THE ACTION OF DRUGS ON RESPIRATION.

II. Ether, Chloroform, Chloral, Urethane, Luminal, Magnesium, Caffeine, Strychnine, and Atropine.

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Plate 7.

(Received for publication, July 21, 1922.)

During the progress of the experiments described in the previous paper (1), it became obvious that a similar study should be made of the action of other depressant drugs. The question whether the selective expiratory action shown to be possessed by morphine and heroine is shared by the aliphatic narcotics is important not only in connection with the pharmacology of respiration but also because of the light which its study might throw on the physiology of the respiratory center. We have therefore used the methods outlined at the beginning of the previous paper in experiments with chloroform and ether, hydrated chloral, urethane, luminal, and magnesium chloride. Observations have also been made on the effects of caffeine, strychnine, and atropine injected after the respiration had been depressed by other drugs.

RESULTS.

With all the drugs tested—ether, chloroform, hydrated chloral, urethane, magnesium, and luminal—there occurred a more or less selective depression of expiration as with morphine and heroine, but narcotic doses were required to produce any effect and inspiration was always definitely depressed; expiration was weakened, but did not become passive until very marked depression of inspiration appeared.

Other than these general effects, there were some characteristic features in their action resulting from indirect effects on respiration.

Ether.—When ether vapor was inhaled by a cat, decerebrated[1] or intact, expiration always became active. If the inhalation was begun during very shallow narcosis, or, in a decerebrated animal, without narcosis, the first effect was usually a series of inspiratory pauses, broken by sharp, active expirations. This was soon followed by a period of acceleration, with an active expiratory rhythm, during which mediastinal pressure rose steadily. This expiratory rhythm persisted through the stage of surgical narcosis—absent corneal reflex, complete muscular relaxation, regular, quiet respiration, high blood pressure. If the inhalation was continued further, active expiration disappeared, sometimes quite suddenly, and respiration became a series of purely inspiratory gasps of diminishing rate and strength, culminating in respiratory failure; blood pressure frequently rose for a brief period after respirations had ceased, but spontaneous breathing rarely began until pressure began to fall; the first respiratory efforts on recovery were always purely inspiratory.

The disappearance of active expiratory efforts was a constant sign of dangerous respiratory depression by ether and we regard it as a fairly reliable sign for use during ether anesthesia in the cat.

The responses to CO_2 inhalation at varying stages of ether narcosis showed that expiration was definitely weakened as narcosis progressed, though it became completely passive only when inspiration was much shallower and slower than before and respiratory failure was imminent. An example of the effects of ether is shown in Fig. 1, a continuous tracing made during ether inhalation by an intact cat, in which a tracheal cannula was used.

At the start, before CO_2, the expiratory level of the mediastinal tracing shows a series of sharp peaks, indicating an active expiratory rhythm. During very shallow narcosis (corneal reflex very active—$C\,R\,+\,+\,+$), CO_2 brought out a very marked expiratory response, with very definite increase in rate, depth, and minute volume.

When ether was applied, there occurred a series of inspiratory pauses, broken by sharp expirations, soon followed by a rise in mediastinal pressure and a more rapid rate, expiration continuing active until blood pressure began to fall—before respiratory failure in this case, ether being removed when the fall began. At this point, the

[1] All operations were performed under ether anesthesia.

mediastinal record looks exactly like that which follows morphine or heroine,[2] and expiration was completely passive, though it is evident that inspiration was also markedly depressed. Narcosis was then very deep, the pupils were dilated, and the corneal reflex was absent (*C R O*).

CO_2 inhalation at this point brought out a purely inspiratory response, much weaker than that during light anesthesia. Following this the sharp expiratory peaks returned to the mediastinal tracing and the corneal reflex reappeared (*C R* ±). CO_2 then brought out a more marked inspiratory response, but expiration was not correspondingly increased and there was little acceleration.

An expiratory response similar to the first one, during light anesthesia, appeared only when the reflexes were again very active.

It is evident that ether depresses expiration more than inspiration, but it definitely depresses both, as seen in the responses to CO_2 at different stages of narcosis.

The active expiratory rhythm which constantly occurred during ether inhalation seems to be due to the irritant action of ether vapor on the respiratory passages, the expiratory efforts being apparently intended to expel the irritant—a series of incomplete coughs. The rise in mediastinal pressure and acceleration in rate which constantly occurred during the induction of anesthesia by ether may also be due to the irritation of the respiratory passages, the sharp expirations leading to more rapid emptying of the lungs, with an effect on rate exactly opposite to that of morphine or heroine, once sufficient ether was absorbed to remove the primary inhibitory effect of irritation.

This expiratory rhythm can be duplicated by inhalation of ammonia vapor. We have not been able to determine whether it is a vagus reflex, or follows another path, for section of the vagi without ether inhalation uniformly caused a similar expiratory rhythm. The rise in mediastinal pressure and acceleration in the early stages of narcosis did not occur when the vagi were cut, so that these effects, at least, seem to result from peripheral vagus stimulation, probably excitatory to the central expiratory mechanism.

Chloroform.—The results of inhalation of this drug were similar to those of ether, the expiratory response to CO_2 being weakened more

[2] See Figs. 2 and 5 of the preceding paper.

than the inspiratory as narcosis progressed, inspiratory efforts being the last to go and the first to return.

The sharp expiratory rhythm, primary acceleration, and rise in mediastinal pressure were much less constant than with ether, probably because of the less irritant action of chloroform vapor in anesthetic concentration.

Another striking, though by no means constant difference from ether was a steady acceleration in rate as narcosis progressed, accompanied by a steady fall in blood pressure. In these exceptional cases, due possibly to inhalation of too strong vapor, respiratory failure occurred quite suddenly, without a period of progressive decrease in rate and depth, such as was seen always with ether and usually with chloroform, and blood pressure did not rise after respiration ceased. In one experiment, this acceleration was so marked as to suggest insufficient narcosis even though reflexes were absent, pupils dilated, and blood pressure was below 50 mm. When blood pressure had fallen to 20 mm., the animal was more dyspneic than during CO_2 inhalation before chloroform was given and respiratory failure occurred very suddenly.

This is another example of an apparent relation between blood pressure and respiration to which reference was made in discussing morphine poisoning. In view of experiments already made on the relation of cerebral blood flow to respiration, we suggest that the unusual results of chloroform inhalation, described above, may be due to a more marked depression of circulation than of respiration, the dyspnea resulting from a reduction in cerebral blood flow to which the respiratory center is able to respond. Further experiments are being made on this subject and will be reported shortly. The possibility of very sudden respiratory failure during extreme dyspnea in chloroform anesthesia is, of course, well known, but it seems justifiable to emphasize it again as illustrative of the danger of being guided by respiration alone in the administration of chloroform.

Hydrated Chloral.—This drug was injected in dosage of 50 to 100 mg., a 5 per cent solution in Ringer's fluid being used; decerebrated animals only were employed and all injections were made into a saphenous vein.

The uniform result of repeated injections was a progressive increase in rate and decrease in depth of respiration as narcosis developed, with a steady fall in blood pressure, until very deep narcosis was obtained. Expiration continued to be active until late in the experiment, and when it became passive the rate was diminished. The expiratory response to CO_2 was progressively decreased until reflexes were abolished by the drug, when there was no increase in the expiratory level of the mediastinal record during the inhalation. Expiration continued to be active until larger doses were given, and the acceleration in rate during CO_2 became less and less marked when definite narcosis developed. At the same time, there was a progressive diminution in depth of respiration. The terminal stage was a series of weak inspiratory efforts, with perfectly passive expiration, and with a markedly depressed circulation.

The results of a typical experiment with hydrated chloral are given in Table I.

It is evident that the expiratory response to CO_2 was progressively reduced, but, while depth of breathing and strength of inspiration were also reduced, there was sufficient acceleration to prevent a diminution in minute volume until expiration became passive. Total respiratory failure soon followed this. When expiration has been paralyzed by chloral, CO_2 inhalation may cause a slowing instead of acceleration, as seen with morphine, but this occurs only in very deep chloral narcosis.

Urethane (*Ethyl Carbamate*).—We have tested this drug in intact and decerebrated animals, injecting it intravenously in dosage of 50 to 100 mg., a 5 per cent solution in Ringer's fluid being used. In general, the results were similar to those described for the alcohol group, but there was less tendency to circulatory depression with urethane and the rate was usually slowed as narcosis progressed. A constant feature was a marked expiratory rhythm—a series of inspiratory pauses, broken by active expirations. This began with the smallest effective doses and persisted almost to the point of respiratory failure. Expiration remained active with urethane longer than with any other drug we have tried in intact or decerebrated animals, but when respiratory failure occurred the last efforts were inspiratory. The expiratory response to CO_2 persisted after reflexes

TABLE I.

Hydrated chloral experiment. December 15, 1921. Cat, male; weight 2.89 kilos. Decerebrated through a trephine opening; left carotid open. Hydrated chloral, 5 per cent in Ringer's fluid, injected into a saphenous vein in 1 to 2 cc. doses. CO_2, 9 per cent, inhaled 1 minute. After 500 mg., CO_2 caused marked depression. No quantitative observations could be made.

Amount of hydrated chloral per kilo.	Maximum rate per min.		Average depth.		Min. volume.		Maximum inspiratory pressure.		Maximum expiratory pressure.		Blood pressure.		Corneal reflex.	Active expiration.	
	Air.	CO_2	Air.	CO_2	Air.	CO_2	Air.	CO_2	Air.	CO_2	Air.	CO_2		Air.	CO_2
mg.			*cc.*	*cc.*	*cc.*	*cc.*	*mm.Hg.*	*mm.Hg.*	*mm.Hg.*	*mm.Hg.*	*mm. Hg.*	*mm. Hg.*			
0	48	92	19	44	930	3,318	−0.3	−2.8	0	+1.2	106	116	+++	±	+++
17	58	100	17	42	1,024	3,516	−0.3	−2.4	0	+2.0	110	124	+++	+	+++
52	68	100	17	40	1,224	3,452	−0.3	−2.0	0	+1.0	100	118	++	++	+++
120	84	108	15	24	1,176	2,316	−0.3	−2.0	0	+1.0	84	104	+	++	+++
190	96	112	14	25	1,408	2,566	−0.3	−1.6	0	+0.3	84	92	±	+	++
310	88	92	20	24	1,760	2,106	−0.3	−1.3	0	0	72	80	0	+	+
400	72	84	12	19	864	1,500	−0.2	−1.0	0	−0.2	46	54	0	±	±
500	48		10		480		−0.08		0		40		0	0	
534	Respiratory failure.										16				

In the tables the last column indicates the character of breathing as observed directly. +++ indicates very active expiratory efforts, ± questionable, and 0 passive expiration.

were abolished, but it was much diminished and usually did not appear until near the end of the inhalation. The rate was often slowed during the first 45 seconds of the inhalation, when inspiration was increased without corresponding increase in expiration. This seems to indicate a more marked depression of expiration than of inspiration.[3]

The results of a typical experiment with urethane are given in Table II.

It is seen that there was a steady diminution in rate as narcosis progressed, but there was a corresponding increase in depth, so that minute volume of air breathing was little affected; the increase in ventilation in response to CO_2, however, was progressively diminished. Expiration remained definitely active, though much less so, until the last injection; this was followed by a few weak inspiratory gasps and blood pressure remained high for several minutes after respiratory failure.

Magnesium.—We have made no effort to study the action of this drug in detail. Only one experiment was made, on a decerebrated cat, in which 5 per cent magnesium chloride was injected intravenously in doses of 50 mg. The results resembled those obtained with the depressants of the alcohol group in that there was no definite effect until narcosis was produced. This occurred after 0.3 gm. of magnesium chloride per kilo. The expiratory response to CO_2 was progressively diminished from this point on, and less and less acceleration was caused by CO_2 as narcosis became deeper. Depth of inspiration was also diminished and minute volume was reduced, while blood pressure remained high. The drug was not pushed to the point of respiratory failure. Its effect on respiration seemed to be a more uniform depression, less complicated by reflex factors or circulatory changes than any of the alcohol depressants.

Luminal Sodium (Phenobarbital).—We have made two experiments with this drug, using intact animals, and injecting a 10 per cent solution during ether anesthesia. In one experiment on a cat weighing 2.6 kilos, a total of 0.18 gm. per kilo was required to maintain narcosis; while in the other, in which the animal weighed 3.1 kilos, 0.06 gm. per kilo produced comparable results.

[3] An example of the expiratory rhythm which followed urethane is shown in Figs. 3, *A* and 4, *A* of the preceding paper, before vagotomy or morphine.

TABLE II.

Urethane experiment. December 16, 1921. Cat, female; weight 3.2 kilos. Decerebrated through a trephine opening; left carotid open; tracheal cannula; urethane 5 per cent in Ringer's fluid, 1 to 2 cc. dose, into a saphenous vein. CO_2, 10 per cent, inhaled 1 minute.

Amount of urethane per kilo.	Maximum rate per min.		Average depth.		Min. volume.		Maximum inspiratory pressure.		Maximum expiratory pressure.		Blood pressure.		Corneal reflex.	Active expiration.	
	Air.	CO_2	Air.	CO_2	Air.	CO_2	Air.	CO_2	Air.	CO_2	Air.	CO_2		Air.	CO_2
mg.			*cc.*	*cc.*	*cc.*	*cc.*	*mm.Hg.*	*mm.Hg.*	*mm.Hg.*	*mm.Hg.*	*mm.Hg.*	*mm.Hg.*			
0	48	56	26	59	1,238	3,094	−1.5	−7.5	0	+3.0	114	134	+++	±	+++
0.5	28	32	30	74	840	2,224	−1.8	−9.5	0	+3.0	136	146	++	±	+++
0.625	24	40	36	73	864	2,328	−1.0	−4.8	0	+0.8	134	144	+	±	++
1.00	20	28	52	81	1,040	1,960	−1.6	−4.4	0	−0.2	112	140	±	±	+
1.25	24	28	46	67	1,104	1,758	−1.6	−4.0	0	+0.6	114	134	0	±	++
1.87	28	28	24	36	672	1,008	−0.8	−1.4	0	+0.2	126	116	0	±	+
2.34	24	20	42	70	1,056	1,518	−1.1	−3.1	0	0	114	112	0	±	+
2.65	Respiratory failure; inspiratory gasps.										106		0	0	

In each experiment there was complete muscular relaxation, but corneal reflexes persisted, as was pointed out by Symes (2). The most striking feature of these experiments was a complete abolition of active expiration, at rest and during CO_2 inhalation, while inspiration continued to be quite deep; respiratory rate was uniformly 20 to 24 per minute, and was accelerated only slightly by CO_2. The effects of luminal resembled those of morphine and heroine more closely than those of any other drug, but were produced only by narcotic doses. Morphine produced no further change in rate in these experiments, but in the one in which the larger dose of luminal was used, 1 mg. of morphine decreased the depth slightly, while 2 mg. produced respiratory failure; in the other experiment morphine up to 20 mg. had no definite effect.

DISCUSSION.

In general, all these drugs exerted a more marked depressant effect on expiration than on inspiration, and in many cases it was possible to induce completely passive expiration before respiratory failure occurred. None of them had any definite effect until narcosis was produced, and none, with the possible exception of luminal, was able to depress expiration selectively in a manner comparable to that of morphine or heroine.

The characteristic features described for the individual drugs were apparently due to action elsewhere than on the respiratory center itself—chiefly to reflexes resulting from local irritation, or to circulatory changes. The sharp expiratory rhythm seen with urethane resembled closely that seen in the early stages of ether narcosis, or the type of breathing which followed vagotomy in the decerebrated or narcotized animal; it was obviously not due to irritation of the respiratory passages, and we have no evidence that urethane selectively depresses the vagus mechanism. While breathing after urethane was slower and deeper, the type of effect was not comparable to that of morphine or heroine, for the animal under urethane narcosis had a labored respiratory rhythm, with active expirations, entirely different from the quiet, even, apparently effortless breathing when expiration is passive. We have no explanation to offer for this expiratory rhythm of urethane.

The Rôle of Expiration in Breathing.

Since all the drugs we have tried either depress expiration selectively, or depress expiration more than inspiration, it seems probable that there is, in the cat, at least, a separate central mechanism for the control of each of the phases of respiration. The fact that expiration is normally largely or wholly a passive act, but becomes active during dyspnea of any sort, seems to indicate that the central expiratory mechanism responds to the same chemical stimuli which affect the inspiratory mechanism. The expiratory center is set at a higher threshold for chemical stimuli than the inspiratory center.[4] Another manifestation of this is seen in the response to CO_2 inhalation,[5] in which the first effect is commonly an increase in depth of inspiration, but expiration becomes definitely increased only at a later period in the inhalation. Similar results may be obtained by inducing dyspnea by means of nitrogen or by rebreathing.

Another characteristic of the expiratory mechanism is its relation to the rate of breathing, of which some mention has already been made. Almost without exception, the maximum increase in rate and depth during CO_2 inhalation occurred when expiration was most active; when expiration failed to become active as inspiration increased in depth, the rate was unchanged, or was decreased.[6] When this is considered in view of the acceleration in rate which followed more rapid emptying of the lungs when expiration was passive, it becomes evident that, if the chemical stimulus remains constant, more rapid expiration entails a more rapid rate. It is possible to obtain a considerable increase in both rate and depth only by the intervention of active expiration; without active expiration an increase in depth may slow the rate.

This tendency to slowing when the depth is increased is to be seen whenever expiration is made passive by any drug. We have seen it with ether, chloroform, hydrated chloral, urethane, and luminal, as well as with morphine and heroine. Cushny (3) and Cushny and Lieb (4) described a similar slowing in rabbits after large doses of

[4] We use the terms expiratory and inspiratory centers for the sake of convenience only.

[5] See Fig. 1 of the preceding paper.

[6] See Fig. 2, *B* of the preceding paper.

chloral or urethane, but did not obtain it with morphine; it is possible that failure of expiration to become active in compensation for an increase in depth may have accounted for their results. That such a failure of expiration prevents adequate ventilation is seen in the fall of pH of the blood during CO_2 inhalation when expiration remained passive,[7] and it is possible that, when the respiratory center is already depressed by a drug, a further increase in CO_2 of the blood may cause depression instead of stimulation, the result being comparable to that of inhalation of a very strong concentration of CO_2.

Since expiration is active only when there is an unusual need for increased ventilation, as in dyspnea, or to expel an irritant, as in cough, or in breathing against obstruction, it seems to furnish an added factor of compensation or protection to the respiratory mechanism, without being absolutely essential to life. It may be for this reason that depressant drugs affect expiration more than inspiration, though the selective action of morphine and heroine seems to deserve separate mention as a specific one.

Respiratory Stimulants.

We have tested caffeine, strychnine, and atropine in many experiments, after respiration had been depressed by drugs. In general, it may be said that caffeine and strychnine were able to remove at least part of the expiratory depression produced by morphine, causing a return of active expiration and an acceleration in rate. The first apparent effect of either drug was usually a return of the expiratory response to CO_2, and the effect of larger doses of caffeine was usually slight; with strychnine the effect of progressive doses was similar to that of large doses of morphine in the decerebrated animal.

Atropine has never shown any signs of a stimulant action in our experiments, but has often acted synergistically with morphine; in some experiments, in which large doses of morphine had had no depressant effect, 0.5 or 1 mg. of atropine immediately made expiration passive and slowed the rate. As Jackson (5) has shown that atropine does not affect the bronchial contraction produced by morphine,

[7] See Table IV of the preceding paper.

this effect must be attributed to circulatory changes, or to an actual synergistic action, and we have uniformly found that small doses of morphine were more effective in producing expiratory depression after atropine had been given.

SUMMARY.

1. The depressant drugs which have been studied in this series of experiments were found to resemble morphine and heroine in that they depressed expiration more than inspiration, but they acted only in narcotic doses and always depressed inspiration at the same time. Ether caused a sharp expiratory rhythm, persisting until narcosis was very deep, probably a result of irritation of the air passages. Chloroform sometimes caused dyspnea, even in very deep narcosis, probably because of circulatory depression. Hydrated chloral made respiration more rapid, but shallower. Urethane usually made expiration active, often with inspiratory pauses, such as may follow vagotomy. Magnesium seemed to produce the most uniform, uncomplicated depression of all the depressants tried. Luminal resembled morphine and heroine more closely than any of the general depressants, making expiration passive without depressing inspiration, but it acted only in narcotic doses, unlike morphine and heroine.

2. Caffeine and strychnine, whenever they caused acceleration after morphine, brought back active expiration. Atropine never stimulated, and commonly acted as a synergist to morphine.

3. It is suggested that the results outlined in this and the preceding paper point to the existence of a separate central mechanism for the control of each of the phases of respiration, and that, while each responds to the same chemical stimuli, the threshold of the expiratory is higher than that of the inspiratory. Evidence is presented to indicate that if expiration remains passive a marked increase in depth of breathing may slow the rate, and a respiratory mechanism that lacks active expiration may be so inefficient that a CO_2 concentration which stimulated when expiration was active may depress when it is passive.

We wish to express our sincere thanks to Professor A. N. Richards, for his invaluable suggestions and assistance in these experiments, and to Dr. A. E. Livingston and Dr. J. B. Brown, of the Department of Pharmacology, for cooperation in many details of this research.

BIBLIOGRAPHY.

1. Schmidt, C. F., and Harer, W. B., *J. Exp. Med.*, 1923, xxxvii, 47.
2. Symes, W. L., *J. Physiol.*, 1914–15, xlix, 126.
3. Cushny, A. R., *J. Pharmacol. and Exp. Therap.*, 1912–13, iv, 363.
4. Cushny, A. R., and Lieb, C. C., *J. Pharmacol. and Exp. Therap.*, 1914–15, vi, 451.
5. Jackson, D. E., *J. Pharmacol. and Exp. Therap.*, 1914–15, vi, 57.

EXPLANATION OF PLATE 7.

FIG. 1.[8] Ether experiment.

The figures under the signal tracing indicate the rates per minute, at 15 second intervals.

C R +++, corneal reflex very active; *C R O*, corneal reflex absent; *C R* ±, corneal reflex very sluggish; *C R* +, corneal reflex definite, but not active.

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

[8] From the same experiment as Fig. 1 of the preceding paper.

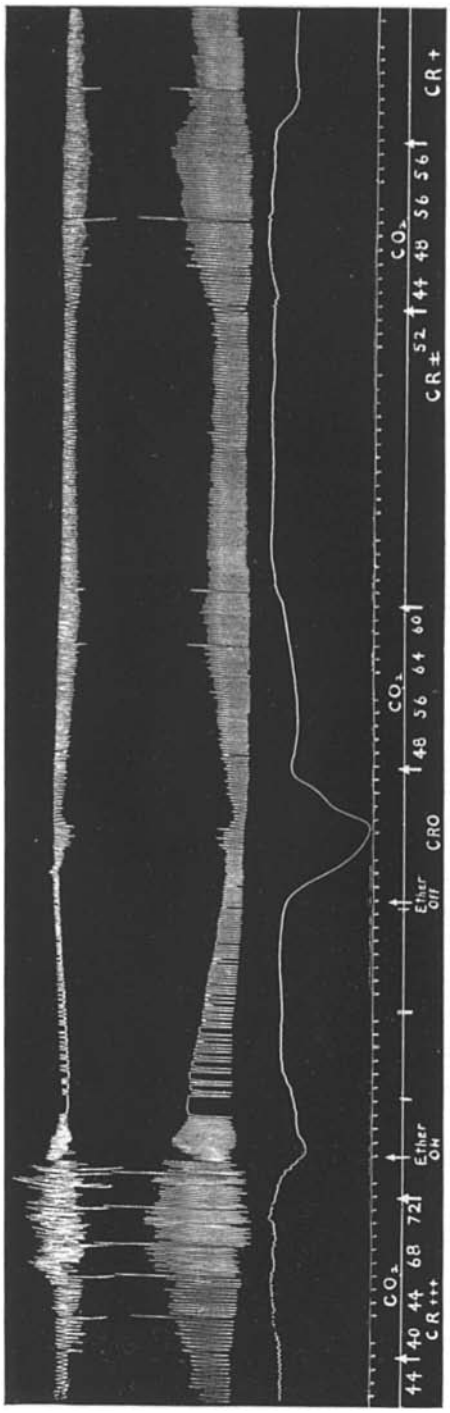

FIG. 1.

(Schmidt and Harer: Action of drugs on respiration. II.)