

THE EFFECTS OF MECHANICAL AND CHEMICAL STIMULATION OF THE TRACHEO-BRONCHIAL MUCOUS MEMBRANE

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A number of studies have appeared on the effect of irritant gases on the epithelium of the air passages. The latest of these is by Craigie (1), who has sufficiently reviewed the earlier contributions. They are, however, at such variance on many points, particularly with reference to the rôle of the branches of the vagus nerves in the pulmonary reflex arc, that it appears desirable to reconsider the problem in the light of more detailed anatomical knowledge of the nerve plexuses and terminations within the lungs. Concerning the effects of various types of stimuli in the nasal and pharyngeal passages there is pretty general agreement. We shall therefore confine our attention entirely to the reflexes caused by stimuli applied to the mucosa of the tracheo-bronchial tree. In addition to the effects of chemical stimulation, our observations on stimulation by mechanical means will also be included.

Since our anatomical knowledge of the innervation of the lung is most complete for the rabbit, this animal was used for most of the work. Forty animals were utilized. They were supplemented with a small number of dogs for comparison. It should be stated that, as Mayer, Magne and Plantefol (2) have pointed out, the rabbit is the most sensitive animal for experiments on the pulmonary reflexes, while the dog is the least sensitive. The combination of anatomical knowledge of the nerve supply of the rabbit's lung which appears to be as complete as present neurological technique will permit, together with the sensitiveness to stimulation to which reference has just been made, should give data of value on the problem under consideration, namely, the response of the tracheo-bronchial mucosa to mechanical and chemical stimulation.

Two series of animals were employed. The first series was given urethane by stomach tube, and then given ether until after a tracheal cannula had been introduced and the vagi isolated. The cannula had a side arm for connection with a recording tambour.

In the case of experiments with mechanical stimulation the animal was placed under the fluoroscope and the stimulus was applied directly to the mucosa by means of a fine camel's hair brush attached with wax to the end of a small brass wire. The outlines of the bronchi were usually faintly discernible and the position of the brush with reference to the points of branching of the bronchial tree could be controlled with a fair degree of accuracy. As one of us (3) has shown, it is at these points of bifurcation particularly that the nerve terminations are located.

Chemical stimulation was effected by causing the animal to inhale fumes of ammonia, ether, acetic acid, tobacco smoke and formaldehyde through a cannula. The most effective way of applying the stimulus without causing the apparatus to interfere in the slightest degree with the normal respiration was by drawing the vapor from a bottle into a rubber bulb with a small neck and then gradually expelling it at the free end of the cannula. The animal thus inhaled air strongly mixed with the irritating vapor. This gave a nearly uniform period of stimulation of four to five seconds' duration. The connection with the tambour recorded the result. Precautions were taken to prevent stimulation of the nasal mucosa by the fumes as they were released.

The second series of animals was not given urethane, but only ether until the cannula was inserted and the vagi isolated. They were then kept under light ether anesthesia. These animals gave better results, both with mechanical and chemical stimulation.

Results of mechanical stimulation. We found early in the course of our experiments that it was necessary to differentiate between stimulation of the carina tracheae and the intrapulmonary portions of the bronchi. This was true for the various types of stimuli which we employed. Stimulation of the carina with a brush elicited a vigorous response (figs. 1, 2 and 6), which consisted of a forced expiration or bechic blast. This was usually repeated several times in quick succession. When the carina was locally anesthetized with cocaine or when the vagi were sectioned, no further response from stimulation at this point was obtainable.

Stimulation of the deeper portions of the tracheobronchial tree produced results which were less marked in degree but were similar in type. Proper mechanical stimulation of the intrapulmonary passages in the rabbit is difficult because of the small diameter of these tubes, and the ease with which the mucosa is injured. Hemorrhage is very easily produced and, even when not soon fatal, vitiates the results, apparently by coating the mucosa in such a manner that the latter is not receptive to stimulation. We found that animals with respiratory infection were also refractory, apparently because the mucosa was coated with secretion. It was necessary to have healthy and active animals. In such rabbits, however, mechanical stimulation of the intrapulmonary bronchi produced reflexes

similar to those from the carina but much less pronounced. These could be best studied by observing the movements of the diaphragm under the fluoroscope. These movements consisted of spasmodic expiratory efforts when a sensitive point of the mucosa was stimulated. Stimulation of the division points of the main bronchus near the hilum gave responses much more marked than those obtained deeper within the lung. In a few animals it was possible to insert the brush along the main stem bronchus almost to the diaphragmatic surface of the lung, but no response

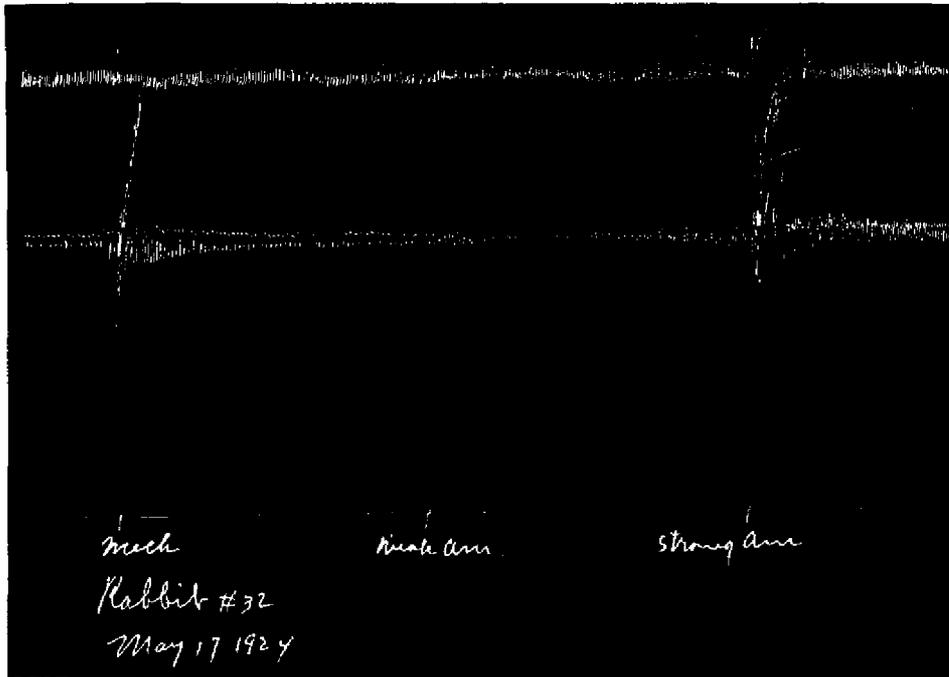


Fig. 1. Result of excitation of lungs of rabbit including carina, with mechanical stimulation, with weak ammonia fumes, and with strong ammonia. Vagi intact. Stimulus applied through tracheal cannula. The animal was under light ether anesthesia.

was obtained below the upper half of this tube. Attempts were made to insert the brush into the primary branches of the main stem bronchus but with only indifferent success in the rabbit. In a few cases there was an apparent slight response, but this was probably due to stimulation of the nerve terminations at the point of division from the main bronchus.

It is an interesting fact that after any of these points were stimulated sufficiently to produce a bechic blast, it was not possible to produce a second reflex from this point again for several minutes (fig. 2). Stimulation of other sensitive areas within the same lung would, however, call

forth the reflex immediately. Chevalier Jackson (4) has reported from his clinical observations phenomena resulting from the entrance into the lungs of foreign bodies of other than organic substance, and also in connection with the insertion of the bronchoscope into the trachea and bronchi. He states that "a fixed foreign body causes very little cough, as compared to a movable foreign body." He also calls attention to the "symptomless interval" after the initial choking and coughing when a

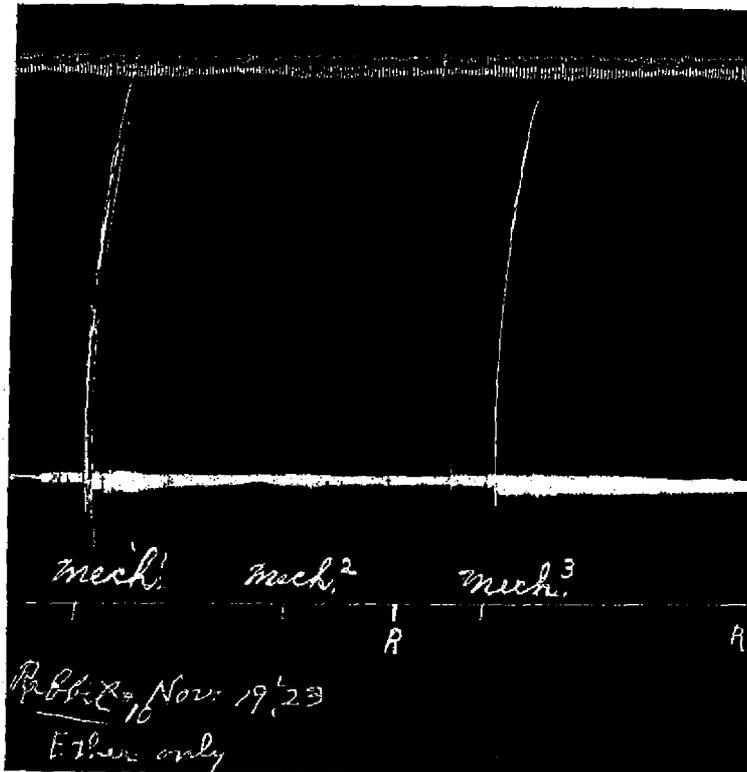


Fig. 2. Result of mechanical stimulation too soon repeated, giving no response the second time, *mech 2*, but after a rest period of about five minutes, *R*, a third application of the stimulus, *mech 3*, gave a marked reflex.

metallic foreign body is aspirated. Jackson attributes the cessation of the cough reflex in such cases to establishment of a "tolerance" by contact with the same mucosal surface over a period of time. Our results however indicate that the reflex is not again elicited for several minutes, usually two to five, in the rabbit even when the brush is withdrawn entirely from the trachea. We are inclined to regard the lack of immediate response as resulting from a fatigue, probably of the receptor mechanism.

Section of the vagus nerves resulted always in lack of response to mechanical stimulation (fig. 3). It is a point of interest that stimulation of the carina after section of one vagus produced varying results. Sometimes a slight response was elicited, sometimes no response, and occasionally a response of considerable violence. This appears to indicate that the right and left vagi share the innervation of the tracheal mucosa in

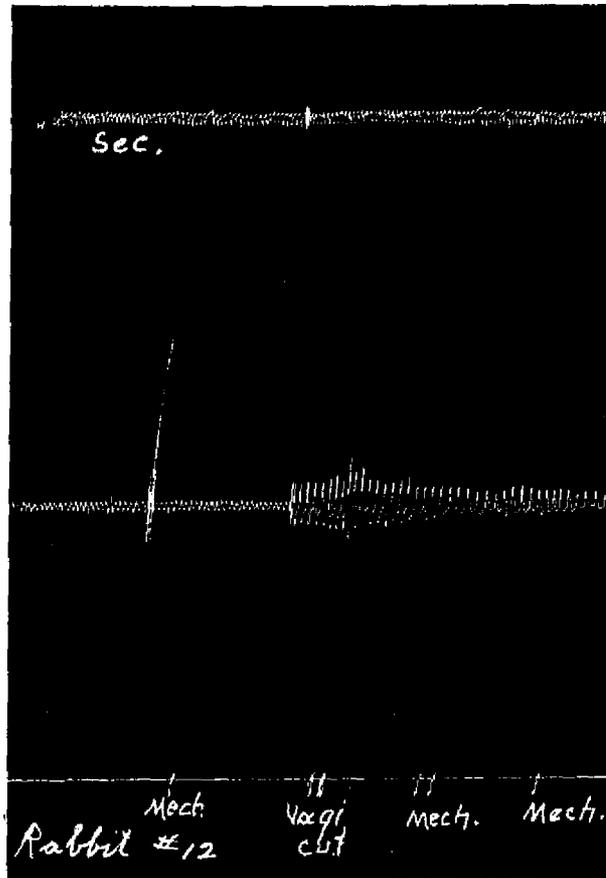


Fig. 3. Result of double vagotomy on response to mechanical stimulus, applied at *mech.* No response.

varying degree. No such results were obtained from the intrapulmonary bronchi, although Schiff (5) long ago pointed out that there is a certain amount of crossing over of the vagi. Larsell and Mason (6) have also observed this anatomically. Evidently, however, it is relatively so limited that stimulation of such crossed-over endings is very rare.

In order to further study the effect of mechanical stimuli within the lungs we employed a bronchoscope on a dog of medium size. The in-

strument was inserted into the trachea about 4 cm. below the larynx and adjusted to various positions within the lungs during the course of the experiment. The animal had been injected intravenously with urethane and was kept under light ether anesthesia in addition. The vagi were isolated preparatory to section. For invaluable assistance in this experiment with the bronchoscope, we are indebted to Dr. Ralph A. Fenton to whom we desire to express our thanks.

Stimulation, with a brush, of the carina produced marked bechic blasts. This was also true when the division points of the main bronchi into the primary branches were touched. A lesser response was induced when the division points of the primary branches into secondary bronchi were stimulated. We were not able to penetrate deeper than these points with the apparatus at hand. No response to stimulation at any of these points was obtained after the vagi were sectioned. This fact, true of both dog and rabbit, is in agreement with the anatomical result reported by Larsell and Mason (6), that nearly all the nerve terminations within the lung disappear after homolateral degeneration of the vagus.

Our experimental results are in harmony in most respects with the clinical observations reported by Chevalier Jackson (4). Both anatomical and experimental results on the rabbit and on the dog so far as they have been checked on the latter animal, show that without question there is present a receptor mechanism in the larger air passages at least, which on mechanical stimulation elicits a forced expiratory response. These receptors are connected with the central nervous system by the vagus nerves. Jackson quotes, with approval, a personal communication from Dr. F. J. Kalteyer that "there is abundant clinical evidence in support of the view that the pulmonary parenchyma is devoid of terminal afferent nerves essential to this reflex arc."

If by "pulmonary parenchyma" is meant only the atria and air-sacs, we would agree with this statement with the reservation that in the atrial walls nerve endings are present whose possible function we will consider below. Larsell (3) has shown that in the rabbit at least there are nerve endings of a type presumably receptive to mechanical stimulation in the air passages as far distally as the beginnings of the alveolar ducts. The general similarity of innervation of the canine and human lung to that of the rabbit in other respects (7), would lead one to suspect that nerve endings are present in the smaller air passages in the dog and human also although they have not yet been demonstrated by histological methods in these forms. It is possible that these terminations are receptive only to other types of stimuli than the tactile involved in the reflexes above described. It is furthermore not impossible that because of their small size and relative isolation one from the other, a large number must be stimulated almost simultaneously, as by collapse of the lung in expiration,

to induce a response. There would thus be produced a sort of summation of stimuli.

Response to chemical stimulation. In studying the effect of this type of irritants on the pulmonary mucosa, we found that fumes of ammonia and acetic acid produced the most marked effects of the irritants employed although ether served very well on animals which had recovered from the anesthetic or were only slightly under its influence.

Brodie and Russell (8) obtained a cardiac response to chloroform vapor, when applied to the nasal passages and the larynx, and also when applied to the lower respiratory passages. They confirm Kratschmer (9) and Francois-Franck (10) on the nasal passages and the results of the latter in obtaining a reflex cardiac and respiratory inhibition by stimulating the laryngeal mucosa with chloroform vapor. The conclusion of Francois-Franck that the respiratory tract below the vocal cords is insensitive to chemical stimuli, Brodie and Russell are unable to share. They state "We have frequently recorded slowing as an immediate result of chloroform administration. There is no question that this part of the respiratory tract is less sensitive than the larynx and nasal mucous membranes. In fact as we proceed downwards along the respiratory tract the mucous membrane is found to be less and less sensitive to chemical irritants."

When our rabbits inhaled ammonia, ether or acetic acid fumes through a tracheal cannula, there ensued a violent expiratory reflex (figs. 1 and 4) which was repeated a number of times if the animal was particularly sensitive. This was frequently followed by a period of apnea of from two to five seconds when ammonia fumes were introduced. This in turn was followed by marked polypnea often continued for many minutes, but we never observed a case continuing for as long as half an hour, as reported by Mayer, Magne and Plantefol (2). When fumes of weak ammonia were employed all response was absent (fig. 1).

Inspiration of acetic acid vapor incited a similar violent cough (fig. 4) which was always followed by the polypnea without an intervening period of apnea. Ether gave results (fig. 5) similar to those of acetic acid. With irritant vapors, as with the mechanical stimulus, a rest period of two to five minutes was necessary between separate applications or failure of the reflex resulted. Double vagotomy is followed by lack of response to stimulation in all cases (figs. 4 and 5).

In an effort to analyze the effect on the deeper bronchi alone we carefully cocaineized the trachea and the carina. After these parts had become so anesthetic that they failed to respond to stimulation with the brush we felt reasonably certain that any effect of chemical irritation must be due to stimulation of the deeper air passages.

The reflex response after this procedure was not so strong, but was almost always easily induced (fig. 6). It consisted in these cases of one

or more beehic blasts, which were followed, irrespective of the vapor employed, by a polypnea. No period of apnea such as that following administration of ammonia fumes when the carina was not cocainized, was ever observed. The response invariably disappeared after double vagotomy.

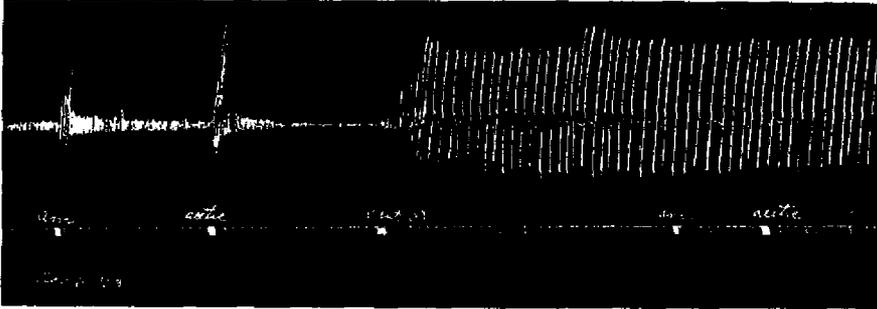


Fig. 4. Result of stimulation with vapor of ammonia and of acetic acid before and after double vagotomy. Animal under light ether anesthesia.

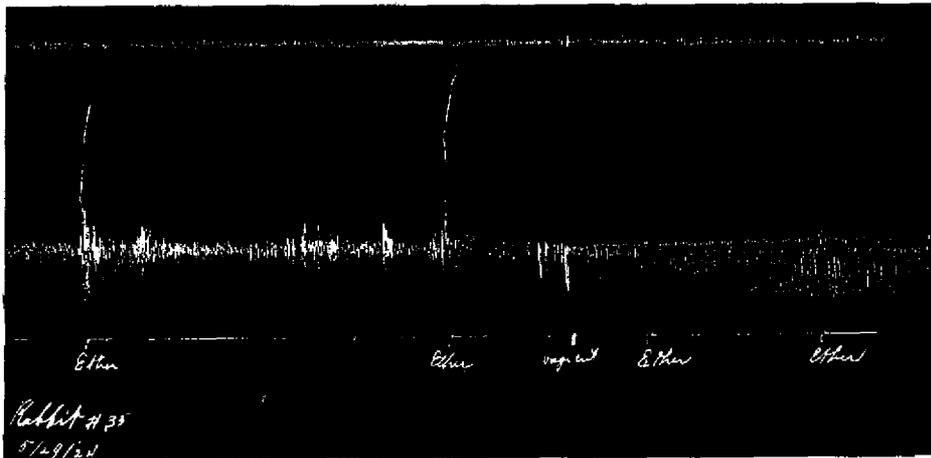


Fig. 5. Result of stimulation with ether before and after double vagotomy. Animal had been allowed to partially emerge from the deep ether anesthesia which was used while the operative work was done.

Brodie and Russell (8) state that chemical "stimulation of the alveolar nerves is about as effective as that of the laryngeal." On histological grounds the only nerve endings which can be regarded as "alveolar" in any strict sense are those located in the walls of the atrial spaces (3). No terminations have been found in the air-sacs proper. It is possible that these atrial terminations are receptors of chemical sense, as indeed one might suspect from their structure and position. One is tempted to

suggest that it is these terminations which account for the results of Suñer (11), (12) and Suñer and Bellido (13). These workers supplied the respiratory center of an experimental dog from the blood stream of an animal not further treated. When the experimental animal was caused to inhale various concentrations of CO₂ gas, respiratory effects similar to those usually attributed to the respiratory center were observed. These effects were no longer produced after section of the vagus nerves.

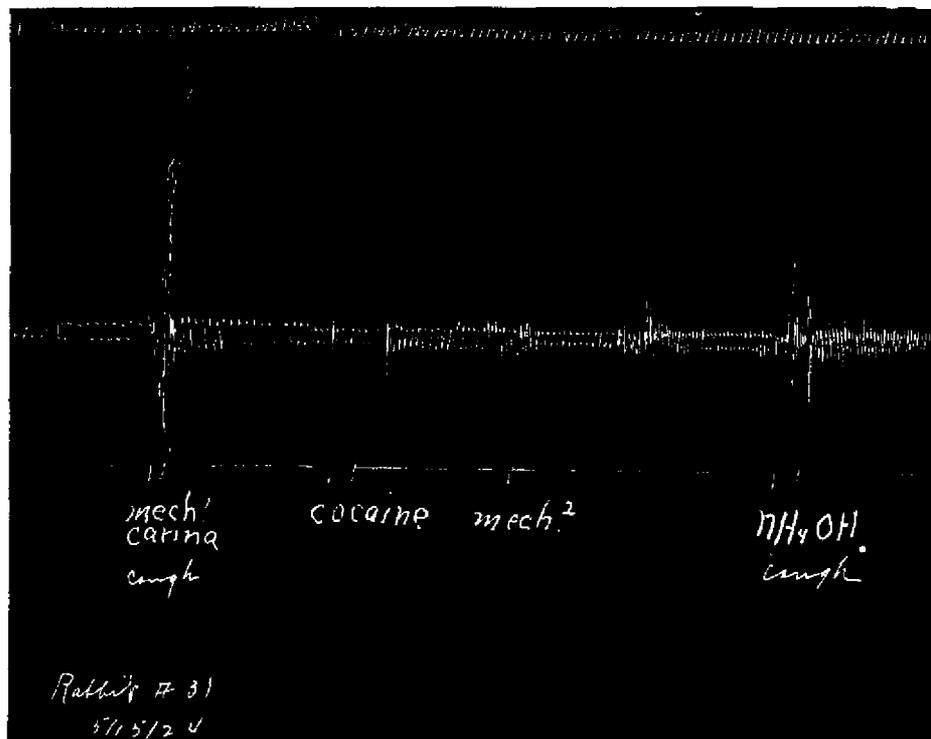


Fig. 6. Result of stimulation of deep air passages with ammonia fumes after the trachea and carina had been treated with cocaine. The preliminary mechanical stimulus, *mech 1*, was to test the sensitiveness of the animal. The second, *mech 2*, was to test the effect of the cocaine on the trachea and carina.

Whether or not it is these endings which were stimulated by the ammonia and the other vapors employed in the present experiments, we have no means of knowing. Anatomical conditions and experimental results are however in close harmony with the conclusions of Suñer (11) that the lung or the final bronchial ramifications are sensitive to certain chemical excitations which cause respiratory reflexes carried by the vagus.

In the main our results with rabbits are similar to those reported by Mayer, Magne and Plantefol (2). We would call attention especially to

the sharp expiratory blast, which these authors as well as we also observed, and to the cessation of the response after double vagotomy, in which again we find ourselves in agreement with the authors named. On both these points we are in disagreement with Roger (14), who also worked on rabbits. Roger's tracings show arrest of respiration in the inspiratory phase after projection of irritant vapors into the trachea, and he states that double vagotomy does not affect the response. Craigie (1), working with dogs, states concerning the reflexes produced by blowing gas into the trachea and bronchi that "These were found to conform more nearly to the description of Mayer, Magne and Plantefol than to that of Roger." This statement is borne out by his tracings which, for normal animals, are very similar to ours, even to the brief period of apnea when ammonia was used. Craigie also states that the reaction commences with an expiratory spasm, and refers to the period of apnea.

He states however that "Both the respiratory and circulatory reflexes are absolutely unaffected by double vagotomy," thus agreeing with Roger so far as the respiratory effect is concerned. Craigie's tracings are far from convincing on this point. His figure 2 B certainly does not show the reflex effect and polypnea so manifest in figure 2 A, although the so-called vagus breathing is very evident. His figure 3 also makes his statement appear over-emphatic. After making due allowance for the difference of animal, and the possibly greater sensory innervation of the lung of the dog from the sympathetic trunk, which we had been led to suspect on anatomical grounds, we should interpret Craigie's results as indicating agreement with our own in the rabbit, that section of the vagus does materially affect the respiratory reflexes, even in the dog. This conclusion is strengthened by the few experiments we ourselves have made on dogs with irritating vapors. Regarding Roger's statement on this point, as it affects rabbits, we have no suggestion to offer.

CONCLUSIONS

1. Mechanical stimulation of the lower respiratory passages including the carina and the bronchi as far as those of the second order, at least, elicits a marked bechic blast or cough.
2. When the trachea or carina are anesthetized with cocaine the intrapulmonary air passages still respond to mechanical stimulation, but the reflex is less violent.
3. Stimulation of the air passages with irritating vapors, as fumes of ammonia, ether, acetic acid, etc., produces violent bechic reflexes.
4. As with the response due to mechanical stimulation these reflexes may still be elicited from the intrapulmonary air passages when the trachea and carina are rendered anesthetic. Under these conditions the response is less violent.

5. Double vagotomy is followed by failure of response to any of the stimuli above named. It appears therefore that sensory terminations within the lung and in the epithelium of the carina are chiefly responsible for initiating the reflexes involved, and that these endings are connected with nerve fibers which pass through the vagus nerves to the medulla oblongata.

6. The deeper air passages give less marked response both to mechanical and chemical stimulation than do the larger bronchi and particularly the carina.

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