THE EFFECT OF ANESTHETIC DRUGS UPON BRONCHI AND BRONCHIOLES OF EXCISED LUNG TISSUE * †

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STUDIES of reactions of bronchial tissues to various drugs have been completed, but they have been limited for the most part to substances other than those exerting anesthetic effects. The recorded observations produced by anesthetic drugs are limited chiefly to the effects of ether, chloroform, and a number of local anesthetic drugs. Trendelenburg (1), Macht and Ting (2), Sollmann and Gilbert (3) have observed a relaxation or a preliminary constriction followed by relaxation with ether and chloroform on excised bronchial tissues obtained from experimental animals. The anesthetic agents recently adopted have not been studied. Interest in their possible behavior has been aroused from the attention directed toward laryngeal spasm from vagal activity during anesthesia in intact animals and man (4). Little thought or study has been directed to bronchial or bronchiolar spasm and constriction as possible sources of obstruction and diminished pulmonary ventilation during general anesthesia. Symptoms of bronchiolar spasm occurring during anesthesia have been reported with cyclopropane (5, 6). Inasmuch as the bronchi and bronchioles are under autonomic control (7) and evidence exists that some anesthetic drugs produce effects of autonomic stimulation (8, 9, 10), the responses of these tissues to anesthetic drugs may be of interest from this point of view also.

This study on excised lung tissue was undertaken to note and compare the effects of various anesthetic drugs on the bronchi and bronchioles, and to observe any possible autonomic effects on these tissues. The newer volatile and nonvolatile drugs—cyclopropane, vinyl ether, cyclopropyl methyl ether, propyl methyl ether, tribromethanol, trichlorethanol, amylene hydrate, and various short- and long-acting barbiturates—have been studied and compared with the established anesthetic drugs—ether, chloroform, ethyl chloride, ethylene, nitrous oxide, paraldehyde, phenobarbital, and others. A preliminary study has been published (11).

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EXPERIMENTS

Freshly excised lung tissue was cut lengthwise into sections 2 to 3 mm. thick by means of a sharp razor in order to cut the bronchi cleanly transversely. Sections were mounted with the flat surface upward in a wide glass chamber and covered with Locke's solution at 38 C. The entire vessel was placed on a warmed mechanical stage of a binocular microscope. Light directed from above permitted visualization of walls and lumina of small, medium, and large bronchi with low power magnification (100 ×). A regularly woven fine silk mesh composed of squares was placed in one eyepiece to permit calibration of the field and moment to moment estimations and recordings of the diameter and area of the lumen. The mechanical stage allowed shifting of the chamber so that bronchi of various sizes could be compared under similar conditions. Records also were made on a standard photographic film by placing a camera over one eyepiece. Drugs were dissolved in Locke's solution in strengths comparable as nearly as possible to those encountered in blood during anesthesia in vivo. Between experiments, the preparations were washed with plain Locke's solution several times at five-minute intervals, or until the control state was restored. Solutions of acid or alkaline substances were readjusted to the hydrogen ion concentration of plain Locke's solution with either hydrochloric acid or sodium bicarbonate. Saturated solutions of gases were prepared by shaking an excess of gas with plain Locke's solution in the exhaustion chamber of the manometric apparatus of Van Slyke and Neill or were bubbled with a fine-tipped cannula into the solution containing the preparation. After mounting, the preparation was allowed to rest for thirty to sixty minutes to eliminate the effects of trauma, since it was noted that satisfactory responses were not obtained if the preparation were used immediately. Inasmuch as the chamber containing the preparation was a wide, flat vessel with a large surface exposed to the air, oxygenation from the air was adequate during the observation. Oxygen was bubbled into the chamber with a fine-tipped cannula during the periods of restoration.

RESULTS

Four hundred and forty-one observations were made on the lungs of 12 rats, 3 dogs and nonpathologic portions of 3 lungs of human beings removed during pneumonectomy. In dog and man, small bronchi and bronchioles were studied; in rats, both large and small bronchi were studied. Results are summarized in tables 1 and 2 and plate 1. Effects on the mucosa and reactions of cilia or peristaltic movements were not closely observed. The intensity of the response varied from one preparation to the next, although they were qualitatively similar.

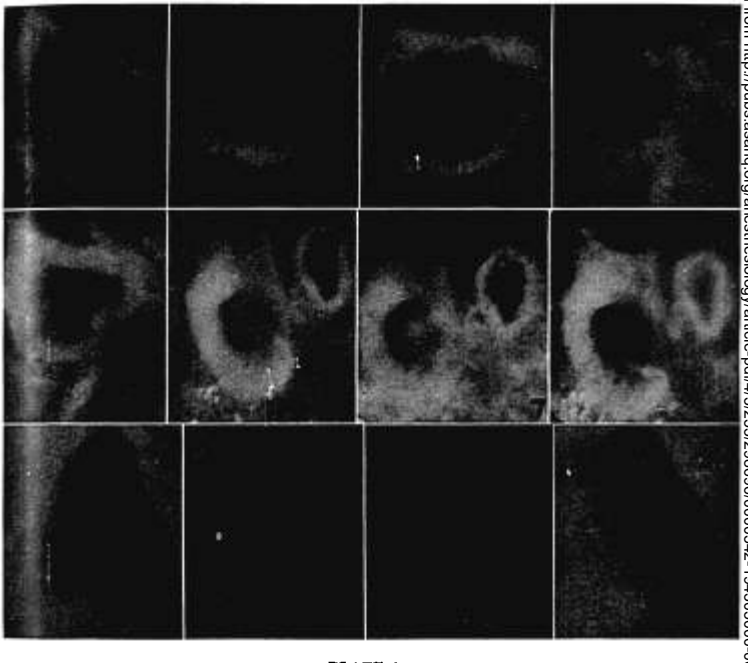

PLATE 1.

Photomicrographs of responses of bronchi of excised lung of the rat to various anesthetic drugs. (1) Small bronchus in its control state. (2) Constriction produced by cyclopropane alone. (3) Atropine after the cyclopropane was added. (4) Effect of acetylcholine on the same bronchus shown in 1. (5) The effect of pentothal. (6) Several small bronchi in the control state. (7) Relaxation produced by vinyl ether. The larger bronchus moves out of focus due to change in length accompanying the dilatation. (8) Constriction produced by evipal. (9) Control state of a large bronchus. (10) Atropine followed by cyclopropane produces relaxation. (11) Constrictor effect of amytal. (12) Constrictor effect of nembutal.

TABLE 1

Drug	Number of Different Animals from Which Specimens Were Obtained			Responses							Remarks
	Rat	Dog	Man	Response to Drug Alone	Atropine Before Drug 1–250,000	Atropine Followed Drug 1–250,000	Eserine Added After Drug (1–100,000)	Procaine Before Drug 1–50,000	Procaine Followed by Drug 1–50,000	Total Observations	
Nitrous oxide (saturated)	3	1	0	+ U	U	R	+	U	R	28	Epinephrine and ephedrine added after drug produces relaxation
Ethylene (saturated)	3	1	1	+ U	U	R	+	U	R	23	Epinephrine and ephedrine added after drug produces relaxation
Cyclopropane	4	2	1	++++	U	R	+++++ +	U	R	35	Prostigmine behaves as eserine. Novatropine, hyoscine behave as do atropine
Paraldehyde 1–10,000	3	1	0	+++	+++	U	+++	++	U R	30	Ephedrine dilates slowly. Ether causes relaxation quickly after the drug
Sodium Pentothal 1–10,000	3	1	1	+++++	+	R	+++++ +	U	R	34	Ephedrine and ether following drug produce dilatation immediately
Sodium Evipal 1–10,000	2	1	1	+++	U	R	++++	U	R	13	
Sodium Amytal 1–10,000	2	1	1	+	U	R	++	U	R	13	
Sodium Nembutal 1–10,000	2	1	1	+	U	R	++	U	R	13	
Sodium Phenobarbital 1–10,000	2	1	1	+	U	R	++	U	R	14	
Ipral Sodium 1–10,000	2	1	1	+	U	R	++	U	R	13	
Morphine Sulfate 1–100,000	1	1	0	+	U	R	++	U	R	15	
Codeine Sulfate 1–100,000	1	1	0	+	U	R	++	U	R	10	

Anesthetic drugs which produce bronchoconstriction are listed. The modifying action of autonomic drugs is summarized. A plus (+) sign indicates a constriction averaging approximately 5 per cent of the diameter of the lumen. "U" indicates there is no modifying action by the autonomic drug added after the anesthetic drug. "R" indicates the autonomic drug produces a relaxation of the constricted bronchus or bronchiole.

TABLE 2

Drug	Number of Different Animals from Which Specimens Were Obtained			Responses							Remarks
	Rat	Dog	Man	Response to Drug Alone	Ergotamine Followed by Drug 1/100,000	Drug Followed by Ergotamine 1/100,000	Procaine Followed by Drug 1–50,000	Drug Followed by Procaine 1–50,000	Drug Followed by Eserine 100,000	Total Observations	
Ethyl ether 1–1,000—1–10,000	3	1	1	— —	— —	— —	U	U	U	30	Larger concentrations constrict
Ethyl propyl ether 1–10,000	2	0	0	— —	— —	— —	U	U	U	20	
Divinyl ether 1–10,000	3	1	1	— —	C	R	U	U	+ −	30	Not modified by atropine
Cyclopropyl methyl ether	2	1	0	— —	C	R	U	U	+ −	20	Not modified by atropine
Chloroform 1–50,000	2	1	0	— —	— —	— —	U	U	U	20	Larger concentrations constrict
Ethyl chloride	2	1	0	—	C	— —	U	U	U	18	
Tribromethanol 1–10,000	4	1	1	—	—	— —	U	U	U	30	
Trichlorethanol 1–10,000	2	1	0	—	—	— —	U	U	U	16	
Amylene hydrate 1–10,000	2	1	0	—	—	— —	U	U	U	16	

Anesthetic drugs which produce bronchodilation and the modifying action of autonomic drugs are summarized. Each minus (—) sign indicates relaxation up to 5 per cent of the control diameter. "C" indicates a reversal of the dilator to a constrictor action. "U" indicates there is no modifying action produced by the autonomic drug when added after the anesthetic drug. Other symbols are the same as in Table 1.

GASES

Cyclopropane, approximately 5 volumes per cent, produced a prompt constriction with a reduction of 10 per cent to 25 per cent of the diameter of the lumen. An increase in amplitude of undulating movements of the bronchial wall in rat lung was observed. The reaction, which was complete in an average of twenty seconds, persisted. Washing with plain Locke's solution restored the preparation to the control state. Dilute solutions of cyclopropane produced similar but less intense responses. A partial restoration to the control state was obtained by allowing the preparation to stand five minutes, but the addition of more gas caused constriction to reappear. This partial relaxation was probably due to loss of gas from the solution. Eserine salicylate (1/100,000), added before cyclopropane, produced a slight constrictor action. When followed by cyclopropane, a prompt constriction occurred which was of greater intensity than with cyclopropane or eserine salicylate alone. Atropine sulfate (1/250,000) reversed this constrictor response of both cyclopropane and cyclopropane combined with eserine salicylate until the control conditions were restored. Atropine sulfate followed by cyclopropane caused a slight dilatation in approximately half the observations. In the remainder, no effect or a slight constriction occurred. Ephedrine sulfate (1/10,000) and epinephrine (1/100,000) also reversed the constrictor effect promptly. Procaine hydrochloride (1/50,000) reversed the constrictor action produced by cyclopropane or prevented it if added previously to the gas. Novatropine (homatropine methyl bromide) and hyoscine hydrobromide produced qualitatively similar responses and reacted exactly as atropine. The responses of cyclopropane, though far less intense, paralleled those of acetylcholine (1/1,000,000). Similar qualitative results were obtained on tissues from dog and man.

Ethylene, 0.2 volume per cent, produced a constriction amounting to less than one-twentieth of the diameter of the lumen in rat tissues. Atropine sulfate, procaine hydrochloride, ephedrine, and eserine salicylate did not inhibit or enhance this response. Nitrous oxide produced similar results. Washing restored the preparations to the control state.

VOLATILE DRUGS

Ethyl ether (1/10,000) produced a dilatation of the lumen of bronchi and bronchioles in the rat up to 20 per cent of the control diameter. Stronger concentrations produced a constriction not inhibited by atropine sulfate, or prevented by procaine hydrochloride, but enhanced by eserine salicylate. The relaxation was not inhibited or enhanced by ergotamine tartrate (1/100,000).

Divinyl ether, one-tenth saturated, produced a dilatation of the lumen; the increase varied from one-tenth to one-quarter of the origi-

nal lumen. The drug escaped rapidly from the solution due to its low boiling point, and, therefore, the response did not persist. If ergotamine tartrate was added before the vinyl ether there was constriction instead of relaxation. The results with ethyl propyl ether were like those with diethyl ether. Cyclopropyl methyl ether produced results similar to vinyl ether. Chloroform (1/5,000) like ethyl ether produced a relaxation not reversed by ergotamine tartrate. Stronger concentrations of chloroform caused a constrictor response not inhibited by atropine sulfate, enhanced by eserine sulfate or prevented by procaine hydrochloride. Ethyl chloride, one-tenth saturated, dilated the lumen approximately one-tenth of the control diameter. Dilatation was often preceded by a constrictor action. The reaction to ergotamine tartrate added prior to the drug was variable. Undulating movements ceased with these drugs. The responses produced by the ethers were not affected by procaine hydrochloride, ephedrine, epinephrine, or atropine sulfate.

NONVOLATILE ALIPHATIC SUBSTANCES

Tribromethanol (1/10,000) produced a relaxation and a cessation of the undulating movements. Ergotamine tartrate did not cause a reversal of the response. Trichlorethanol behaved similarly. Amylene hydrate (1/10,000) produced a dilatation also. Paraldehyde (1/10,000), freed of aldehyde, produced a constriction and inhibition of undulating movements. The constriction appeared gradually and required intervals of two to three minutes for stabilization. Washing with plain Locke's solution was followed by almost complete restoration of the control state. Recovery was slow, requiring as a rule four to five minutes. Ethyl ether promptly reversed the constriction to a relaxation. Atropine sulfate required an interval of four to five minutes for reversal and even then did not produce complete relaxation. Atropine sulfate given beforehand inhibited the appearance of the constrictor action slightly, and in some instances not at all. The constrictor response was not enhanced by eserine salicylate. Ephedrine sulfate, likewise, slowly reversed the constrictor action but required four to five minutes for the effect, which was only partial.

BARBITURATES

Sodium phenobarbital (1/10,000) produced a constriction which was complete in thirty seconds. Prompt relaxation followed the addition of ether. A less rapid relaxation followed atropine sulfate and hyoscine hydrobromide. Washing completely restored the control state. Sodium ipral (5'–5 isopropyl ethyl, sodium barbiturate), an intermediate-acting barbiturate, likewise produced constriction. Sodium evipal (5'–5 cyclohexenyl methyl N-methyl sodium barbiturate) and sodium

pentothal (5′ ethyl, 5′ methyl butyl sodium thiobarbiturate), which are both ultra-short-acting barbiturates, produced a prompt constriction. The constriction was pronounced and amounted to almost 25 per cent of the diameter of the lumen in the rat's bronchi. Atropine sulfate, hyoscine hydrobromide, and procaine hydrochloride prevented the response almost entirely. Although no response was obtained with pentothal in the atropinized preparation when paraldehyde followed this combination, the constriction did occur. Ephedrine sulfate, diethyl ether, vinyl ether, tribromethanol, and procaine hydrochloride all reversed the constrictor effect produced by pentothal. Eserine salicylate and cyclopropane enhanced the constriction. More pronounced responses were obtained with the shorter-acting than with the longer-acting barbiturates. Morphine sulfate (1/10,000) produced a constrictor action which was inhibited by atropine sulfate and hyoscine hydrobromide.

Responses of tissues obtained from dog and man were qualitatively similar to those of the rat. The human lung preparations responded sluggishly, most likely due to the fact that specimens were not obtained under ideal conditions. The responses and modifications of hyoscine hydrobromide, novatropine, and atropine sulfate were qualitatively similar. Prostigmine and eserine salicylate were consistently similar and could be readily interchanged. Bronchi and bronchioles examined in the same specimen responded qualitatively similarly.

DISCUSSION

Dilatation of bronchi and bronchioles may result from stimulation of the sympathetic division of the autonomic nervous system, from a direct depressant action on the muscle, or a combination of both effects. Likewise, constriction may result from parasympathetic stimulation or a direct stimulation, or irritating action on the muscle. Since the constrictor effect of cyclopropane was enhanced by eserine salicylate, released or prevented by atropine sulfate, hyoscine hydrobromide, novatropine, ephedrine sulfate, and procaine hydrochloride, it is presumed that the effect is due to a local parasympathetic stimulation in these preparations. The slight transient constrictor effect of ethylene and nitrous oxide is a result of action directly on the muscle, since the response is neither enhanced by eserine salicylate nor prevented by atropine sulfate, hyoscine hydrobromide, or procaine hydrochloride. After procaine hydrochloride or atropine sulfate, a dilator response follows cyclopropane, suggesting that the gas narcotizes the muscle when the nervous influence is removed. The dilator effect of vinyl ether, cyclopropyl methyl ether, and ethyl chloride is converted to a constrictor effect by ergotamine tartrate, suggesting that release of the neural mechanism possibly allows an irritating effect on the muscle. The di-

lator effect of ether, chloroform, and the halogenated ethanols and amylene hydrate was not reversed, suggesting a direct depressant action on the muscle, or possibly a combined neural and muscular effect. No qualitative differences were noted in dilatation with ergotamine tartrate. The sluggish response was not altered dramatically by atropine sulfate, eserine salicylate, paraldehyde or ephedrine sulfate, but was altered quickly by ethyl ether. The constrictor effect is due to an irritant action on the muscle, which is antagonized by ether. Although quantitative differences exist between various barbiturates, their reactions were essentially similar. The inhibition with atropine sulfate, novatropine, hyoscine hydrobromide, and procaine hydrochloride, the relaxation with ephedrine sulfate, ether and the enhancement with eserine salicylate and prostigmine suggest that the response of the barbiturates is one of parasympathetic stimulation.

A slight preliminary and fleeting constrictor effect was noted in most preparations regardless of the drug used. This persisted for five or six seconds when the action of the drug itself finally became established. This was probably a response of the tissue to the chemical itself and was disregarded. The more potent drugs, such as ether, chloroform and cyclopropane, relaxed the muscles when neural mechanisms were paralyzed. The milder drugs, such as vinethene, nitrous oxide and ethylene, paraldehyde, and barbiturates, constricted slightly when the neuromechanism was blocked. This suggests that these drugs act on the muscle to a slight extent.

SUMMARY

The effects of anesthetic drugs upon the bronchi and bronchioles of excised lung tissue from rats, dogs and human beings have been observed. The modifications obtained by autonomic drugs have been recorded.

Ethyl, vinyl, n-propyl ethyl, and cyclopropyl ethers, chloroform, ethyl chloride, tribromethanol and trichlorethanol, and amylene hydrate are bronchodilators. Cyclopropane, the sodium salts of pentothal, phenobarbital, barbital, ipral, evipal, amytal, and nembutal, morphine sulfate, and paraldehyde are bronchoconstrictors. Nitrous oxide and ethylene produced no characteristic effect.

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For the information of anesthesiologists who are contemplating application for certification by the American Board of Anesthesiology, Inc., or who are training physicians for the specialty, the following questions have been employed for Part I (written) examination in the past in *Pathology:*

1. A young man known to have a peptic ulcer became ill with pain in the abdomen and back accompanied by nausea, vomiting and diarrhea. A diagnosis of acute appendicitis was made. One month later he was operated upon. A retrocecal normal appendix was removed and a partial gastrectomy performed. Recovery was satisfactory for thirty-six hours at which time a sudden change took place. Blood pressures could not be estimated and the pulse was impalpable although he was conscious, and his skin was not extremely pale or cold. Six hours later, the pulse could be palpated with difficulty but pulmonary edema was obvious. How would you explain his condition and what prognosis would you offer?
2. If a major coronary occlusion took place while you were administering general anesthesia, what physical signs would you expect to observe and what occurrences other than coronary occlusion might cause similar signs?
3. A patient in excellent condition, but unconscious, was left alone in his room after his return from the operating room. Fifteen minutes later he was found dead. At postmortem examination what regions would you wish the pathologist to examine most carefully and what findings are the more likely?
4. A psychologist who writes a column for the press describes the following case: A normal child of 5 was found to be an idiot after recovery from a general anesthetic. Over a period of months, gradual recovery and re-education took place. What explanations would you suggest as the probable causes of the sudden loss of mental acuity and its gradual recovery?
5. What are the usual pathological findings in a case of death from pneumonia following anesthesia?
6. Explain how and why a lumbar sympathetic block with procaine may aid in the differential diagnosis of arteriosclerotic and vasospastic disease of the lower extremity.