyperventilation due to breathing 5% CO_2. In four cats, when codeine had caused an average increase in the infla-

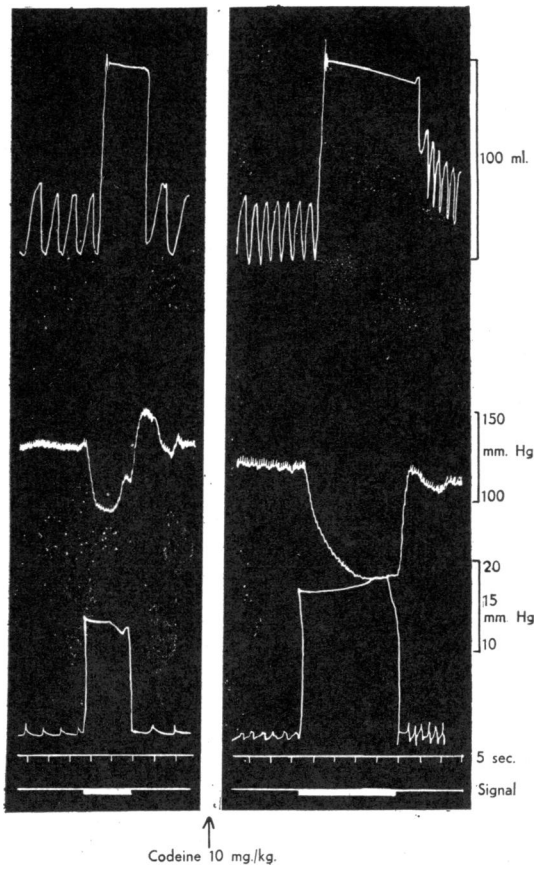

FIG. 5.—Cat 3.8 kg. Enhancement of the Hering-Breuer inflation reflex by codeine. Upper trace: volume changes of respiration. Middle trace: blood pressure. Lowest trace: intratracheal pressure. The lungs were artificially inflated at the beginning of the signal, and the distension released at the first inspiratory effort after this time. Thus the duration of the large rise in intratracheal pressure and of the signal is a measure of the duration of the respiratory inhibition. After giving codeine (10 mg./kg. at the arrow) inflation with the same volume produced a far longer relative and absolute delay in breathing, and a greater peak intratracheal pressure.

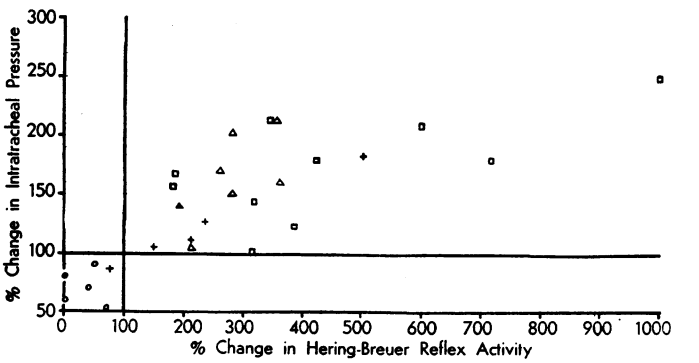

FIG. 6.—Changes in the Hering-Breuer inflation reflex and the intratracheal pressure on constant volume inflation of the lungs. Each point represents a single cat. O—pentobarbitone. +—morphine. □—codeine. △—pholcodine.

tion reflex of 220%, CO_2 still produced an increase in minute volume which was 87% of that seen before administration of the drug.

A more likely explanation is that changes in bronchial tone were associated with a direct action on the pulmonary receptors for the Hering-Breuer inflation reflex; this has been shown for other drugs that cause bronchoconstriction (Widdicombe, 1954c). The greatest enhancements of Hering-Breuer activity after the opium derivatives were seen when there was the greatest increase in pulmonary resistance to positive pressure inflation. Pentobarbitone, which never elicited a maintained increase in the inflation reflex, never caused an increase in pulmonary resistance. The opium derivatives failed to enhance the inflation reflex in only one cat, and this cat showed a small decrease in resistance to inflation. Fig. 6 gives results with all four drugs, showing the relation between resistance to inflation and change in the Hering-Breuer inflation reflex. The two variables were measured (and recorded in Fig. 6) when each cat had received just sufficient of the appropriate drug to block the expiratory effort of the mechanical cough reflex.

In these experiments the Hering-Breuer reflex was elicited by positive pressure inflations, and the resistance to inflation derived from the rise in intratracheal pressure. Since the cats' chests were closed respiratory muscle tone would contribute to this pressure, and if the tone altered after administration of a drug it would cause a change in *total* resistance to inflation. Although it seemed unlikely that this was happening, in two cats intraoesophageal pressures were recorded during the experiments. In both cats the changes in resistance to inflation and in the inflation reflex described above were observed, with no increase in expiratory muscle tone. The raised *pulmonary* resistance to inflation was shown by the increased pressure drop across the lung (intratracheal pressure minus intraoesophageal pressure) on constant volume inflation. Furthermore, changes in expiratory volume were measured from the plethysmograph record; after the opium derivatives there was little change in expiratory volume.

In Fig. 5 it will be seen that the respiratory pattern *following* artificial inflation of the lungs is changed by administration of codeine; the expiratory volume did not reach the control value until nearly 30 sec. had elapsed. This was frequently seen when the respiratory rate was rapid, and is presumably because the expiratory pauses were not sufficiently long to allow the lungs to collapse quickly to their expiratory volume. With a low rate of respiration this took place in one or two breaths (Fig. 5). It is also likely that bronchoconstriction after the opium derivatives would retard expiration and contribute to this effect, but this has not been assessed.

Discussion

The respiratory effects of the opium derivatives have often been studied (for references see Kruger *et al.*, 1941; Wikler, 1950), but their activity in suppressing the cough reflex has received meagre attention. Most of the techniques have involved indirect stimulation of coughing, such as electrical excitation of the superior laryngeal nerve (Toner and Macko, 1952), artificial pleuritis (Ernst, 1938), inhalation of sulphuric acid aerosol (Eichler and Smiatek, 1940), and inhalation of soap powder (Kroepfli, 1950). The methods used in our work were based on the demonstration of two types of sensory receptors and nervous pathways for coughing. The stimuli were physiological in so far as they correspond to an endotracheal foreign body and to inhalation of a common irritant gas; the methods were simple and gave reproducible results with a minimum number of animals. The actions of the drugs on respiration and on other respiratory reflexes could be measured at the same time.

These techniques have been used to investigate depression of the cough reflex in cats by pholcodine. It is more active in blocking the expiratory efforts caused by an endotracheal foreign body than codeine, but less active than morphine; it differed from morphine and codeine in seldom causing respiratory depression, and gave far more consistent results than codeine. Chabrier, Giudicelli, and Thiullier (1950) have investigated its respiratory actions in the rabbit; they concluded that, although it was slightly more active on the respiratory centre than codeine, it was 5–7 times less toxic.

Morphine, and to a less extent pentobarbitone, are more effective in depressing the *inspiratory* gasps than the *expiratory* efforts in both types of coughing, while pholcodine has the opposite action. A direct action of the drugs on the cough receptors has not been eliminated, but, since the afferent nervous pathways for the two cough reflexes are distinct, the main effect is probably central. It is unlikely that coughing is depressed by an action on the respiratory half-centres themselves, for pentobarbitone strongly inhibited respiration without blocking the cough reflex, whereas pholcodine prevented coughing with little respiratory depres-

sion. The explanation may be that there is a relay station in the arc for the cough reflex proximal to the respiratory centre, and that at this "cough centre" the movements of coughing are co-ordinated. Some such "centre" seems inevitable when the complexity of coughing is considered; for example, the closure of the glottis which is co-ordinated with expiratory efforts is unlikely to be controlled directly from the respiratory centre. The fact that the respiratory patterns for the two types of cough reflex are somewhat dissimilar could be due to the existence of separate "centres" for the two reflexes, or to differences in the centripetal innervation of a common "cough centre" by the two systems of afferent cough nerves.

Other workers (Dooley and Andrews, 1922; Cohen and McGuigan, 1924) have shown that the Hering-Breuer inflation reflex is enhanced by morphine, but the sites of action of the drug have not been analysed. From the results described in this paper it has been suggested that the increase in reflex activity after the opium derivatives is due in part to potentiation of the pulmonary stretch receptors, since the drugs cause bronchoconstriction which is known to increase the activity of these receptors (Widdicombe, 1954c). A central potentiation of the reflex by morphine has been considered by Henderson and Rice (1939). They showed that the inhibition of respiration caused by stimulation of the central end of the cut cervical vagi was enhanced by morphine in the rabbit; they concluded that this was an increase in the Hering-Breuer inflation reflex due to a central action of the drug. These experiments are difficult to interpret owing to the composite nature of the vagi, which contain several types of afferent nerve fibre causing respiratory arrest, and others causing stimulation; it is possible that both central and peripheral mechanisms are involved in the enhancement of the inflation reflex.

Schmidt (1940) has shown that morphine depresses the response of the respiratory centre to CO_2; after this drug inflation of the lungs might cause a longer inhibition of breathing, since the accumulation of CO_2 would be a weaker respiratory stimulus. Our results with codeine suggest that this mechanism could play only a small part in the enhancement of the inflation reflex.

With the vagi cut, codeine and pholcodine were without effect on respiratory movements in doses equivalent to those needed to enhance the Hering-Breuer inflation reflex. Rapid shallow respiration was seen only in cats with intact vagi, and could be due to an increase in activity of the pulmonary stretch receptors secondary to bronchoconstriction.

Summary

1. The actions of pentobarbitone sodium, morphine, codeine, and pholcodine (morpholinylethylmorphine) have been investigated on respiration, the cough reflexes, and the Hering-Breuer inflation reflex, using cats.

2. A simple method of assaying drugs that depress coughing is described, the procedure reproducing natural conditions as closely as possible.

3. Pholcodine is three times as active as codeine and half as active as morphine in inhibiting the expiratory efforts due to mechanical irritation of the trachea.

4. The inspiratory gasps after inhalation of SO_2 were more readily abolished by morphine than by codeine; pholcodine was the least active of the three.

5. The opium derivatives greatly enhanced the Hering-Breuer inflation reflex elicited by positive pressure distension of the lungs; it is suggested that this enhancement is secondary to bronchoconstriction and consequently to increased activity of the pulmonary stretch receptors.

6. Central inter-relationships between the cough reflexes and the respiratory centre are discussed.

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